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(54) **AMYLOID PRECURSOR PROTEIN AS A DIAGNOSTIC MARKER FOR BILIARY ATRESIA**

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CPC G01N 33/6893; G01N 2333/705; G01N 2333/4709; G01N 2800/085; C12Q 1/6883; C12Q 2600/158
See application file for complete search history.

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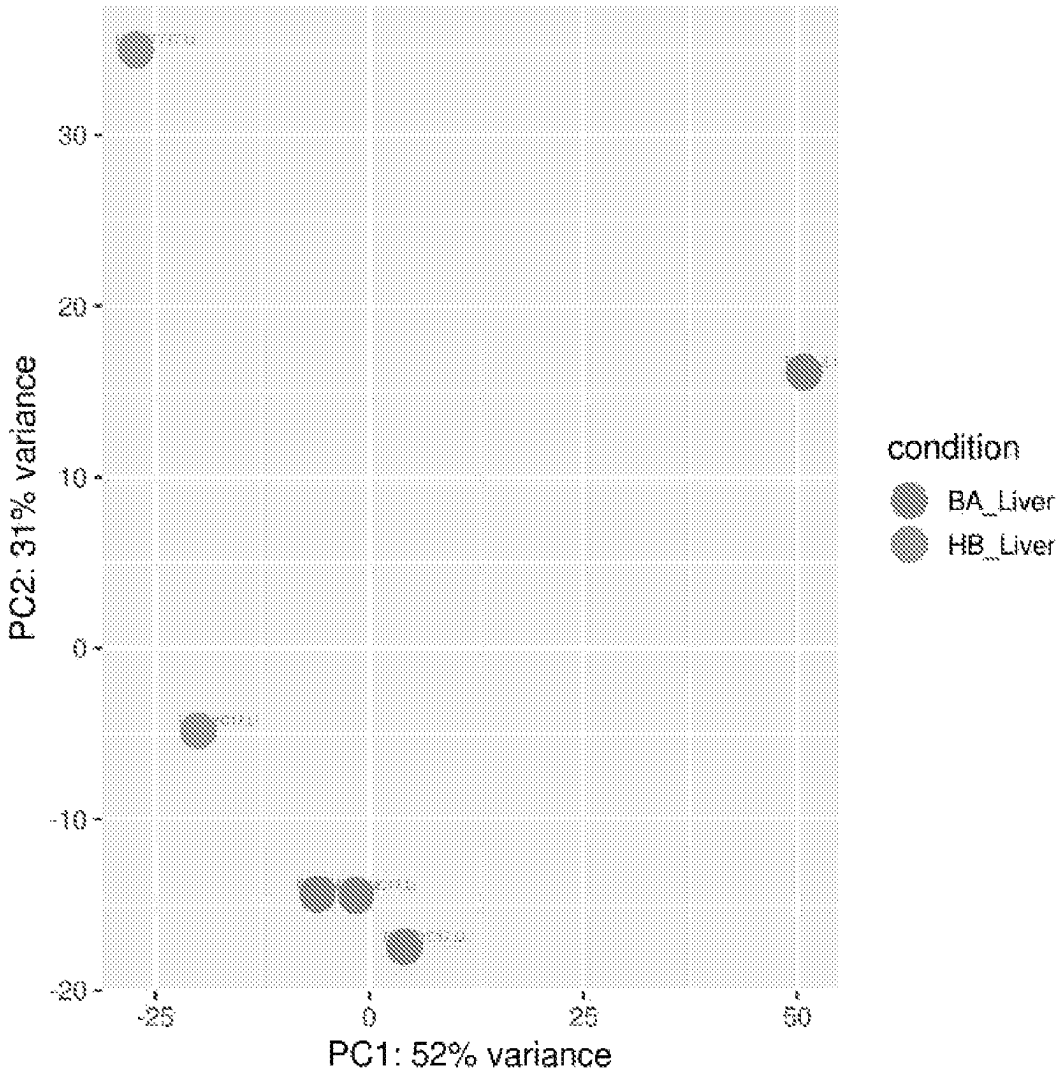
(57) **ABSTRACT**

Provided are novel diagnostic and prognostic methods for biliary atresia using amyloid precursor protein.

15 Claims, 2 Drawing Sheets

Specification includes a Sequence Listing.

Figure 1 PCA plot for liver biopsies RNA-seq analysis



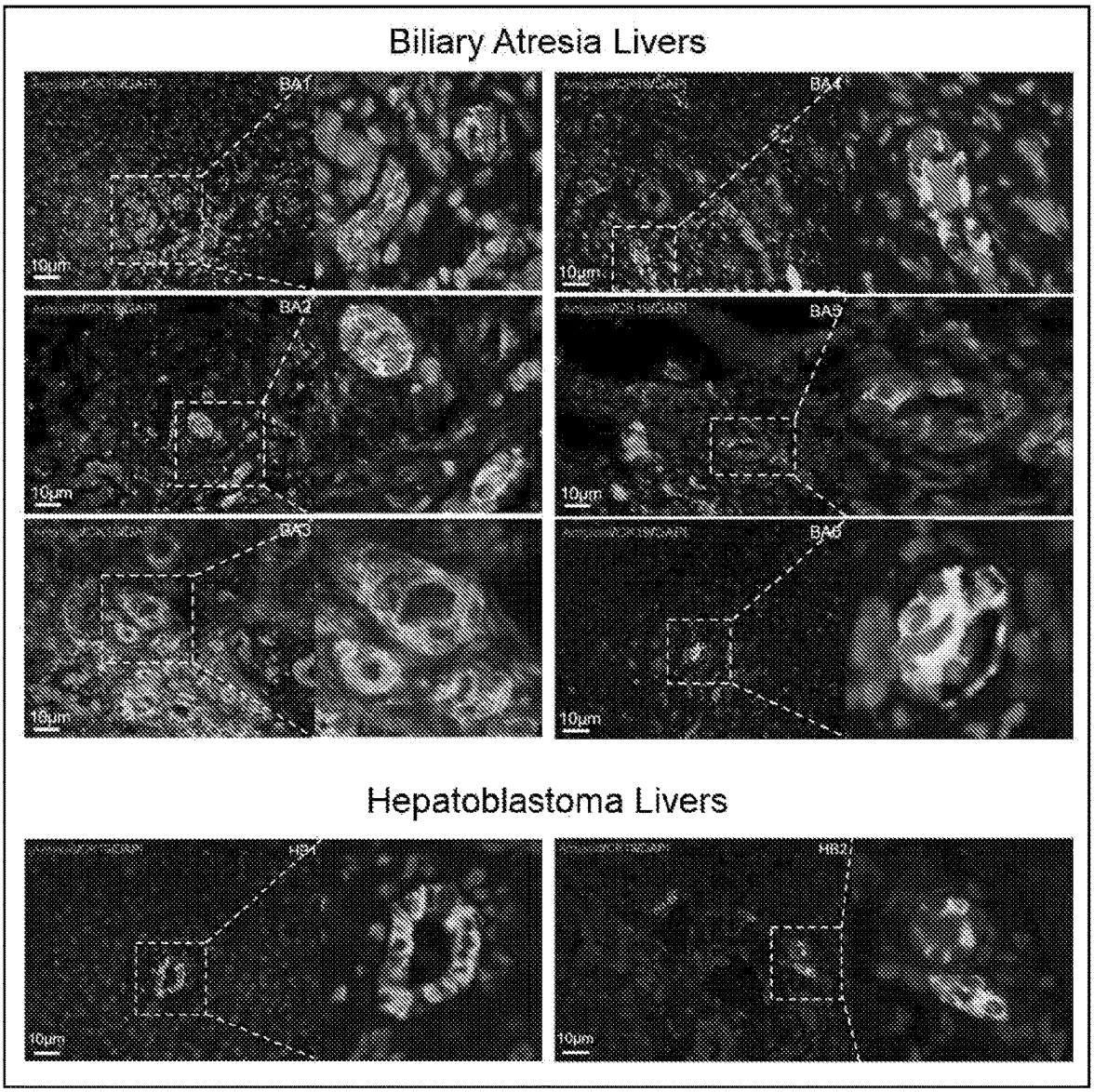

Biliary Atresia Livers
BA1
BA4
BA2
BA5
BA3
BA6
Hepatoblastoma Livers
HB1
HB2
10μm

Figure 2

AMYLOID PRECURSOR PROTEIN AS A DIAGNOSTIC MARKER FOR BILIARY ATRESIA

SEQUENCE LISTING

A Sequence Listing conforming to the rules of for Application filed prior to Jul. 1, 2022 is hereby incorporated by reference. Said Sequence Listing has been filed as an electronic document via the USPTO patent electronic filing system in ASCII formatted text. The electronic document, created on May 17, 2025 is entitled "104525-1253597-000310US_ST25", and is 82,065 bytes in size.

BACKGROUND

Biliary atresia is a disease of the liver and bile ducts that occurs in infants. Typically, symptoms of biliary atresia appear or develop about two to eight weeks after birth. Cells within the liver produce bile, a digestive liquid that helps digest fat. It also carries waste products from the liver to the intestines for excretion. This network of channels and ducts in which bile is produced, digests fat, and eventually moves to intestines is called the biliary system. Under the normal physiological conditions, the biliary system allows the bile to drain from the liver into the intestines. When a baby has biliary atresia, however, bile flow from the liver to the gallbladder is blocked. This causes the bile to be trapped inside the liver, which can quickly cause damage and scarring of the liver cells, resulting in liver cirrhosis and eventually liver failure.

While the exact cause of biliary atresia is yet to be fully illustrated, it is believed that some infants develop biliary atresia due to their bile ducts not formed properly during pregnancy. For most other children with biliary atresia, their bile ducts may be damaged by the body's immune system in response to a viral infection acquired after birth. Although biliary atresia is a rare disease, it affects the Asian population at a notably higher rate than other ethnicities. Diagnosis of biliary atresia relies on blood tests, ultrasound of the abdomen, liver biopsy, as well as diagnostic surgery (which may include an operative cholangiogram). Once diagnosed, biliary atresia is treated by Kasai procedure or hepatoportoenterostomy. With a 65-85% success rate routinely achieved by this procedure, failure still can result in a small percentage of infants, who will then likely require a liver transplant for long term survival. Because of this life-threatening potential of biliary atresia, there exists an urgent need for new and more reliable methods for the early diagnosis of infants suspected of having biliary atresia and for risk assessment among those who have undergone Kasai operation. This invention fulfills this and other related needs.

SUMMARY OF THE INVENTION

The present inventors observed increased expression of amyloid precursor protein in the liver tissue of an infant who is at risk of developing biliary atresia or is suffering from biliary atresia and has a poor outcome of biliary atresia treatment by Kasai operation. This discovery thus allows new methods to be devised for use in the diagnosis or prognosis of biliary atresia.

In the first aspect, the present invention provides a method for diagnosing or assessing the risk of biliary atresia (BA) in an infant by detecting in a liver sample taken from the infant the level of amyloid precursor protein (APP). The method includes these steps: (i) determining the expression level of APP in a liver sample taken from the infant; (ii) detecting an increase in the APP expression level in comparison to a standard control level; and (iii) determining the infant as having BA or at an increased risk of developing biliary atresia.

In some embodiments, the APP expression level is APP mRNA level or protein level. In some embodiments, step (i) comprises a reverse transcription polymerase chain reaction (RT-PCR) or an immunoassay. In some embodiments, the liver sample is a liver biopsy. In some embodiments, the method further includes after step (iii) a step of performing at least one additional diagnostic test for BA to confirm the diagnosis. In some embodiments, the method may further include after step (iii) a step of treating the infant with Kasai procedure.

In the second aspect, the present invention provides a method for assessing the likelihood of poor outcome (e.g., ineffective Kasai procedure) in an infant after the infant has been diagnosed with BA and has received Kasai operation. The method includes these steps: (i) determining the expression level of APP in a liver sample taken from the infant; (ii) detecting an increase in the APP expression level in comparison to a standard control level; and (iii) determining that the Kasai procedure is likely a failure.

In some embodiments, the APP expression level is APP mRNA level or protein level. In some embodiments, step (i) comprises a reverse transcription polymerase chain reaction (RT-PCR) or an immunoassay. In some embodiments, the liver sample is a liver biopsy. In some embodiments, the method further includes after step (iii) a step of performing at least one additional diagnostic test for BA to confirm the prognosis-if the additional test for BA indicates presence of BA, one may conclude the treatment has likely failed. In some embodiments, the method may further include after step (iii) a step of providing the infant with further treatment such as liver transplant.

In a third aspect, the present invention provides a kit for diagnosing BA, assessing risk of developing BA, or prognosing unsuccessful Kasai procedure in an infant. The kit comprises a first container containing at least one reagent for detecting the mRNA or protein level of APP and a second container containing a standard control sample having an average level of APP expression in healthy liver tissue.

In some embodiments, the APP expression level is APP mRNA level or APP protein level. In some embodiments, the first container contains one or more reagents for an RT-PCR. In some embodiments, the first container contains one or more reagents for an immunoassay. In some embodiments, one or more reagents contained in the first container include a set of primers for PCR. In some embodiments, one or more reagents contained in the first container include an antibody against APP. In some embodiments, the kit further includes user instructions for using the kit.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Principal component analysis of control and BA liver.

FIG. **2**. Expression of APP in BA bile ducts. Sections of livers of biliary atresia (A) and normal controls (B; Hepatoblastoma) were immuno-fluorescent stained for APP (red) and CK19 (green; bile duct marker). Photos of liver sections of six BA patients (BA1 to BA6) and two HB patients (HB1 and HB2) were shown for comparison. Regions highlighted were enlarged and shown on the right.

DEFINITIONS

As used herein, an "amyloid precursor protein (APP)" refers to a membrane protein encoded by a gene located on

chromosome 21 (in human). A highly conserved protein found in many species, there are several known isoforms of human APP due to alternative splicing, ranging in length from 639 to 770 amino acids, with certain isoforms preferentially expressed in neurons. An integral membrane protein expressed in many tissues and concentrated in the synapses of neurons, APP has been implicated as a regulator of synapse formation, neural plasticity, and iron export, although its precise functions are yet to be fully understood. The term "amyloid precursor protein" or "APP" is used herein to broadly encompass any isoforms of the protein such as naturally occurring homologues or orthologues or mutants, including proteins or peptides derived from the full-length APP such as peptides generated by its proteolysis, for instance, beta amyloid (Aβ), a polypeptide containing about 37 to about 49 amino acid residues, whose amyloid fibrillar form is the primary component of amyloid plaques found in the brains of Alzheimer's disease patients. Preferably, an APP is specifically recognized by an antibody that specifically recognizes the full-length APP, e.g., a polypeptide encoded by any one of the polynucleotide sequences set forth in Table 3.

Biliary atresia (BA) is a disease of blocked biliary system in the liver and bile ducts that typically occurs in infants in the age range of 2 weeks to 2 months. Symptoms of biliary atresia include jaundice, dark urine, acholic stools (clay-colored stools), weight loss and irritability. The preferred treatment method for BA is the Kasai procedure or operation, a surgical bypass procedure that allows bile to drain from the liver thus avoiding permanent damage to the liver. As used herein, a subject suffering from BA is an infant (for examples, aged about 1 week or about 2 weeks or about 3 weeks to about 1 month or about 2 months or about 3 months) who has been diagnosed with BA but is yet to receive the Kasai operation, or who has been diagnosed with BA, received the Kasai operation, yet still has symptoms relevant to the disease despite having received the Kasai operation.

In this disclosure the term "biological sample" or "sample" includes sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histologic purposes, or processed forms of any of such samples. Biological samples include blood and blood fractions or products (e.g., serum, plasma, platelets, red blood cells, and the like), sputum or saliva, lymph and tongue tissue, oral swab, cultured cells, e.g., primary cultures, explants, transformed cells, stool, urine, and biopsy taken from a preselected organ or tissue (such as liver cells or hepatic tissue sample) as well as cells or tissue derived from biopsy. A biological sample is typically obtained from a eukaryotic organism, which may be a mammal, may be a primate and may be a human subject.

The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides which have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., *Nucleic Acid Res.,* 19:5081 (1991); Ohtsuka et al., *J. Biol. Chem.,* 260:2605-2608 (1985); and Cassol et al., (1992); Rossolini et al., *Mol. Cell. Probes,* 8:91-98 (1994)). The terms nucleic acid and polynucleotide are used interchangeably with gene, cDNA, and mRNA encoded by a gene.

The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. As used herein, the terms encompass amino acid chains of any length, including full length proteins (i.e., antigens), wherein the amino acid residues are linked by covalent peptide bonds.

The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an a carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. "Amino acid mimetics" refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

A "polynucleotide hybridization method" as used herein refers to a method for detecting the presence and/or quantity of a pre-determined polynucleotide sequence based on its ability to form Watson-Crick base-pairing, under appropriate hybridization conditions, with a polynucleotide probe of a known sequence. Examples of such hybridization methods include Southern blot, Northern blot, and in situ hybridization.

"Primers" as used herein refer to oligonucleotides that can be used in an amplification method, such as a polymerase chain reaction (PCR), to amplify a nucleotide sequence based on the polynucleotide sequence corresponding to a gene of interest, e.g., the polynucleotide sequence encoding an APP or a derivative thereof. Typically at least one, possibly two, of the PCR primers for amplification of a polynucleotide sequence is sequence-specific for that polynucleotide sequence. The exact length of the primer will depend upon many factors, including temperature, source of the primer, and the method used. For example, for diagnostic and prognostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains at least 10, or 15, or 20, or 25 or more nucleotides, although it may contain fewer nucleotides or more nucleotides. The factors involved in determining the appropriate length of primer are readily known to one of ordinary skill in the art. The primers used in particular embodiments may

be designed to specifically amplify a coding sequence for an APP or its variant or derivative. Also, the primers may be designed for specifically amplify only one segment of the APP coding sequence for a fragment of APP. In this disclosure the term "primer pair" means a pair of primers that hybridize to opposite strands a target DNA molecule or to regions of the target DNA which flank a nucleotide sequence to be amplified (e.g., encoding an APP for the purpose of detection such as for assessing BA risk or disease prospect, especially after Kasai operation). In this disclosure the term "primer site" means the area of the target DNA or other nucleic acid to which a primer hybridizes.

A "label," "detectable label," or "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include radioactive isotopes, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins that can be made detectable, e.g., by incorporating a radioactive component into the peptide or used to detect antibodies specifically reactive with the peptide. Typically a detectable label is attached to a probe or a molecule with defined binding characteristics (e.g., a polypeptide with a known binding specificity or a polynucleotide), so as to allow the presence of the probe (and therefore its binding target, e.g., a coding sequence for an APP or a fragment or variant thereof) to be readily detectable.

The term "treat" or "treating," as used in this application, describes to an act that leads to the elimination, reduction, alleviation, reversal, or prevention or delay of onset or recurrence of any symptom of a relevant condition (e.g., BA). In other words, "treating" a condition encompasses both therapeutic and prophylactic intervention against the condition: for example, upon testing positive to have elevated APP expression either at mRNA or protein level, an infant will be given additional diagnostic tests (such as blood tests, ultrasound of the abdomen, liver biopsy, as well as diagnostic surgery, which may include an operative cholangiogram) and, upon confirmation of the diagnosis of BA, undergoes therapeutic or prophylactic regimen under the supervision of a medical professional including Kasai operation. For an infant who has received treatment for BA by Kasai operation but still has BA symptoms without improvement or even with worsening symptoms, subsequent treatment will likely require liver transplant depending on physicians' decision upon careful monitoring of the infant. Administration of steroids and/or antibiotics may serve as additional/adjuvant treatment post-Kasai operation with an aim to slow down or halt further inflammation.

The term "effective amount" as used herein refers to an amount of a given substance that is sufficient in quantity to produce a desired effect. For example, when an effective amount of a therapeutic agent for treating BA by way of suppressing or eliminating the expression and/or activity of APP especially in an infant's liver is administered to the infant, the symptoms of BA are reduced, reversed, eliminated, prevented, or delayed of the onset in the infant. An amount adequate to accomplish this is defined as the "therapeutically effective dose" when administration takes place after BA symptoms have become detectable, or is defined as the "prophylactically effective dose" when administration takes place before any symptom has arisen. The dosing range varies with the nature of the therapeutic agent being administered and other factors such as the route of administration and the severity of a patient's BA and related condition.

The term "subject" or "subject in need of treatment," as used herein, includes individuals who seek medical attention due to risk of, or actual suffering from, biliary atresia. Subjects also include individuals currently undergoing therapy that seek manipulation of the therapeutic regimen. Subjects or individuals in need of treatment include those that demonstrate symptoms of biliary atresia, or those at are at risk of suffering from biliary atresia or its symptoms, or those have been tested positive for amyloid precursor protein expression but may not may not have any known risk and/or may or may not have any potentially relevant symptoms. For example, subjects in need of treatment include individuals with a genetic predisposition or family history for biliary atresia, those that are acutely suffering from relevant symptoms, those that have been exposed to a triggering substance or event, as well as those have received treatment for BA (e.g., Kasai operation) but are continuing to suffer from symptoms of the condition. A subject in need of treatment for BA may be any gender and typically an infant at the age of 3 months or younger, for example, between about 1 week to about 3 months, or between about 2 weeks to about 2 months.

The term "about" when used in reference to a predetermined value denotes a range encompassing ±10% of the value.

DETAILED DESCRIPTION

I. General

The present invention relates to the detection of APP expression in the liver cells or tissue of infants who are suffering from or at risk of suffering from biliary atresia, or who are at risk of suffering from undesirable clinical outcome after receiving the Kasai operation. This invention thus provides methods for diagnosis of biliary atresia and prognosis for clinical outcome post-Kasai operation in infants based on detection of APP expression in a liver sample obtained from infants suspected of suffering from biliary atresia or having undergone the Kasai procedure.

Basic texts disclosing general methods and techniques in the field of recombinant genetics include Sambrook and Russell, *Molecular Cloning, A Laboratory Manual* (3rd ed. 2001); Kriegler, *Gene Transfer and Expression: A Laboratory Manual* (1990); and Ausubel et al., eds., *Current Protocols in Molecular Biology* (1994).

For nucleic acids, sizes are given in either kilobases (kb) or base pairs (bp). These are estimates derived from agarose or acrylamide gel electrophoresis, from sequenced nucleic acids, or from published DNA sequences. For proteins, sizes are given in kilodaltons (kDa) or amino acid residue numbers. Proteins sizes are estimated from gel electrophoresis, from sequenced proteins, from derived amino acid sequences, or from published protein sequences.

Oligonucleotides that are not commercially available can be chemically synthesized, e.g., according to the solid phase phosphoramidite triester method first described by Beaucage & Caruthers, *Tetrahedron Lett.* 22:1859-1862 (1981), using an automated synthesizer, as described in Van Devanter et. al., *Nucleic Acids Res.* 12:6159-6168 (1984). Purification of oligonucleotides is performed using any art-recognized strategy, e.g., native acrylamide gel electrophoresis or anion-exchange HPLC as described in Pearson & Reanier, *J. Chrom.* 255:137-149 (1983).

The polynucleotide sequence encoding a polypeptide of interest, e.g., an amyloid precursor protein or a variant or derivative thereof, and synthetic oligonucleotides can be

verified after cloning or subcloning using, e.g., the chain termination method for sequencing double-stranded templates of Wallace et al., *Gene* 16:21-26 (1981).

II. Acquisition of Samples and Analysis of mRNA

The present invention relates to detecting the expression level of APP, either at the mRNA or protein level, in the liver cells or tissue taken from an infant suspected of suffering from biliary atresia (BA) or an infant who has been diagnosed with BA and has received the Kasai operation, as a means to detect the presence of BA, to assess the risk of developing of BA, and/or to provide prognosis of BA treatment such as the Kasai operation in an infant, so as to allow the correct treatment and/or follow-up strategies after Kasai operation. Thus, the first steps of practicing this invention are to obtain an appropriate sample from a test subject and extract mRNA from the sample.

A. Acquisition and Preparation of Samples

An appropriate sample such as a liver cell or tissue sample obtained from an infant, who may or may not exhibit BA symptoms, to be tested or monitored for BA or treatment outcome using a method of the present invention. Collection of a liver biopsy sample from an individual is performed in accordance with the standard protocol hospitals or clinics generally follow. An appropriate amount of tissue sample, including biopsy samples, is collected and may be stored according to standard procedures prior to further preparation.

B. Extraction of RNA

There are numerous methods for extracting RNA from a biological sample. The general methods of RNA preparation (e.g., described by Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* 3d ed., 2001) can be followed; various commercially available reagents or kits, such as Trizol reagent (Invitrogen, Carlsbad, CA), Oligotex Direct mRNA Kits (Qiagen, Valencia, CA), RNeasy Mini Kits (Qiagen, Hilden, Germany), and PolyATtract® Series 9600™ (Promega, Madison, WI), may also be used to obtain RNA from a liver sample from an infant. Combinations of more than one of these methods may also be used.

It is preferable in some applications that all or most of the contaminating DNA be eliminated from the RNA preparations. Thus, careful handling of the samples, thorough treatment with DNase, and proper negative controls in the amplification and quantification steps should be used.

C. PCR-Based Quantitative Determination of RNA Level

Once RNA is extracted from a biological sample, the amount of RNA derived from a genetic locus of interest, e.g., and encoding for a protein of interest such as APP, may be quantified. The preferred method for determining the RNA level is an amplification-based method, e.g., by PCR.

Prior to the amplification step, a DNA copy (cDNA) of the RNA of interest must be synthesized. This is achieved by reverse transcription, which can be carried out as a separate step, or in a homogeneous reverse transcription-polymerase chain reaction (RT-PCR), a modification of the polymerase chain reaction for amplifying RNA. Methods suitable for PCR amplification of ribonucleic acids are described by Romero and Rotbart in *Diagnostic Molecular Biology: Principles and Applications* pp. 401-406; Persing et al., eds., Mayo Foundation, Rochester, MN, 1993; Egger et al., *J. Clin. Microbiol.* 33:1442-1447, 1995; and U.S. Pat. No. 5,075,212.

The general methods of PCR are well known in the art and are thus not described in detail herein. For a review of PCR methods, protocols, and principles in designing primers, see, e.g., Innis, et al., *PCR Protocols: A Guide to Methods and Applications*, Academic Press, Inc. N.Y., 1990. PCR reagents and protocols are also available from commercial vendors, such as Roche Molecular Systems.

PCR is most usually carried out as an automated process with a thermostable enzyme. In this process, the temperature of the reaction mixture is typically cycled through a denaturing region, a primer annealing region, and an extension reaction region automatically. In some protocols, the annealing region and the extension reaction region are merged. Machines specifically adapted for this purpose are commercially available.

Although PCR amplification of the target RNA is typically used in practicing the present invention. One of skill in the art will recognize, however, that amplification of these RNA species in a maternal blood sample may be accomplished by any known method, such as ligase chain reaction (LCR), transcription-mediated amplification, and self-sustained sequence replication or nucleic acid sequence-based amplification (NASBA), each of which provides sufficient amplification. More recently developed branched-DNA technology may also be used to quantitatively determining the amount of RNA markers in maternal blood. For a review of branched-DNA signal amplification for direct quantitation of nucleic acid sequences in clinical samples, see Nolte, Adv. *Clin. Chem.* 33:201-235, 1998.

C. Other Quantitative Methods

The RNA species of interest (such as the APP mRNA) can also be detected using other standard techniques, well-known to those of skill in the art. Although the detection step is typically preceded by an amplification step, amplification is not required in the methods of the invention. For instance, the RNA species of interest may be identified by size fractionation (e.g., gel electrophoresis), whether or not proceeded by an amplification step. After running a sample in an agarose or polyacrylamide gel and labeling with ethidium bromide according to well-known techniques (see, e.g., Sambrook and Russell, supra), the presence of a band of the same size as the standard control is an indication of the presence of a target RNA, the amount of which may then be compared to the control based on the intensity of the band. Alternatively, oligonucleotide probes specific to RNA transcribed from a genetic locus, e.g., the APP gene, can be used to detect the presence of such RNA species and indicate the amount of RNA in comparison to the standard control, based on the intensity of signal imparted by the probe.

Sequence-specific probe hybridization is a well-known method of detecting a particular nucleic acid comprising other species of nucleic acids. Under sufficiently stringent hybridization conditions, the probes hybridize specifically only to substantially complementary sequences. The stringency of the hybridization conditions can be relaxed to tolerate varying amounts of sequence mismatch.

A number of hybridization formats are well-known in the art, including but not limited to, solution phase, solid phase, or mixed phase hybridization assays. The following articles provide an overview of the various hybridization assay formats: Singer et al., *Biotechniques* 4:230, 1986; Haase et al., *Methods in Virology*, pp. 189-226, 1984; Wilkinson, *In situ Hybridization*, Wilkinson ed., IRL Press, Oxford University Press, Oxford; and Hames and Higgins eds., *Nucleic Acid Hybridization: A Practical Approach*, IRL Press, 1987.

The hybridization complexes are detected according to well-known techniques and the detection is not a critical aspect of the present invention. Nucleic acid probes capable of specifically hybridizing to a target nucleic acid, i.e., the APP mRNA species or the amplified DNA, can be labeled by

any one of several methods typically used to detect the presence of hybridized nucleic acids. One common method of detection is the use of autoradiography using probes labeled with ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P, or the like. The choice of radioactive isotope depends on research preferences due to ease of synthesis, stability, and half-lives of the selected isotopes. Other labels include compounds (e.g., biotin and digoxigenin), which bind to antiligands or antibodies labeled with fluorophores, chemiluminescent agents, and enzymes. Alternatively, probes can be conjugated directly with labels such as fluorophores, chemiluminescent agents or enzymes. The choice of label depends on sensitivity required, ease of conjugation with the probe, stability requirements, and available instrumentation.

The probes and primers necessary for practicing the present invention can be synthesized and labeled using well known techniques. Oligonucleotides used as probes and primers may be chemically synthesized according to the solid phase phosphoramidite triester method first described by Beaucage and Caruthers, *Tetrahedron Letts.,* 22:1859-1862, 1981, using an automated synthesizer, as described in Needham-VanDevanter et al., *Nucleic Acids Res.* 12:6159-6168, 1984. Purification of oligonucleotides is by either native acrylamide gel electrophoresis or by anion-exchange high performance liquid chromatography (HPLC) as described in Pearson and Regnier, *J. Chrom.,* 255:137-149, 1983.

III. Immunoassays for Detection of Amyloid Precursor Protein

One aspect of this invention provides immunoassays used in the detection of APP in order to determine the expression level of the protein for the purpose of diagnosis and prognosis of BA. Antibodies against APP described herein are useful for carrying out these immunological assays.

A. Production of Antibodies Against APP

Methods for producing polyclonal and monoclonal antibodies that react specifically with an immunogen of interest are known to those of skill in the art (see, e.g., Coligan, *Current Protocols in Immunology Wiley*/Greene, NY, 1991; Harlow and Lane, *Antibodies: A Laboratory Manual* Cold Spring Harbor Press, NY, 1989; Stites et al. (eds.) *Basic and Clinical Immunology* (4th ed.) Lange Medical Publications, Los Altos, CA, and references cited therein; Goding, *Monoclonal Antibodies: Principles and Practice* (2d ed.) Academic Press, New York, NY, 1986; and Kohler and Milstein *Nature* 256:495-497, 1975). Such techniques include antibody preparation by selection of antibodies from libraries of recombinant antibodies in phage or similar vectors (see, Huse et al., *Science* 246:1275-1281, 1989; and Ward et al., *Nature* 341:544-546, 1989).

In order to produce antisera containing antibodies with desired specificity, the polypeptide of interest (e.g., APP) or an antigenic fragment thereof can be used to immunize suitable animals, e.g., mice, rabbits, or primates. A standard adjuvant, such as Freund's adjuvant, can be used in accordance with a standard immunization protocol. Alternatively, a synthetic antigenic peptide derived from that particular polypeptide can be conjugated to a carrier protein and subsequently used as an immunogen.

The animal's immune response to the immunogen preparation is monitored by taking test bleeds and determining the titer of reactivity to the antigen of interest. When appropriately high titers of antibody to the antigen are obtained, blood is collected from the animal and antisera are prepared. Further fractionation of the antisera to enrich antibodies specifically reactive to the antigen and purification of the antibodies can be performed subsequently, see, Harlow and Lane, supra, and the general descriptions of protein purification provided above.

Monoclonal antibodies are obtained using various techniques familiar to those of skill in the art. Typically, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell (see, Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976). Alternative methods of immortalization include, e.g., transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods well known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired specificity and affinity for the antigen, and the yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host.

Additionally, monoclonal antibodies may also be recombinantly produced upon identification of nucleic acid sequences encoding an antibody with desired specificity or a binding fragment of such antibody by screening a human B cell cDNA library according to the general protocol outlined by Huse et al., supra. The general principles and methods of recombinant polypeptide production discussed above are applicable for antibody production by recombinant methods.

B. Immunoassays for APP

Once antibodies specific for APP are available, the expression of APP at protein level in a sample, e.g., a liver cell or tissue sample, can be measured by a variety of immunoassay methods providing qualitative and quantitative results to a skilled artisan. For a review of immunological and immunoassay procedures in general see, e.g., Stites, supra; U.S. Pat. Nos. 4,366,241; 4,376,110; 4,517,288; and 4,837,168.

1. Labeling in Immunoassays

Immunoassays often utilize a labeling agent to specifically bind to and label the binding complex formed by the antibody and the target protein (e.g., APP). The labeling agent may itself be one of the moieties comprising the antibody/target protein complex, or may be a third moiety, such as another antibody, that specifically binds to the antibody/target protein complex. A label may be detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Examples include, but are not limited to, magnetic beads (e.g., Dynabeads™), fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (e.g., ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase, and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads.

In some cases, the labeling agent is a second antibody bearing a detectable label. Alternatively, the second antibody may lack a label, but it may, in turn, be bound by a labeled third antibody specific to antibodies of the species from which the second antibody is derived. The second antibody can be modified with a detectable moiety, such as biotin, to which a third labeled molecule can specifically bind, such as enzyme-labeled streptavidin.

Other proteins capable of specifically binding immunoglobulin constant regions, such as protein A or protein G, can also be used as the label agents. These proteins are normal constituents of the cell walls of streptococcal bacteria. They exhibit a strong non-immunogenic reactivity with immuno-

globulin constant regions from a variety of species (see, generally, Kronval, et al. *J. Immunol.,* 111:1401-1406 (1973); and Akerstrom, et al., *J. Immunol.,* 135:2589-2542 (1985)).

2. Immunoassay Formats

Immunoassays for detecting a target protein of interest (e.g., APP) from samples may be either competitive or noncompetitive. Noncompetitive immunoassays are assays in which the amount of captured target protein is directly measured. In one preferred "sandwich" assay, for example, the antibody specific for the target protein can be bound directly to a solid substrate where the antibody is immobilized. It then captures the target protein in test samples. The antibody/target protein complex thus immobilized is then bound by a labeling agent, such as a second or third antibody bearing a label, as described above.

In competitive assays, the amount of target protein in a sample is measured indirectly by measuring the amount of an added (exogenous) target protein displaced (or competed away) from an antibody specific for the target protein by the target protein present in the sample. In a typical example of such an assay, the antibody is immobilized and the exogenous target protein is labeled. Since the amount of the exogenous target protein bound to the antibody is inversely proportional to the concentration of the target protein present in the sample, the target protein level in the sample can thus be determined based on the amount of exogenous target protein bound to the antibody and thus immobilized.

In some cases, western blot (immunoblot) analysis is used to detect and quantify the presence of APP in the samples. The technique generally comprises separating sample proteins by gel electrophoresis on the basis of molecular weight, transferring the separated proteins to a suitable solid support (such as a nitrocellulose filter, a nylon filter, or a derivatized nylon filter) and incubating the samples with the antibodies that specifically bind the target protein. These antibodies may be directly labeled or alternatively may be subsequently detected using labeled antibodies (e.g., labeled sheep anti-mouse antibodies) that specifically bind to the antibodies against APP.

Other assay formats include liposome immunoassays (LIA), which use liposomes designed to bind specific molecules (e.g., antibodies) and release encapsulated reagents or markers. The released chemicals are then detected according to standard techniques (see, Monroe et al., *Amer. Clin. Prod. Rev.,* 5:34-41 (1986)).

For these immunoassays, the patient being tested may be an infant who is at risk of developing BA or may be one who has been diagnosed with BA, has undergone treatment such as Kasai operation, and is now being assessed for likelihood of a desirable outcome of the treatment.

IV. Treatment Options

One practical application of this invention is intended for early detection of BA among infants who are suspected of suffering from the disease or are at increased risk of developing the disease. Once they are tested according to any one of the methods of this invention and are determined as at risk of suffering from or later developing this disease, they can be subject to additional diagnostic tests, such as blood tests, ultrasound of the abdomen, liver biopsy, and diagnostic surgery (which may include an operative cholangiogram) in order to confirm whether they indeed suffer from the disease. Upon confirmation of the diagnosis of BA, they can then undergo appropriate treatment (e.g., the Kasai operation) as prescribed by their attending physician.

Another application is intended for predicting the likelihood of success among infants who have been diagnosed with BA and have been given appropriate treatment such as the Kasai operation. As it is known that a minority of all infant BA patients who underwent the operation will fail to properly recover, and the symptoms and damaging effects of BA will continue and even worsen. The claimed method of this invention allows physicians to quickly obtain an assessment of the likelihood of treatment outcome (e.g., shortly after the Kasai procedure such as 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or up to 10 days or 2 weeks post-operation) when the infant may or may not yet to show any signs of persistent or deteriorating BA symptoms: whether it will result in desirable outcome, where the infant patient will fully recover from the disease, or it will result in failure, where the infant patient will require additional treatment, such as another Kasai procedure or even liver transplant.

A further aspect of the present invention is the treatment of BA. Since the expression of APP, both at mRNA level and at protein level, has been found to increase in the liver of infants who suffer from BA, or who are at increased risk of later developing BA while exhibiting no BA symptoms for the time being, or who have been diagnosed with BA and given appropriate treatment such as the Kasai procedure but suffer from undesirable outcome (i.e., failure of treatment to alleviate BA symptoms and damages to liver), one treatment method for BA is to target APP by suppressing its expression (both at mRNA and protein level) and/or activity. For instance, specific inhibitors targeting APP expression and/or activity may be administered to an infant who suffers from BA, or who is at heightened risk of later developing BA, or who has received a diagnosis of BA and received treatment (e.g., the Kasai procedure) but is at risk of suffering from treatment failure. Such specific inhibitors include a broad spectrum of possible compounds of distinct chemical and structural features such as a dominant negative APP mutant or its encoding nucleic acid, a nucleic acid encoding an antisense or miRNA, miniRNA, long non-coding RNA targeting APP, an inactivating anti-APP antibody, small chemicals, peptides, proteins, natural extract compounds from herbs, etc., and they are useful in both prophylactic and therapeutic applications for treating BA. Also, APP expression may be suppressed by genetic manipulation techniques including CRISPR.

V. Establishing Standard Controls

For the application of this invention for the purpose of diagnosing BA or assessing risk of developing BA at a later time, in order to establish a standard control, a group of healthy infants without any liver disorders, especially BA, should first be selected before liver samples are obtained. These infants should be of similar age, which is within the appropriate time frame (for example, aged from about 2 weeks to about 8 weeks) when infants may be tested using the methods of the present invention. The health status of the selected infants should be confirmed by well established, routinely employed methods including but not limited to blood tests and abdominal ultrasound.

The selected group of healthy infants must be of a reasonable size, such that the average amount of APP mRNA and protein found in the liver tissue samples (e.g., liver biopsy) calculated from the group can be reasonably regarded as representative of the normal or average amount among the general population of healthy infants not suffer-

ing from BA and not at heightened risk of developing BA. Preferably, the selected group comprises at least 10 healthy infants.

For the application of this invention for the purpose of providing a prognosis of BA treatment (especially the Kasai procedure) outcome among infants who have already been diagnosed with BA and received appropriate treatment such as the Kasai procedure, the same standard control described above may be used. In the alternative, a slightly different standard control can be established: a group of infants who suffered from BA and have undergone the same BA treatment such as Kasai operation and successfully recovered should be selected for collection of liver samples. Similar to the description above, these infants should be of similar age and make up a group of a reasonable size, e.g., at least 10 in the group.

Once an average value is established for the amount of APP mRNA or protein based on the individual values found in the liver tissue of each infant of the selected group, this value is considered a standard control value for APP mRNA or protein. Any liver tissue sample that contains a similar amount of APP mRNA or protein can thus be used as a standard control sample.

VI. Kits

The invention also provides kits for detecting APP mRNA or protein, especially in a liver sample taken from an infant, according to the method of the present invention for the purpose of detecting the presence of BA, assessing the risk of later developing BA, or assessing likelihood of a successful BA treatment (such as the Kasai operation) outcome. The kits typically include a first container that contains a first container containing at least one, possibly more, reagent for detecting expression level of APP and a second container containing a composition having a standard control level of APP expression (or a standard control sample). The one or more reagents in the first container may be used for measuring APP mRNA level, such as oligonucleotide primers useful for RT-PCR and/or oligonucleotide probe(s) for specific hybridization with an APP-specific polynucleotide sequence. Other possible reagents may include the necessary enzyme(s) and buffer(s) for performing assays to detect APP mRNA such as RT-PCR or nucleotide hybridization.

For the purpose of determining the APP protein level in a liver sample, the one or more reagents contained in the first container may be those useful for immunoassays capable of specifically detecting and quantifying APP level as a protein, such as ELISA or western blot analysis. One useful reagent is an anti-APP antibody, which may be a polyclonal antibody or a monoclonal antibody capable of specific binding to APP. Further included may be a secondary antibody, for example, an antibody against the anti-APP antibody, preferably conjugated with a detectable label.

In addition, the kit may further include informational material containing instructions for a user on how to use the kit for performing an assay and determining whether increased APP mRNA or protein is present in a patient sample.

EXAMPLES

The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially the same or similar results.

Example 1: Amyloid Precursor Protein Expression in Biliary Atresia

This study reveals, for the first time, the specific expression of amyloid precursor protein and/or its processed forms in the bile duct of livers in patients suffering from biliary atresia (BA). This discovery allows one to devise new and reliable diagnostic methods for early detection of BA as well as for predicting the therapeutic outcome of BA treatment such as Kasai operation.

Introduction

Biliary atresia (BA [OMIM 210500]) is characterized by progressive fibro-obliterative cholangiopathy (disease of the bile duct) affecting both the intra- and extra-hepatic bile ducts and resulting in obstructive bile flow, cholestasis, and jaundice in neonates. BA occurs in some infants two to six weeks after birth, and symptoms of BA are usually evident between two and six weeks after birth, in that babies with BA develop progressive cholestasis, a condition in which the liver is unable to excrete bilirubin through the bile ducts in the form of bile. Bilirubin builds up inside of liver and begins to accumulate in the blood, causing symptoms including yellowing of the skin, itchiness, poor absorption of nutrients, pale stools, dark urine, and a swollen abdomen.

The differential diagnosis of BA allows for identification of patients suffering from BA as opposed to other disorders such as neonatal cholestasis (NC) like neonatal hepatitis (NH), paucity of interlobular bile ducts (PILBD), progressive familial intrahepatic cholestasis (PFIC), and various metabolic diseases like galactosemia and a-1 antitrypsin deficiency. The most important objective in such cases is to distinguish obstructive cholestasis from non-obstructive causes. The diagnosis of BA, particularly distinguishing it from other causes of liver injury in the neonatal period, is challenging as there is a high degree of overlap in clinical, biochemical, imaging, and histological characteristics of BA and other causes of NC.

Without surgical treatment (Kasai operation) to re-establish the bile drainage from microscopic residual bile ductules within the liver, progressive hepatic fibrosis leads to cirrhosis, portal vein hypertension, liver failure and death by the age of two (1, 2). However, postsurgical complications, including cholangitis (50%) and portal hypertension (>60%), remain a problem (3-7). Furthermore, regardless of drainage after successful surgery, patients will often develop inflammation and sclerosis of the biliary tree, leading to secondary biliary cirrhosis. To these patients and those who failed the surgical intervention, liver transplantation becomes the only treatment option. Indeed, BA has been the most common indication for liver transplantation during childhood for the past 20 years. Due to liver graft scarcity, many patients die before transplantation.

Urgently, there exists a distinct need to address the following problems: first, diagnosis of BA needs to be improved, in particular at early stages of the disease. The optimal age for Kasai operation is 60-75 days; delayed in diagnosis and surgery will lead to poor outcome. In fact, early diagnosis allows the family and surgeon for better planning of disease management. Second, despite the same Kasai operation, the outcome can vary from patient to patient, suggesting the existence of subsets of patient but there are no reliable markers for prognosis to guide stratified treatments for optimal outcomes. Third, regardless of drainage after Kasai operation, patients will often develop bile duct inflammation and sclerosis, leading to secondary biliary cirrhosis. To these patients and those who failed surgery, liver transplantation is the only option. For those BA patients

who are predicted to have poor outcome after Kasai operation may be selected to undergo liver transplantation as the treatment from the start without first undergoing Kasai operation. There is an urgent need to find new and effective therapies that ameliorate BA.

Materials and Methods

Liver Tissues

Control liver: "Quasi-normal" human liver tissues were obtained from non-tumour margin of hepatoblastoma (HB). BA liver: Liver biopsies of BA patients taken during Kasai operation or at transplantation. All tissues were obtained during operations with full informed consent from parents or patients, and the study was approved by Hong Kong West Cluster-Hong Kong University Cluster Research Ethics Committee/Institutional Review Board (UW 16-052).

Antibodies

Anti-β-Amyloid (4G8; Biolegend) reacts to precursor forms, as well as abnormally processed isoforms of amyloid precursor protein. Anti-CK19 (ab52625; abcam) reacts to human cytokeratin 19.

Liver Biopsies

Wedge biopsies (50×50 mm) were obtained from non-syndromic BA patients during laparoscopic cholangiography, hepatoblastoma (HB)).

RNA Sequencing of Liver Tissues

Total RNAs were prepared from 30 mg of control livers (HB; n=2) and BA livers (n=4) using RNeasy Mini Kit (Qiagen) following manufacturer's protocol. Reverse transcription, amplification of 50 ng total RNA of each liver samples, and library construction were performed using single cell RNA-seq technology (Smart-seq 2.0) with minor modifications (8). Qualities of the pre-amplified products of normal and BA livers were confirmed to be optimal by Bioanalyzer. Library construction was performed using Nextera XT Kit following manufacturer's protocol. Libraries were pooled and sequenced by pair ends of 100 base pairs (PE100) on illumina HiSeq 2500 System.

Immuno-Fluorescence Staining

Tissues were fixed in 4% paraformaldehyde (w/v) in PBS (phosphate-buffered saline, pH 7.2) for 48 h at 4° C., dehydrated in graded series of alcohol, cleared in xylene before being embedded in paraffin. Sections (8 μm in thickness) were prepared, mounted onto TESPA-coated microscope glass. Sections were dewaxed in xylene, hydrated in a graded series of alcohol and finally in distilled water. Antigen was retrieved by two steps: (i) incubating in 70% Formic acid for 10 minutes and washing in water; (ii) incubating in 10 mM sodium citrate buffer (pH 6.0) at 95° C. for 10 min and washing in water. After blocking in PBS-T (PBS with 0.1% Triton) supplemented with 1% Bovine Serum Albumin for 1 h at room temperature, sections were incubated with anti-β-Amyloid (4G8, 1:200; Biolegend) and anti-CK19 (ab52625, 1:250; abcam) diluted in PBS-T/BSA for overnight at 4° C. After washing in PBS-T, sections were incubated with appropriate fluorescent tagged secondary antibodies in PBS-T/BSA at 37° C. for 1 h. After PBS-T washings, sections were mounted in Dapi-containing anti-fade mounting fluid. Images were taken with Nikon Eclipse 80i microscope mounted with SPOT RT3 microscope digital camera under fluorescence illumination. Photos were compiled using Adobe Photoshop 7.

Results

Transcriptome Analysis of Normal and BA Liver by RNAseq

The RNA-seq reads were first subjected to quality check using FastQC version 0.11.1. Further the adapter contamination and low-quality regions were filtered using Cutadapt version 1.8.3 with the parameter –q=33 and retained only reads with length≥30. The percentage of high quality bases in the filtered raw reads were greater than 90% for all the samples, with the quality score cut-off=20. Subsequently, sequencing reads were filtered for rRNA sequence by aligning to human rRNA sequences using Bowtie 2 (default parameters). The remaining reads were mapped to the reference genome. The transcriptome mapping/alignment and identification of exon-exon splice junctions with the human genome reference (GRCh38, downloaded from Ensembl database) was done by using TopHat version 2.0.10 (default parameters). All the samples had an overall alignment of >80% with human reference. Counting of aligned reads per gene were done using HTSeq version 0.9.1 for further differential expression analysis. The counts for each gene per samples were presented as table in DESeq2 to accurately detect significant differentially expressed genes across the conditions. Visualization was done using R and Bioconductor (FIG. **5***c*?).

Principal component analysis (PCA) of liver biopsies revealed the following observations:

1. Normal liver and BA liver displayed distinctive molecular signatures.
2. The two normal liver controls showed differences among themselves, which may indicate the genetic differences between the patients or the tissue stages during isolation.
3. Three of the BA livers were clustering very closely to each other while the other patient showed enormous difference, which may indicate progression of disease.

TABLE 1

Pathways involvement of the 1558 differentially expressed genes	
Integrin signalling pathway (P00034)	28
Gonadotropin-releasing hormone receptor pathway (P06664)	25
Inflammation mediated by chemokine and cytokine signaling pathway (P00031)	21
CCKR signaling map (P06959)	20
Wnt signaling pathway (P00057)	17
Angiogenesis (P00005)	12
PDGF signaling pathway (P00047)	12
Apoptosis signaling pathway (P00006)	11
Nicotinic acetylcholine receptor signaling pathway (P00044)	10
Huntington disease (P00029)	9
Alzheimer disease-presenilin pathway (P00004)	8
Heterotrimeric G-protein signaling pathway-Gq alpha and Go alpha mediated pathway (P00027)	8
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway (P00026)	8
Parkinson disease (P00049)	7

TABLE 1-continued

Pathways involvement of the 1558 differentially expressed genes	
Interleukin signaling pathway (P00036)	7
EGF receptor signaling pathway (P00018)	7
T cell activation (P00053)	6
TGF-beta signaling pathway (P00052)	6
FGF signaling pathway (P00021)	6
FAS signaling pathway (P00020)	6
Cadherin signaling pathway (P00012)	6
B cell activation (P00010)	6
Axon guidance mediated by Slit/Robo (P00008)	5
Toll receptor signaling pathway (P00054)	5
Oxidative stress response (P00046)	5
Muscarinic acetylcholine receptor 1 and 3 signaling pathway (P00042)	5
Insulin/IGF pathway-protein kinase B signaling cascade (P00033)	5
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade (P00032)	5
Dopamine receptor mediated signaling pathway (P05912)	5
Pyrimidine Metabolism (P02771)	5
Endothelin signaling pathway (P00019)	5
Blood coagulation (P00011)	5
Adrenaline and noradrenaline biosynthesis (P00001)	4
De novo purine biosynthesis (P02738)	4
PI3 kinase pathway (P00048)	4
Notch signaling pathway (P00045)	4
Muscarinic acetylcholine receptor 2 and 4 signaling pathway (P00043)	4
Nicotine degradation (P05914)	4
5-Hydroxytryptamine degredation (P04372)	4
Axon guidance mediated by semaphorins (P00007)	3
Alpha adrenergic receptor signaling pathway (P00002)	3
Ubiquitin proteasome pathway (P00060)	3
p53 pathway (P00059)	3
Formyltetrahydroformate biosynthesis (P02743)	3
Plasminogen activating cascade (P00050)	3
Synaptic vesicle trafficking (P05734)	3
Metabotropic glutamate receptor group III pathway (P00039)	3
Ionotropic glutamate receptor pathway (P00037)	3
Thyrotropin-releasing hormone receptor signaling pathway (P04394)	3
2-arachidonoylglycerol biosynthesis (P05726)	3
Serine glycine biosynthesis (P02776)	3
Nicotine pharmacodynamics pathway (P06587)	3
Cytoskeletal regulation by Rho GTPase (P00016)	3
Purine metabolism (P02769)	3
5HT2 type receptor mediated signaling pathway (P04374)	3
Axon guidance mediated by netrin (P00009)	2
Pyridoxal-5-phosphate biosynthesis (P02759)	2
Alzheimer disease-amyloid secretase pathway (P00003)	2
Heme biosynthesis (P02746)	2
VEGF signaling pathway (P00056)	2
Tetrahydrofolate biosynthesis (P02742)	2
De novo pyrimidine ribonucleotides biosythesis (P02740)	2
Androgen/estrogene/progesterone biosynthesis (P02727)	2
JAK/STAT signaling pathway (P00038)	2
Vitamin B6 metabolism (P02787)	2
p53 pathway by glucose deprivation (P04397)	2
Hypoxia response via HIF activation (P00030)	2
Vitamin D metabolism and pathway (P04396)	2
Ras Pathway (P04393)	2
Oxytocin receptor mediated signaling pathway (P04391)	2
p38 MAPK pathway (P05918)	2
Hedgehog signaling pathway (P00025)	2
Glycolysis (P00024)	2
General transcription by RNA polymerase I (P00022)	2
Pyruvate metabolism (P02772)	2
Histamine H1 receptor mediated signaling pathway (P04385)	2
Cortocotropin releasing factor receptor signaling pathway (P04380)	2
Circadian clock system (P00015)	2
5HT4 type receptor mediated signaling pathway (P04376)	2
5HT3 type receptor mediated signaling pathway (P04375)	2
5HT1 type receptor mediated signaling pathway (P04373)	2
Toll pathway-drosophila (P06217)	1
SCW signaling pathway (P06216)	1
GBB signaling pathway (P06214)	1
DPP signaling pathway (P06213)	1
DPP-SCW signaling pathway (P06212)	1
BMP/activin signaling pathway-drosophila (P06211)	1
N-acetylglucosamine metabolism (P02756)	1
Methylmalonyl pathway (P02755)	1
Methionine biosynthesis (P02753)	1
Leucine biosynthesis (P02749)	1

TABLE 1-continued

Pathways involvement of the 1558 differentially expressed genes	
Isoleucine biosynthesis (P02748)	1
mRNA splicing (P00058)	1
Histidine biosynthesis (P02747)	1
Transcription regulation by bZIP transcription factor (P00055)	1
Fructose galactose metabolism (P02744)	1
De novo pyrimidine deoxyribonucleotide biosynthesis (P02739)	1
Metabotropic glutamate receptor group I pathway (P00041)	1
Asparagine and aspartate biosynthesis (P02730)	1
Metabotropic glutamate receptor group II pathway (P00040)	1
GABA-B receptor II signaling (P05731)	1
Alanine biosynthesis (P02724)	1
Interferon-gamma signaling pathway (P00035)	1
Adenine and hypoxanthine salvage pathway (P02723)	1
p53 pathway feedback loops 2 (P04398)	1
Valine biosynthesis (P02785)	1
Threonine biosynthesis (P02781)	1
P53 pathway feedback loops 1 (P04392)	1
Bupropion degradation (P05729)	1
Heterotrimeric G-protein signaling pathway-rod outer segment phototransduction (P00028)	1
Opioid proopiomelanocortin pathway (P05917)	1
Sulfate assimilation (P02778)	1
Opioid prodynorphin pathway (P05916)	1
Succinate to proprionate conversion (P02777)	1
Opioid proenkephalin pathway (P05915)	1
General transcription regulation (P00023)	1
Salvage pyrimidine ribonucleotides (P02775)	1
Salvage pyrimidine deoxyribonucleotides (P02774)	1
Angiotensin II-stimulated signaling through G proteins and beta-arrestin (P05911)	1
Pyridoxal phosphate salvage pathway (P02770)	1
DNA replication (P00017)	1
Cholesterol biosynthesis (P00014)	1
Beta3 adrenergic receptor signaling pathway (P04379)	1
Beta2 adrenergic receptor signaling pathway (P04378)	1
Beta1 adrenergic receptor signaling pathway (P04377)	1

TABLE 2

List of amyloid pathway genes being differentially expressed

Gene id	$\log_2$ Fold Change
A2M	−1.13
ADAM9	1.53
APBB3	0.98
APH1B	2.06
APOL1	−1.66
ATP2A3	1.89
CAPN1	1.13
FAS	−1.98
FSTL1	0.96
ITPR3	2.22
LPL	2.74
MMP19	3.21
MMP2	2.76
MMP7	5.75
NDUFA6	−1.57
NDUFB1	−0.78
NDUFB3	−0.75
NDUFV3	−0.86
NOTCH3	2.66
TCF3	1.34
TTR	−2.11

Genes Involved in Amyloid Precursor Protein (APP) Metabolism were Differentially Expressed in BA Liver

Pathway analysis for differentially expressed genes (1558) were done using PANTHER (website: www.pantherdb.org/), KEGG Mapper (https://www.genome.jp/kegg/mapper.html), DAVID (website: david.ncifcrf.gov/) and also from literatures. Among the list of pathways (Table 1), apart from hormonal and metabolic pathways, few disease related pathways were observed. Alzheimer disease presenilin and amyloid secretase pathway genes (10 nos.) were observed from panther pathways. KEGG pathway analysis also revealed few more genes to be involved in amyloid pathway genes from whole liver RNA-seq analysis. There were a total of 21 genes from total differentially expressed genes involved in amyloid pathway. The list of 21 genes along with log 2FoldChange are displayed in Table 2. Among which, MMP7 (Matrilysin, involved in amyloid-presenilin pathway) being the highest upregulated gene (log 2FoldChange=5.752) among the total (1558) differentially expressed genes.

Expression of APP and its Processed Forms in BA Liver

Immuno-fluorescence analysis for APP on liver sections of BA (n=18) and control (HB, n=5; CC, n=13; CS, n=2) patients revealed elevated expression of APP and/or its processed forms in the bile ducts of all the BA livers but not in all the control livers (FIG. **2**).

All patents, patent applications, and other publications, including GenBank Accession Numbers or equivalent sequence identification numbers, cited in this application are incorporated by reference in the entirety of their contents for all purposes.

TABLE 3

APP_transcrips_final

Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
1	ENSP00000284981	>TCONS_00180767|ENST00000346798 (SEQ ID NO: 1) GGTACCCACTGATGGTAATGCTGGCCTGCTGGCTGAACC CCAGATTGCCATGTTCTGTGGCAGACTGAACATGCACAT GAATGTCCAGAATGGGAAGTGGGATTCAGATCCATCAGG GACCAAAACCTGCATTGATACCAAGGAAGGCATCCTGCA GTATTGCCAAGAAGTCTACCCTGAACTGCAGATCACCAAT GTGGTAGAAGCCAACCAACCAGTGACCATCCAGAACTGG TGCAAGCGGGGCCGCAAGCAGTGCAAGACCCATCCCCA CTTTGTGATTCCCTACCGCTGCTTAGTTGGTGAGTTTGTA AGTGATGCCCTTCTCGTTCCTGACAAGTGCAAATTCTTAC ACCAGGAGAGGATGGATGTTTGCGAAACTCATCTTCACT GGCACACCGTCGCCAAAGAGACATGCAGTGAGAAGAGTA CCAACTTGCATGACTACGGCATGTTGCTGCCCTGCGGAA TTGACAAGTTCCGAGGGGTAGAGTTTGTGTGTTGCCCAC TGGCTGAAGAAAGTGACAATGTGGATTCTGCTGATGCGG AGGAGGATGACTCGGATGTCTGGTGGGGCGGAGCAGAC ACAGACTATGCAGATGGGAGTGAAGACAAAGTAGTAGAA GTAGCAGAGGAGGAAGAAGTGGCTGAGGTGGAAGAAGA AGAAGCCGATGATGACGAGGACGATGAGGATGGTGATGA GGTAGAGGAAGAGGCTGAGGAACCCTACGAAGAAGCCA CAGAGAGAACCACCAGCATTGCCACCACCACCACCACCA CCACAGAGTCTGTGGAAGAGGTGGTTCGAGAGGTGTGCT CTGAACAAGCCGAGACGGGGCCGTGCCGAGCAATGATC TCCCGCTGGTACTTTGATGTGACTGAAGGGAAGTGTGCC CCATTCTTTTACGGCGGATGTGGCGGCAACCGGAACAAC TTTGACACAGAAGAGTACTGCATGGCCGTGTGTGGCAGC GCCATGTCCCAAAGTTTACTCAAGACTACCCAGGAACCTC TTGCCCGAGATCCTGTTAAACTTCCTACAACAGCAGCCAG TACCCCTGATGCCGTTGACAAGTATCTCGAGACACCTGG GGATGAGAATGAACATGCCCATTTCCAGAAAGCCAAAGA GAGGCTTGAGGCCAAGCACCGAGAGAGAATGTCCCAGG TCATGAGAGAATGGGAAGAGGCAGAACGTCAAGCAAAGA ACTTGCCTAAAGCTGATAAGAAGGCAGTTATCCAGCATTT CCAGGAGAAAGTGGAATCTTTGGAACAGGAAGCAGCCAA CGAGAGACAGCAGCTGGTGGAGACACACATGGCCAGAG TGGAAGCCATGCTCAATGACCGCCGCCGCCTGGCCCTG GAGAACTACATCACCGCTCTGCAGGCTGTTCCTCCTCGG CCTCGTCACGTGTTCAATATGCTAAAGAAGTATGTCCGCG CAGAACAGAAGGACAGACAGCACACCCTAAAGCATTTCG AGCATGTGCGCATGGTGGATCCCAAGAAAGCCGCTCAGA TCCGGTCCCAGGTTATGACACACCTCCGTGTGATTTATGA GCGCATGAATCAGTCTCTCTCCCTGCTCTACAACGTGCCT GCAGTGGCCGAGGAGATTCAGGATGAAGTTGATGAGCTG CTTCAGAAAGAGCAAAACTATTCAGATGACGTCTTGGCCA ACATGATTAGTGAACCAAGGATCAGTTACGGAAACGATG CTCTCATGCCATCTTTGACCGAAACGAAAACCACCGTGG AGCTCCTTCCCGTGAATGGAGAGTTCAGCCTGGACGATC TCCAGCCGTGGCATTCTTTTGGGGCTGACTCTGTGCCAG CCAACACAGAAAACGAAGTTGAGCCTGTTGATGCCCGCC CTGCTGCCGACCGAGGACTGACCACTCGACCAGGTTCTG GGTTGACAAATATCAAGACGGAGGAGATCTCTGAAGTGA AGATGGATGCAGAATTCCGACATGACTCAGGATATGAAG TTCATCATCAAAAATTGGTGTTCTTTGCAGAAGATGTGGG TTCAAACAAAGGTGCAATCATTGGACTCATGGTGGGCGG TGTTGTCATAGCGACAGTGATCGTCATCACCTTGGTGATG CTGAAGAAGAAACAGTACACATCCATTCATCATGGTGTGG TGGAGGTTGACGCCGCTGTCACCCCAGAGGAGCGCCAC CTGTCCAAGATGCAGCAGAACGGCTACGAAAATCCAACC TACAAGTTCTTTGAGCAGATGCAGAACTAGACCCCCGCC ACAGCAGCCTCTGAAGTTGGACAGCAAAACCATTGCTTC ACTACCCATCGGTGTCCATTTATAGAATAATGTGGGAAGA AACAAACCCGTTTTATGATTTACTCATTATCGCCTTTTGAC AGCTGTGCTGTAACACAAGTAGATGCCTGAACTTGAATTA ATCCACACATCAGTAATGTATTCTATCTCTCTTTACATTTT GGTCTCTATACTACATTATTAATGGGTTTTGTGTACTGTAA AGAATTTAGCTGTATCAAACTAGTGCATGAATAGATTCTCT CCTGATTATTTATCACATAGCCCCTTAGCCAGTTGTATATT ATTCTTGTGGTTTGTGACCCAATTAAGTCCTACTTTACATA TGCTTTAAGAATCGATGGGGGATGCTTCATGTGAACGTG GGAGTTCAGCTGCTTCTCTTGCCTAAGTATTCCTTTCCTG ATCACTATGCATTTTAAAGTTAAACATTTTTAAGTATTTCA GATGCTTTAGAGAGATTTTTTTTCCATGACTGCATTTTACT GTACAGATTGCTGCTTCTGCTATATTTGTGATATAGGAATT AAGAGGATACACACGTTTGTTTCTTCGTGCCTGTTTTATG TGCACACATTAGGCATTGAGACTTCAAGCTTTTCTTTTTTT

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		GTCCACGTATCTTTGGGTCTTTGATAAAGAAAAGAATCCC
		TGTTCATTGTAAGCACTTTTACGGGGGGGGTGGGGAGGG
		GTGCTCTGCTGGTCTTCAATTACCAAGAATTCTCCAAAAC
		AATTTTCTGCAGGATGATTGTACAGAATCATTGCTTATGA
		CATGATCGCTTTCTACACTGTATTACATAAATAAATTAAAT
		AAAATAACCCCGGGCAAGACTTTTCTTTGAAGGATGACTA
		CAGACATTAAATAATCGAAGTAATTTTGGGTGGGGAGAAG
		AGGCAGATTCAATTTTCTTTAACCAGTCTGAAGTTTCATTT
		ATGATACAAAAGAAGATGAAAATGGAAGTGGCAATATAAG
		GGGATGAGGAAGGCATGCCTGGACAAACCCTTCTTTTAA
		GATGTGTCTTCAATTTGTATAAAATGGTGTTTTCATGTAAA
		TAAATACATTCTTGGAGGAGCACCATTG
2	ENSP00000284981	>TCONS_00180768|ENST00000346798 (SEQ ID NO: 2)
		ATTGAGTGAAGATTAAGACGGAGAAGATGGCGCCTCTGC
		AGTGCAGCAAAGAAAAGCTGTGTGGAGGCTGCAGCCTAG
		TGAAATCCACCCACCACTAGGTACCCACTGATGGTAATG
		CTGGCCTGCTGGCTGAACCCCAGATTGCCATGTTCTGTG
		GCAGACTGAACATGCACATGAATGTCCAGAATGGGAAGT
		GGGATTCAGATCCATCAGGGACCAAAACCTGCATTGATA
		CCAAGGAAGGCATCCTGCAGTATTGCCAAGAAGTCTACC
		CTGAACTGCAGATCACCAATGTGGTAGAAGCCAACCAAC
		CAGTGACCATCCAGAACTGGTGCAAGCGGGGCCGCAAG
		CAGTGCAAGACCCATCCCCACTTTGTGATTCCCTACCGCT
		GCTTAGTTGGTGAGTTTGTAAGTGATGCCCTTCTCGTTCC
		TGACAAGTGCAAATTCTTACACCAGGAGAGGATGGATGTT
		TGCGAAACTCATCTTCACTGGCACACCGTCGCCAAAGAG
		ACATGCAGTGAGAAGAGTACCAACTTGCATGACTACGGC
		ATGTTGCTGCCCTGCGGAATTGACAAGTTCCGAGGGGTA
		GAGTTTGTGTGTTGCCCACTGGCTGAAGAAAGTGACAAT
		GTGGATTCTGCTGATGCGGAGGAGGATGACTCGGATGTC
		TGGTGGGGCGGAGCAGACACAGACTATGCAGATGGGAG
		TGAAGACAAAGTAGTAGAAGTAGCAGAGGAGGAAGAAGT
		GGCTGAGGTGGAAGAAGAAGAAGCCGATGATGACGAGG
		ACGATGAGGATGGTGATGAGGTAGAGGAAGAGGCTGAG
		GAACCCTACGAAGAAGCCACAGAGAGAACCACCAGCATT
		GCCACCACCACCACCACCACCACAGAGTCTGTGGAAGAG
		GTGGTTCGAGAGGTGTGCTCTGAACAAGCCGAGACGGG
		GCCGTGCCGAGCAATGATCTCCCGCTGGTACTTTGATGT
		GACTGAAGGGAAGTGTGCCCCATTCTTTTACGGCGGATG
		TGGCGGCAACCGGAACAACTTTGACACAGAAGAGTACTG
		CATGGCCGTGTGTGGCAGCGCCATTCCTACAACAGCAGC
		CAGTACCCCTGATGCCGTTGACAAGTATCTCGAGACACC
		TGGGGATGAGAATGAACATGCCCATTTCCAGAAAGCCAA
		AGAGAGGCTTGAGGCCAAGCACCGAGAGAGAATGTCCC
		AGGTCATGAGAGAATGGGAAGAGGCAGAACGTCAAGCAA
		AGAACTTGCCTAAAGCTGATAAGAAGGCAGTTATCCAGCA
		TTTCCAGGAGAAAGTGGAATCTTTGGAACAGGAAGCAGC
		CAACGAGAGACAGCAGCTGGTGGAGACACACATGGCCA
		GAGTGGAAGCCATGCTCAATGACCGCCGCCGCCTGGCC
		CTGGAGAACTACATCACCGCTCTGCAGGCTGTTCCTCCT
		CGGCCTCGTCACGTGTTCAATATGCTAAAGAAGTATGTCC
		GCGCAGAACAGAAGGACAGACAGCACACCCTAAAGCATT
		TCGAGCATGTGCGCATGGTGGATCCCAAGAAAGCCGCTC
		AGATCCGGTCCCAGGTTATGACACACCTCCGTGTGATTTA
		TGAGCGCATGAATCAGTCTCTCTCCCTGCTCTACAACGTG
		CCTGCAGTGGCCGAGGAGATTCAGGATGAAGTTGATGAG
		CTGCTTCAGAAAGAGCAAAACTATTCAGATGACGTCTTGG
		CCAACATGATTAGTGAACCAAGGATCAGTTACGGAAACG
		ATGCTCTCATGCCATCTTTGACCGAAACGAAAACCACCGT
		GGAGCTCCTTCCCGTGAATGGAGAGTTCAGCCTGGACGA
		TCTCCAGCCGTGGCATTCTTTTGGGGCTGACTCTGTGCC
		AGCCAACACAGAAAACGAAGTTGAGCCTGTTGATGCCCG
		CCCTGCTGCCGACCGAGGACTGACCACTCGACCAGGTTC
		TGGGTTGACAAATATCAAGACGGAGGAGATCTCTGAAGT
		GAAGATGGATGCAGAATTCCGACATGACTCAGGATATGA
		AGTTCATCATCAAAAATTGGTGTTCTTTGCAGAAGATGTG
		GGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGGC
		GGTGTTGTCATAGCGACAGTGATCGTCATCACCTTGGTG
		ATGCTGAAGAAGAAACAGTACACATCCATTCATCATGGTG
		TGGTGGAGGTTGACGCCGCTGTCACCCCAGAGGAGCGC
		CACCTGTCCAAGATGCAGCAGAACGGCTACGAAAATCCA
		ACCTACAAGTTCTTTGAGCAGATGCAGAACTAGACCCCC
		GCCACAGCAGCCTCTGAAGTTGGACAGCAAAACCATTGC
		TTCACTACCCATCGGTGTCCATTTATAGAATAATGTGGGA

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		AGAAACAAACCCGTTTTATGATTTACTCATTATCGCCTTTT
		GACAGCTGTGCTGTAACACAAGTAGATGCCTGAACTTGA
		ATTAATCCACACATCAGTAATGTATTCTATCTCTCTTTACA
		TTTTGGTCTCTATACTACATTATTAATGGGTTTTGTGTACT
		GTAAAGAATTTAGCTGTATCAAACTAGTGCATGAATAGAT
		TCTCTCCTGATTATTTATCACATAGCCCCTTAGCCAGTTGT
		ATATTATTCTTGTGGTTTGTGACCCAATTAAGTCCTACTTT
		ACATATGCTTTAAGAATCGATGGGGGATGCTTCATGTGAA
		CGTGGGAGTTCAGCTGCTTCTCTTGCCTAAGTATTCCTTT
		CCTGATCACTATGCATTTTAAAGTTAAACATTTTTAAGTAT
		TTCAGATGCTTTAGAGAGATTTTTTTTCCATGACTGCATTT
		TACTGTACAGATTGCTGCTTCTGCTATATTTGTGATATAG
		GAATTAAGAGGATACACACGTTTGTTTCTTCGTGCCTGTT
		TTATGTGCACACATTAGGCATTGAGACTTCAAGCTTTTCTT
		TTTTTGTCCACGTATCTTTGGGTCTTTGATAAAGAAAAGAA
		TCCCTGTTCATTGTAAGCACTTTTACGGGGGGGGTGGGG
		AGGGGTGCTCTGCTGGTCTTCAATTACCAAGAATTCTCCA
		AAACAATTTTCTGCAGGATGATTGTACAGAATCATTGCTTA
		TGACATGATCGCTTTCTACACTGTATTACATAAATAAATTA
		AATAAAATAACCCCGGGCAAGACTTTTCTTTGAAGGATGA
		CTACAGACATTAAATAATCGAAGTAATTTTGGGTGGGGAG
		AAGAGGCAGATTCAATTTTCTTTAACCAGTCTGAAGTTTC
		ATTTATGATACAAAAGAAGATGAAAATGGAAGTGGCAATA
		TAAGGGGATGAGGAAGGCATGCCTGGACAAACCCTTCTT
		TTAAGATGTGTCTTCAATTTGTATAAAATGGTGTTTTCATG
		TAAATAAATACATTCTTGGAGGAGCACCATTG
3	ENSP00000284981	>TCONS_00180769|ENST00000346798 (SEQ ID NO: 3)
		CGCCGCGCTCGGGCTCCGTCAGTTTCCTCGGCAGCGGT
		AGGCGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCC
		GGGAGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGG
		ACGCGGCGGATCCCACTCGCACAGCAGCGCACTCGGTG
		CCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTG
		CTCCTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGT
		CTACCCTGAACTGCAGATCACCAATGTGGTAGAAGCCAA
		CCAACCAGTGACCATCCAGAACTGGTGCAAGCGGGGCC
		GCAAGCAGTGCAAGACCCATCCCCACTTTGTGATTCCCT
		ACCGCTGCTTAGTTGGTGAGTTTGTAAGTGATGCCCTTCT
		CGTTCCTGACAAGTGCAAATTCTTACACCAGGAGAGGAT
		GGATGTTTGCGAAACTCATCTTCACTGGCACACCGTCGC
		CAAAGAGACATGCAGTGAGAAGAGTACCAACTTGCATGA
		CTACGGCATGTTGCTGCCCTGCGGAATTGACAAGTTCCG
		AGGGGTAGAGTTTGTGTGTTGCCCACTGGCTGAAGAAAG
		TGACAATGTGGATTCTGCTGATGCGGAGGAGGATGACTC
		GGATGTCTGGTGGGGCGGAGCAGACACAGACTATGCAG
		ATGGGAGTGAAGACAAAGTAGTAGAAGTAGCAGAGGAGG
		AAGAAGTGGCTGAGGTGGAAGAAGAAGAAGCCGATGATG
		ACGAGGACGATGAGGATGGTGATGAGGTAGAGGAAGAG
		GCTGAGGAACCCTACGAAGAAGCCACAGAGAGAACCACC
		AGCATTGCCACCACCACCACCACCACCACAGAGTCTGTG
		GAAGAGGTGGTTCGAGAGGTGTGCTCTGAACAAGCCGA
		GACGGGGCCGTGCCGAGCAATGATCTCCCGCTGGTACTT
		TGATGTGACTGAAGGGAAGTGTGCCCCATTCTTTTACGG
		CGGATGTGGCGGCAACCGGAACAACTTTGACACAGAAGA
		GTACTGCATGGCCGTGTGTGGCAGCGCCATGTCCCAAAG
		TTTACTCAAGACTACCCAGGAACCTCTTGCCCGAGATCCT
		GTTAAACTTCCTACAACAGCAGCCAGTACCCCTGATGCC
		GTTGACAAGTATCTCGAGACACCTGGGGATGAGAATGAA
		CATGCCCATTTCCAGAAAGCCAAAGAGAGGCTTGAGGCC
		AAGCACCGAGAGAGAATGTCCCAGCCTCGTCACGTGTTC
		AATATGCTAAAGAAGTATGTCCGCGCAGAACAGAAGGAC
		AGACAGCACACCCTAAAGCATTTCGAGCATGTGCGCATG
		GTGGATCCCAAGAAAGCCGCTCAGATCCGGTCCCAGGTT
		ATGACACACCTCCGTGTGATTTATGAGCGCATGAATCAGT
		CTCTCTCCCTGCTCTACAACGTGCCTGCAGTGGCCGAGG
		AGATTCAGGATGAAGTTGATGAGCTGCTTCAGAAAGAGC
		AAAACTATTCAGATGACGTCTTGGCCAACATGATTAGTGA
		ACCAAGGATCAGTTACGGAAACGATGCTCTCATGCCATCT
		TTGACCGAAACGAAAACCACCGTGGAGCTCCTTCCCGTG
		AATGGAGAGTTCAGCCTGGACGATCTCCAGCCGTGGCAT
		TCTTTTGGGGCTGACTCTGTGCCAGCCAACACAGAAAAC
		GAAGTTGAGCCTGTTGATGCCCGCCCTGCTGCCGACCGA
		GGACTGACCACTCGACCAGGTTCTGGGTTGACAAATATC
		AAGACGGAGGAGATCTCTGAAGTGAAGATGGATGCAGAA
		TTCCGACATGACTCAGGATATGAAGTTCATCATCAAAAAT

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		TGGTGTTCTTTGCAGAAGATGTGGGTTCAAACAAAGGTG CAATCATTGGACTCATGGTGGGCGGTGTTGTCATAGCGA CAGTGATCGTCATCACCTTGGTGATGCTGAAGAAGAAAC AGTACACATCCATTCATCATGGTGTGGTGGAGGTTGACG CCGCTGTCACCCCAGAGGAGCGCCACCTGTCCAAGATG CAGCAGAACGGCTACGAAAATCCAACCTACAAGTTCTTTG AGCAGATGCAGAACTAGACCCCCGCCACAGCAGCCTCTG AAGTTGGACAGCAAAACCATTGCTTCACTACCCATCGGTG TCCATTTATAGAATAATGTGGGAAGAAACAAACCCGTTTT ATGATTTACTCATTATCGCCTTTTGACAGCTGTGCTGTAA CACAAGTAGATGCCTGAACTTGAATTAATCCACACATCAG TAATGTATTCTATCTCTCTTTACATTTTGGTCTCTATACTAC ATTATTAATGGGTTTTGTGTACTGTAAAGAATTTAGCTGTA TCAAACTAGTGCATGAATAGATTCTCTCCTGATTATTTATC ACATAGCCCCTTAGCCAGTTGTATATTATTCTTGTGGTTT GTGACCCAATTAAGTCCTACTTTACATATGCTTTAAGAATC GATGGGGGATGCTTCATGTGAACGTGGGAGTTCAGCTGC TTCTCTTGCCTAAGTATTCCTTTCCTGATCACTATGCATTT TAAAGTTAAACATTTTTAAGTATTTCAGATGCTTTAGAGAG ATTTTTTTTTCCATGACTGCATTTTACTGTACAGATTGCTGC TTCTGCTATATTTGTGATATAGGAATTAAGAGGATACACA CGTTTGTTTCTTCGTGCCTGTTTTATGTGCACACATTAGG CATTGAGACTTCAAGCTTTTCTTTTTTTGTCCACGTATCTT TGGGTCTTTGATAAAGAAAAGAATCCCTGTTCATTGTAAG CACTTTTACGGGGGGGGTGGGGAGGGGTGCTCTGCTGG TCTTCAATTACCAAGAATTCTCCAAAACAATTTTCTGCAGG ATGATTGTACAGAATCATTGCTTATGACATGATCGCTTTCT ACACTGTATTACATAAATAAATTAAATAAAATAACCCCGGG CAAGACTTTTCTTTGAAGGATGACTACAGACATTAAATAAT CGAAGTAATTTTGGGTGGGGAGAAGAGGCAGATTCAATT TTCTTTAACCAGTCTGAAGTTTCATTTATGATACAAAAGAA GATGAAAATGGAAGTGGCAATATAAGGGGATGAGGAAGG CATGCCTGGACAAACCCTTCTTTTAAGATGTGTCTTCAAT TTGTATAAAATGGTGTTTTCATGTAAATAAATACATTCTTG GAGGAGCACCATTG
4	ENSP00000284981	>TCONS_00180771|ENST00000346798 (SEQ ID NO: 4) CGCCGCGCTCGGGCTCCGTCAGTTTCCTCGGCAGCGGT AGGCGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCC GGGAGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGG ACGCGGCGGATCCCACTCGCACAGCAGCGCACTCGGTG CCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTG CTCCTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGT ACCCACTGATGGTAATGCTGGCCTGCTGGCTGAACCCCA GATTGCCATGTTCTGTGGCAGACTGAACATGCACATGAAT GTCCAGAATGGGAAGTGGGATTCAGATCCATCAGGGACC AAAACCTGCATTGATACCAAGGAAGGCATCCTGCAGTATT GCCAAGAAGTCTACCCTGAACTGCAGATCACCAATGTGG TAGAAGCCAACCAACCAGTGACCATCCAGAACTGGTGCA AGCGGGGCCGCAAGCAGTGCAAGACCCATCCCCACTTT GTGATTCCCTACCGCTGCTTAGTTGGTGAGTTTGTAAGTG ATGCCCTTCTCGTTCCTGACAAGTGCAAATTCTTACACCA GGAGAGGATGGATGTTTGCGAAACTCATCTTCACTGGCA CACCGTCGCCAAAGAGACATGCAGTGAGAAGAGTACCAA CTTGCATGACTACGGCATGTTGCTGCCCTGCGGAATTGA CAAGTTCCGAGGGGTAGAGTTTGTGTGTTGCCCACTGGC TGAAGAAAGTGACAATGTGGATTCTGCTGATGCGGAGGA GGATGACTCGGATGTCTGGTGGGGCGGAGCAGACACAG ACTATGCAGATGGGAGTGAAGACAAAGTAGTAGAAGTAG CAGAGGAGGAAGAAGTGGCTGAGGTGGAAGAAGAAGAA GCCGATGATGACGAGGACGATGAGGATGGTGATGAGGT AGAGGAAGAGGCTGAGGAACCCTACGAAGAAGCCACAG AGAGAACCACCAGCATTGCCACCACCACCACCACCACCA CAGAGTCTGTGGAAGAGGTGGTTCGAGAGGTGTGCTCTG AACAAGCCGAGACGGGGCCGTGCCGAGCAATGATCTCC CGCTGGTACTTTGATGTGACTGAAGGGAAGTGTGCCCCA TTCTTTTACGGCGGATGTGGCGGCAACCGGAACAACTTT GACACAGAAGAGTACTGCATGGCCGTGTGTGGCAGCGC CATTCCTACAACAGCAGCCAGTACCCCTGATGCCGTTGA CAAGTATCTCGAGACACCTGGGGATGAGAATGAACATGC CCATTTCCAGAAAGCCAAAGAGAGGCTTGAGGCCAAGCA CCGAGAGAGAATGTCCCAGGTCATGAGAGAATGGGAAGA GGCAGAACGTCAAGCAAAGAACTTGCCTAAAGCTGATAA GAAGGCAGTTATCCAGCATTTCCAGGAGAAAGTGGAATC TTTGGAACAGGAAGCAGCCAACGAGAGACAGCAGCTGGT

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		GGAGACACACATGGCCAGAGTGGAAGCCATGCTCAATGA
		CCGCCGCCGCCTGGCCCTGGAGAACTACATCACCGCTCT
		GCAGGCTGTTCCTCCTCGGCCTCGTCACGTGTTCAATAT
		GCTAAAGAAGTATGTCCGCGCAGAACAGAAGGACAGACA
		GCACACCCTAAAGCATTTCGAGCATGTGCGCATGGTGGA
		TCCCAAGAAAGCCGCTCAGATCCGGTCCCAGGTTATGAC
		ACACCTCCGTGTGATTTATGAGCGCATGAATCAGTCTCTC
		TCCCTGCTCTACAACGTGCCTGCAGTGGCCGAGGAGATT
		CAGGATGAAGTTGATGAGCTGCTTCAGAAAGAGCAAAAC
		TATTCAGATGACGTCTTGGCCAACATGATTAGTGAACCAA
		GGATCAGTTACGGAAACGATGCTCTCATGCCATCTTTGAC
		CGAAACGAAAACCACCGTGGAGCTCCTTCCCGTGAATGG
		AGAGTTCAGCCTGGACGATCTCCAGCCGTGGCATTCTTT
		TGGGGCTGACTCTGTGCCAGCCAACACAGAAAACGAAGG
		TTCTGGGTTGACAAATATCAAGACGGAGGAGATCTCTGAA
		GTGAAGATGGATGCAGAATTCCGACATGACTCAGGATAT
		GAAGTTCATCATCAAAAATTGGTGTTCTTTGCAGAAGATG
		TGGGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGG
		GCGGTGTTGTCATAGCGACAGTGATCGTCATCACCTTGG
		TGATGCTGAAGAAGAAACAGTACACATCCATTCATCATGG
		TGTGGTGGAGGTTGACGCCGCTGTCACCCCAGAGGAGC
		GCCACCTGTCCAAGATGCAGCAGAACGGCTACGAAAATC
		CAACCTACAAGTTCTTTGAGCAGATGCAGAACTAGACCCC
		CGCCACAGCAGCCTCTGAAGTTGGACAGCAAAACCATTG
		CTTCACTACCCATCGGTGTCCATTTATAGAATAATGTGGG
		AAGAAACAAACCCGTTTTATGATTTACTCATTATCGCCTTT
		TGACAGCTGTGCTGTAACACAAGTAGATGCCTGAACTTGA
		ATTAATCCACACATCAGTAATGTATTCTATCTCTCTTTACA
		TTTTGGTCTCTATACTACATTATTAATGGGTTTTGTGTACT
		GTAAAGAATTTAGCTGTATCAAACTAGTGCATGAATAGAT
		TCTCTCCTGATTATTTATCACATAGCCCCTTAGCCAGTTGT
		ATATTATTCTTGTGGTTTGTGACCCAATTAAGTCCTACTTT
		ACATATGCTTTAAGAATCGATGGGGGATGCTTCATGTGAA
		CGTGGGAGTTCAGCTGCTTCTCTTGCCTAAGTATTCCTTT
		CCTGATCACTATGCATTTTAAAGTTAAACATTTTTAAGTAT
		TTCAGATGCTTTAGAGAGATTTTTTTTCCATGACTGCATTT
		TACTGTACAGATTGCTGCTTCTGCTATATTTGTGATATAG
		GAATTAAGAGGATACACACGTTTGTTTCTTCGTGCCTGTT
		TTATGTGCACACATTAGGCATTGAGACTTCAAGCTTTTCTT
		TTTTTGTCCACGTATCTTTGGGTCTTTGATAAAGAAAAGAA
		TCCCTGTTCATTGTAAGCACTTTTACGGGGGGGGTGGGG
		AGGGGTGCTCTGCTGGTCTTCAATTACCAAGAATTCTCCA
		AAACAATTTTCTGCAGGATGATTGTACAGAATCATTGCTTA
		TGACATGATCGCTTTCTACACTGTATTACATAAATAAATTA
		AATAAAATAACCCCGGGCAAGACTTTTCTTTGAAGGATGA
		CTACAGACATTAAATAATCGAAGTAATTTTGGGTGGGGAG
		AAGAGGCAGATTCAATTTTCTTTAACCAGTCTGAAGTTTC
		ATTTATGATACAAAAGAAGATGAAAATGGAAGTGGCAATA
		TAAGGGGATGAGGAAGGCATGCCTGGACAAACCCTTCTT
		TTAAGATGTGTCTTCAATTTGTATAAAATGGTGTTTTCATG
		TAAATAAATACATTCTTGGAGGAGCACCATTG
5	ENSP00000284981	>TCONS_00180772|ENST00000346798 (SEQ ID NO: 5)
		CGCCGCGCTCGGGCTCCGTCAGTTTCCTCGGCAGCGGT
		AGGCGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCC
		GGGAGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGG
		ACGCGGCGGATCCCACTCGCACAGCAGCGCACTCGGTG
		CCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTG
		CTCCTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGT
		ACCCACTGATGGTAATGCTGGCCTGCTGGCTGAACCCCA
		GATTGCCATGTTCTGTGGCAGACTGAACATGCACATGAAT
		GTCCAGAATGGGAAGTGGGATTCAGATCCATCAGGGACC
		AAAACCTGCATTGATACCAAGGAAGGCATCCTGCAGTATT
		GCCAAGAAGTCTACCCTGAACTGCAGATCACCAATGTGG
		TAGAAGCCAACCAACCAGTGACCATCCAGAACTGGTGCA
		AGCGGGGCCGCAAGCAGTGCAAGACCCATCCCCACTTT
		GTGATTCCCTACCGCTGCTTAGTTGGTGAGTTTGTAAGTG
		ATGCCCTTCTCGTTCCTGACAAGTGCAAATTCTTACACCA
		GGAGAGGATGGATGTTTGCGAAACTCATCTTCACTGGCA
		CACCGTCGCCAAAGAGACATGCAGTGAGAAGAGTACCAA
		CTTGCATGACTACGGCATGTTGCTGCCCTGCGGAATTGA
		CAAGTTCCGAGGGGTAGAGTTTGTGTGTTGCCCACTGGC
		TGAAGAAAGTGACAATGTGGATTCTGCTGATGCGGAGGA
		GGATGACTCGGATGTCTGGTGGGGCGGAGCAGACACAG
		ACTATGCAGATGGGAGTGAAGACAAAGTAGTAGAAGTAG

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		CAGAGGAGGAAGAAGTGGCTGAGGTGGAAGAAGAAGAA
		GCCGATGATGACGAGGACGATGAGGATGGTGATGAGGT
		AGAGGAAGAGGCTGAGGAACCCTACGAAGAAGCCACAG
		AGAGAACCACCAGCATTGCCACCACCACCACCACCACCA
		CAGAGTCTGTGGAAGAGGTGGTTCGAGAGGTGTGCTCTG
		AACAAGCCGAGACGGGGCCGTGCCGAGCAATGATCTCC
		CGCTGGTACTTTGATGTGACTGAAGGGAAGTGTGCCCCA
		TTCTTTTACGGCGGATGTGGCGGCAACCGGAACAACTTT
		GACACAGAAGAGTACTGCATGGCCGTGTGTGGCAGCGC
		CATGTCCCAAAGTTTACTCAAGACTACCCAGGAACCTCTT
		GCCCGAGATCCTGTTAAACTTCCTACAACAGCAGCCAGT
		ACCCCTGATGCCGTTGACAAGTATCTCGAGACACCTGGG
		GATGAGAATGAACATGCCCATTTCCAGAAAGCCAAAGAG
		AGGCTTGAGGCCAAGCACCGAGAGAGAATGTCCCAGGT
		CATGAGAGAATGGGAAGAGGCAGAACGTCAAGCAAAGAA
		CTTGCCTAAAGCTGATAAGAAGGCAGTTATCCAGCATTTC
		CAGGAGAAAGTGGAATCTTTGGAACAGGAAGCAGCCAAC
		GAGAGACAGCAGCTGGTGGAGACACACATGGCCAGAGT
		GGAAGCCATGCTCAATGACCGCCGCCGCCTGGCCCTGG
		AGAACTACATCACCGCTCTGCAGGCTGTTCCTCCTCGGC
		CTCGTCACGTGTTCAATATGCTAAAGAAGTATGTCCGCGC
		AGAACAGAAGGACAGACAGCACACCCTAAAGCATTTOGA
		GCATGTGCGCATGGTGGATCCCAAGAAAGCCGCTCAGAT
		CCGGTCCCAGGTTATGACACACCTCCGTGTGATTTATGA
		GCGCATGAATCAGTCTCTCTCCCTGCTCTACAACGTGCCT
		GCAGTGGCCGAGGAGATTCAGGATGAAGTTGATGAGCTG
		CTTCAGAAAGAGCAAAACTATTCAGATGACGTCTTGGCCA
		ACATGATTAGTGAACCAAGGATCAGTTACGGAAACGATG
		CTCTCATGCCATCTTTGACCGAAACGAAAACCACCGTGG
		AGCTCCTTCCCGTGAATGGAGAGTTCAGCCTGGACGATC
		TCCAGCCGTGGCATTCTTTTGGGGCTGACTCTGTGCCAG
		CCAACACAGAAAACGAAGGTTCTGGGTTGACAAATATCAA
		GACGGAGGAGATCTCTGAAGTGAAGATGGATGCAGAATT
		CCGACATGACTCAGGATATGAAGTTCATCATCAAAAATTG
		GTGTTCTTTGCAGAAGATGTGGGTTCAAACAAAGGTGCAA
		TCATTGGACTCATGGTGGGCGGTGTTGTCATAGCGACAG
		TGATCGTCATCACCTTGGTGATGCTGAAGAAGAAACAGTA
		CACATCCATTCATCATGGTGTGGTGGAGGTTGACGCCGC
		TGTCACCCCAGAGGAGCGCCACCTGTCCAAGATGCAGCA
		GAACGGCTACGAAAATCCAACCTACAAGTTCTTTGAGCAG
		ATGCAGAACTAGACCCCCGCCACAGCAGCCTCTGAAGTT
		GGACAGCAAAACCATTGCTTCACTACCCATCGGTGTCCAT
		TTATAGAATAATGTGGGAAGAAACAAACCCGTTTTATGAT
		TTACTCATTATCGCCTTTTGACAGCTGTGCTGTAACACAA
		GTAGATGCCTGAACTTGAATTAATCCACACATCAGTAATG
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		TAATGGGTTTTGTGTACTGTAAAGAATTTAGCTGTATCAAA
		CTAGTGCATGAATAGATTCTCTCCTGATTATTTATCACATA
		GCCCCTTAGCCAGTTGTATATTATTCTTGTGGTTTGTGAC
		CCAATTAAGTCCTACTTTACATATGCTTTAAGAATCGATGG
		GGGATGCTTCATGTGAACGTGGGAGTTCAGCTGCTTCTC
		TTGCCTAAGTATTCCTTTCCTGATCACTATGCATTTTAAAG
		TTAAACATTTTTAAGTATTTCAGATGCTTTAGAGAGATTTT
		TTTTCCATGATCGCTTTCTACACTGTATTACATAAATAAAT
		TAAATAAAATAACCCCGGGCAAGACTTTTCTTTGAAGGAT
		GACTACAGACATTAAATAATCGAAGTAATTTTGGGTGGGG
		AGAAGAGGCAGATTCAATTTTCTTTAACCAGTCTGAAGTT
		TCATTTATGATACAAAAGAAGATGAAAATGGAAGTGGCAA
		TATAAGGGGATGAGGAAGGCATGCCTGGACAAACCCTTC
		TTTTAAGATGTGTCTTCAATTTGTATAAAATGGTGTTTTCA
		TGTAAATAAATACATTCTTGGAGGAGCACCATTG
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		TGCCCGGTTTGGCACTGCTCCTGCTGGCCGCCTGGACG
		GCTCGGGCGCTGGAGGTACCCACTGATGGTAATGCTGG
		CCTGCTGGCTGAACCCCAGATTGCCATGTTCTGTGGCAG
		ACTGAACATGCACATGAATGTCCAGAATGGGAAGTGGGA
		TTCAGATCCATCAGGGACCAAAACCTGCATTGATACCAAG
		GAAGGCATCCTGCAGTATTGCCAAGAAGTCTACCCTGAA
		CTGCAGATCACCAATGTGGTAGAAGCCAACCAACCAGTG
		ACCATCCAGAACTGGTGCAAGCGGGGCCGCAAGCAGTG
		CAAGACCCATCCCCACTTTGTGATTCCCTACCGCTGCTTA
		GTTGGTGAGTTTGTAAGTGATGCCCTTCTCGTTCCTGACA
		AGTGCAAATTCTTACACCAGGAGAGGATGGATGTTTGCG

TABLE 3-continued

APP_transcrips_final	
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		AAACTCATCTTCACTGGCACACCGTCGCCAAAGAGACAT
		GCAGTGAGAAGAGTACCAACTTGCATGACTACGGCATGT
		TGCTGCCCTGCGGAATTGACAAGTTCCGAGGGGTAGAGT
		TTGTGTGTTGCCCACTGGCTGAAGAAAGTGACAATGTGG
		ATTCTGCTGATGCGGAGGAGGATGACTCGGATGTCTGGT
		GGGGCGGAGCAGACACAGACTATGCAGATGGGAGTGAA
		GACAAAGTAGTAGAAGTAGCAGAGGAGGAAGAAGTGGCT
		GAGGTGGAAGAAGAAGAAGCCGATGATGACGAGGACGA
		TGAGGATGGTGATGAGGTAGAGGAAGAGGCTGAGGAAC
		CCTACGAAGAAGCCACAGAGAGAACCACCAGCATTGCCA
		CCACCACCACCACCACCACAGAGTCTGTGGAAGAGGTGG
		TTCGAGAGGTGTGCTCTGAACAAGCCGAGACGGGGCCG
		TGCCGAGCAATGATCTCCCGCTGGTACTTTGATGTGACT
		GAAGGGAAGTGTGCCCCATTCTTTTACGGCGGATGTGGC
		GGCAACCGGAACAACTTTGACACAGAAGAGTACTGCATG
		GCCGTGTGTGGCAGCGCCATGTCCCAAAGTTTACTCAAG
		ACTACCCAGGAACCTCTTGCCCGAGATCCTGTTAAACTTC
		CTACAACAGCAGCCAGTACCCCTGATGCCGTTGACAAGT
		ATCTCGAGACACCTGGGGATGAGAATGAACATGCCCATT
		TCCAGAAAGCCAAAGAGAGGCTTGAGGCCAAGCACCGA
		GAGAGAATGTCCCAGGTCATGAGAGAATGGGAAGAGGCA
		GAACGTCAAGCAAAGAACTTGCCTAAAGCTGATAAGAAG
		GCAGTTATCCAGCATTTCCAGGAGAAAGTGGAATCTTTGG
		AACAGGAAGCAGCCAACGAGAGACAGCAGCTGGTGGAG
		ACACACATGGCCAGAGTGGAAGCCATGCTCAATGACCGC
		CGCCGCCTGGCCCTGGAGAACTACATCACCGCTCTGCAG
		GCTGTTCCTCCTCGGCCTCGTCACGTGTTCAATATGCTAA
		AGAAGTATGTCCGCGCAGAACAGAAGGACAGACAGCACA
		CCCTAAAGCATTTCGAGCATGTGCGCATGGTGGATCCCA
		AGAAAGCCGCTCAGATCCGGTCCCAGGTTATGACACACC
		TCCGTGTGATTTATGAGCGCATGAATCAGTCTCTCTCCCT
		GCTCTACAACGTGCCTGCAGTGGCCGAGGAGATTCAGGA
		TGAAGTTGATGAGCTGCTTCAGAAAGAGCAAAACTATTCA
		GATGACGTCTTGGCCAACATGATTAGTGAACCAAGGATC
		AGTTACGGAAACGATGCTCTCATGCCATCTTTGACCGAAA
		CGAAAACCACCGTGGAGCTCCTTCCCGTGAATGGAGAGT
		TCAGCCTGGACGATCTCCAGCCGTGGCATTCTTTTGGGG
		CTGACTCTGTGCCAGCCAACACAGAAAACGAAGTTGAGC
		CTGTTGATGCCCGCCCTGCTGCCGACCGAGGACTGACCA
		CTCGACCAGGTTCTGGGTTGACAAATATCAAGACGGAGG
		AGATCTCTGAAGTGAAGATGGATGCAGAATTCCGACATG
		ACTCAGGATATGAAGTTCATCATCAAAAATTGGTGTTCTTT
		GCAGAAGATGTGGGTTCAAACAAAGGTGCAATCATTGGA
		CTCATGGTGGGCGGTGTTGTCATAGCGACAGTGATCGTC
		ATCACCTTGGTGATGCTGAAGAAGAAACAGTACACATCCA
		TTCATCATGGTGTGGTGGAGGTTGACGCCGCTGTCACCC
		CAGAGGAGCGCCACCTGTCCAAGATGCAGCAGAACGGC
		TACGAAAATCCAACCTACAAGTTCTTTGAGCAGATGCAGA
		ACTAGACCCCCGCCACAGCAGCCTCTGAAGTTGGACAGC
		AAAACCATTGCTTCACTACCCATCGGTGTCCATTTATAGA
		ATAATGTGGGAAGAAACAAACCCGTTTTATGATTTACTCA
		TTATCGCCTTTTGACAGCTGTGCTGTAACACAAGTAGATG
		CCTGAACTTGAATTAATCCACACATCAGTAATGTATTCTAT
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		TTTTGTGTACTGTAAAGAATTTAGCTGTATCAAACTAGTGC
		ATGAATAGATTCTCTCCTGATTATTTATCACATAGCCCCTT
		AGCCAGTTGTATATTATTCTTGTGGTTTGTGACCCAATTAA
		GTCCTACTTTACATATGCTTTAAGAATCGATGGGGGATGC
		TTCATGTGAACGTGGGAGTTCAGCTGCTTCTCTTGCCTAA
		GTATTCCTTTCCTGATCACTATGCATTTTAAAGTTAAACAT
		TTTTAAGTATTTCAGATGCTTTAGAGAGATTTTTTTTCCAT
		GACTGCATTTTACTGTACAGATTGCTGCTTCTGCTATATTT
		GTGATATAGGAATTAAGAGGATACACACGTTTGTTTCTTC
		GTGCCTGTTTTATGTGCACACATTAGGCATTGAGACTTCA
		AGCTTTTCTTTTTTTGTCCACGTATCTTTGGGTCTTTGATA
		AAGAAAAGAATCCCTGTTCATTGTAAGCACTTTTACGGGG
		CGGGTGGGGAGGGGTGCTCTGCTGGTCTTCAATTACCAA
		GAATTCTCCAAAACAATTTTCTGCAGGATGATTGTACAGA
		ATCATTGCTTATGACATGATCGCTTTCTACACTGTATTACA
		TAAATAAATTAAATAAAATAACCCCGGGCAAGACTTTTCTT
		TGAAGGATGACTACAGACATTAAATAATCGAAGTAATTTT
		GGGTGGGGAGAAGAGGCAGATTCAATTTTCTTTAACCAG
		TCTGAAGTTTCATTTATGATACAAAAGAAGATGAAAATGG
		AAGTGGCAATATAAGGGGATGAGGAAGGCATGCCTGGAC

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		AAACCCTTCTTTTAAGATGTGTCTTCAATTTGTATAAAATG
		GTGTTTTCATGTAAATAAATACATTCTTGGAGGAGCA
7	ENSP00000345463	>TCONS_00180775|ENST00000348990 (SEQ ID NO: 7)
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		GCGTGCGCGGGGGCCCCGGGAGACGGCGGCGGTGGCG
		GCGCGGGCAGAGCAAGGACGCGGCGGATCCCACTCGCA
		CAGCAGCGCACTCGGTGCCCCGCGCAGGGTCGCGATGC
		TGCCCGGTTTGGCACTGCTCCTGCTGGCCGCCTGGACG
		GCTCGGGCGCTGGAGGTACCCACTGATGGTAATGCTGG
		CCTGCTGGCTGAACCCCAGATTGCCATGTTCTGTGGCAG
		ACTGAACATGCACATGAATGTCCAGAATGGGAAGTGGGA
		TTCAGATCCATCAGGGACCAAAACCTGCATTGATACCAAG
		GAAGGCATCCTGCAGTATTGCCAAGAAGTCTACCCTGAA
		CTGCAGATCACCAATGTGGTAGAAGCCAACCAACCAGTG
		ACCATCCAGAACTGGTGCAAGCGGGGCCGCAAGCAGTG
		CAAGACCCATCCCCACTTTGTGATTCCCTACCGCTGCTTA
		GTTGGTGAGTTTGTAAGTGATGCCCTTCTCGTTCCTGACA
		AGTGCAAATTCTTACACCAGGAGAGGATGGATGTTTGCG
		AAACTCATCTTCACTGGCACACCGTCGCCAAAGAGACAT
		GCAGTGAGAAGAGTACCAACTTGCATGACTACGGCATGT
		TGCTGCCCTGCGGAATTGACAAGTTCCGAGGGGTAGAGT
		TTGTGTGTTGCCCACTGGCTGAAGAAAGTGACAATGTGG
		ATTCTGCTGATGCGGAGGAGGATGACTCGGATGTCTGGT
		GGGGCGGAGCAGACACAGACTATGCAGATGGGAGTGAA
		GACAAAGTAGTAGAAGTAGCAGAGGAGGAAGAAGTGGCT
		GAGGTGGAAGAAGAAGAAGCCGATGATGACGAGGACGA
		TGAGGATGGTGATGAGGTAGAGGAAGAGGCTGAGGAAC
		CCTACGAAGAAGCCACAGAGAGAACCACCAGCATTGCCA
		CCACCACCACCACCACCACAGAGTCTGTGGAAGAGGTGG
		TTCGAGTTCCTACAACAGCAGCCAGTACCCCTGATGCCG
		TTGACAAGTATCTCGAGACACCTGGGGATGAGAATGAAC
		ATGCCCATTTCCAGAAAGCCAAAGAGAGGCTTGAGGCCA
		AGCACCGAGAGAGAATGTCCCAGGTCATGAGAGAATGGG
		AAGAGGCAGAACGTCAAGCAAAGAACTTGCCTAAAGCTG
		ATAAGAAGGCAGTTATCCAGCATTTCCAGGAGAAAGTGG
		AATCTTTGGAACAGGAAGCAGCCAACGAGAGACAGCAGC
		TGGTGGAGACACACATGGCCAGAGTGGAAGCCATGCTCA
		ATGACCGCCGCCGCCTGGCCCTGGAGAACTACATCACC
		GCTCTGCAGGCTGTTCCTCCTCGGCCTCGTCACGTGTTC
		AATATGCTAAAGAAGTATGTCCGCGCAGAACAGAAGGAC
		AGACAGCACACCCTAAAGCATTTCGAGCATGTGCGCATG
		GTGGATCCCAAGAAAGCCGCTCAGATCCGGTCCCAGGTT
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		ACCAAGGATCAGTTACGGAAACGATGCTCTCATGCCATCT
		TTGACCGAAACGAAAACCACCGTGGAGCTCCTTCCCGTG
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		GGACTGACCACTCGACCAGGTTCTGGGTTGACAAATATC
		AAGACGGAGGAGATCTCTGAAGTGAAGATGGATGCAGAA
		TTCCGACATGACTCAGGATATGAAGTTCATCATCAAAAAT
		TGGTGTTCTTTGCAGAAGATGTGGGTTCAAACAAAGGTG
		CAATCATTGGACTCATGGTGGGCGGTGTTGTCATAGCGA
		CAGTGATCGTCATCACCTTGGTGATGCTGAAGAAGAAAC
		AGTACACATCCATTCATCATGGTGTGGTGGAGGTTGACG
		CCGCTGTCACCCCAGAGGAGCGCCACCTGTCCAAGATG
		CAGCAGAACGGCTACGAAAATCCAACCTACAAGTTCTTTG
		AGCAGATGCAGAACTAGACCCCCGCCACAGCAGCCTCTG
		AAGTTGGACAGCAAAACCATTGCTTCACTACCCATCGGTG
		TCCATTTATAGAATAATGTGGGAAGAAACAAACCCGTTTT
		ATGATTTACTCATTATCGCCTTTTGACAGCTGTGCTGTAA
		CACAAGTAGATGCCTGAACTTGAATTAATCCACACATCAG
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		ATTATTAATGGGTTTTGTGTACTGTAAAGAATTTAGCTGTA
		TCAAACTAGTGCATGAATAGATTCTCTCCTGATTATTTATC
		ACATAGCCCCTTAGCCAGTTGTATATTATTCTTGTGGTTT
		GTGACCCAATTAAGTCCTACTTTACATATGCTTTAAGAATC
		GATGGGGGATGCTTCATGTGAACGTGGGAGTTCAGCTGC
		TTCTCTTGCCTAAGTATTCCTTTCCTGATCACTATGCATTT
		TAAAGTTAAACATTTTTAAGTATTTCAGATGCTTTAGAGAG
		ATTTTTTTTCCATGACTGCATTTTACTGTACAGATTGCTGC

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		TTCTGCTATATTTGTGATATAGGAATTAAGAGGATACACA CGTTTGTTTCTTCGTGCCTGTTTTATGTGCACACATTAGG CATTGAGACTTCAAGCTTTTCTTTTTTTTGTCCACGTATCTT TGGGTCTTTGATAAAGAAAAGAATCCCTGTTCATTGTAAG CACTTTTACGGGGGGGGTGGGGAGGGGTGCTCTGCTGG TCTTCAATTACCAAGAATTCTCCAAAACAATTTTCTGCAGG ATGATTGTACAGAATCATTGCTTATGACATGATCGCTTTCT ACACTGTATTACATAAATAAATTAAATAAAATAACCCCGGG CAAGACTTTTCTTTGAAGGATGACTACAGACATTAAATAAT CGAAGTAATTTTGGGTGGGGAGAAGAGGCAGATTCAATT TTCTTTAACCAGTCTGAAGTTTCATTTATGATACAAAAGAA GATGAAAATGGAAGTGGCAATATAAGGGGATGAGGAAGG CATGCCTGGACAAACCCTTCTTTTAAGATGTGTCTTCAAT TTGTATAAAATGGTGTTTTCATGTAAATAAATACATTCTTG GAGGAGCA
8	ENSP00000346129	>TCONS_00180774|ENST00000354192 (SEQ ID NO: 8) GCGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCCGG GAGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGGAC GCGGCGGATCCCACTCGCACAGCAGCGCACTCGGTGCC CCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTGCT CCTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGTCT ACCCTGAACTGCAGATCACCAATGTGGTAGAAGCCAACC AACCAGTGACCATCCAGAACTGGTGCAAGCGGGGCCGC AAGCAGTGCAAGACCCATCCCCACTTTGTGATTCCCTACC GCTGCTTAGTTGGTGAGTTTGTAAGTGATGCCCTTCTCGT TCCTGACAAGTGCAAATTCTTACACCAGGAGAGGATGGA TGTTTGCGAAACTCATCTTCACTGGCACACCGTCGCCAAA GAGACATGCAGTGAGAAGAGTACCAACTTGCATGACTAC GGCATGTTGCTGCCCTGCGGAATTGACAAGTTCCGAGGG GTAGAGTTTGTGTGTTGCCCACTGGCTGAAGAAAGTGAC AATGTGGATTCTGCTGATGCGGAGGAGGATGACTCGGAT GTCTGGTGGGGCGGAGCAGACACAGACTATGCAGATGG GAGTGAAGACAAAGTAGTAGAAGTAGCAGAGGAGGAAGA AGTGGCTGAGGTGGAAGAAGAAGAAGCCGATGATGACG AGGACGATGAGGATGGTGATGAGGTAGAGGAAGAGGCT GAGGAACCCTACGAAGAAGCCACAGAGAGAACCACCAG CATTGCCACCACCACCACCACCACCACAGAGTCTGTGGA AGAGGTGGTTCGAGTTCCTACAACAGCAGCCAGTACCCC TGATGCCGTTGACAAGTATCTCGAGACACCTGGGGATGA GAATGAACATGCCCATTTCCAGAAAGCCAAAGAGAGGCT TGAGGCCAAGCACCGAGAGAGAATGTCCCAGGTCATGAG AGAATGGGAAGAGGCAGAACGTCAAGCAAAGAACTTGCC TAAAGCTGATAAGAAGGCAGTTATCCAGCATTTCCAGGAG AAAGTGGAATCTTTGGAACAGGAAGCAGCCAACGAGAGA CAGCAGCTGGTGGAGACACACATGGCCAGAGTGGAAGC CATGCTCAATGACCGCCGCCGCCTGGCCCTGGAGAACTA CATCACCGCTCTGCAGGCTGTTCCTCCTCGGCCTCGTCA CGTGTTCAATATGCTAAAGAAGTATGTCCGCGCAGAACA GAAGGACAGACAGCACACCCTAAAGCATTTCGAGCATGT GCGCATGGTGGATCCCAAGAAAGCCGCTCAGATCCGGTC CCAGGTTATGACACACCTCCGTGTGATTTATGAGCGCAT GAATCAGTCTCTCTCCCTGCTCTACAACGTGCCTGCAGT GGCCGAGGAGATTCAGGATGAAGTTGATGAGCTGCTTCA GAAAGAGCAAAACTATTCAGATGACGTCTTGGCCAACATG ATTAGTGAACCAAGGATCAGTTACGGAAACGATGCTCTCA TGCCATCTTTGACCGAAACGAAAACCACCGTGGAGCTCC TTCCCGTGAATGGAGAGTTCAGCCTGGACGATCTCCAGC CGTGGCATTCTTTTGGGGCTGACTCTGTGCCAGCCAACA CAGAAAACGAAGTTGAGCCTGTTGATGCCCGCCCTGCTG CCGACCGAGGACTGACCACTCGACCAGGTTCTGGGTTGA CAAATATCAAGACGGAGGAGATCTCTGAAGTGAAGATGG ATGCAGAATTCCGACATGACTCAGGATATGAAGTTCATCA TCAAAAATTGGTGTTCTTTGCAGAAGATGTGGGTTCAAAC AAAGGTGCAATCATTGGACTCATGGTGGGCGGTGTTGTC ATAGCGACAGTGATCGTCATCACCTTGGTGATGCTGAAG AAGAAACAGTACACATCCATTCATCATGGTGTGGTGGAG GTTGACGCCGCTGTCACCCCAGAGGAGCGCCACCTGTC CAAGATGCAGCAGAACGGCTACGAAAATCCAACCTACAA GTTCTTTGAGCAGATGCAGAACTAGACCCCCGCCACAGC AGCCTCTGAAGTTGGACAGCAAAACCATTGCTTCACTACC CATCGGTGTCCATTTATAGAATAATGTGGGAAGAAACAAA CCCGTTTTATGATTTACTCATTATCGCCTTTTGACAGCTGT GCTGTAACACAAGTAGATGCCTGAACTTGAATTAATCCAC ACATCAGTAATGTATTCTATCTCTCTTTACATTTTGGTCTC

TABLE 3-continued

APP_transcrips_final

Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
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		TAGCTGTATCAAACTAGTGCATGAATAGATTCTCTCCTGA
		TTATTTATCACATAGCCCCTTAGCCAGTTGTATATTATTCT
		TGTGGTTTGTGACCCAATTAAGTCCTACTTTACATATGCTT
		TAAGAATCGATGGGGGATGCTTCATGTGAACGTGGGAGT
		TCAGCTGCTTCTCTTGCCTAAGTATTCCTTTCCTGATCACT
		ATGCATTTTAAAGTTAAACATTTTTAAGTATTTCAGATGCT
		TTAGAGAGATTTTTTTTCCATGACTGCATTTTACTGTACAG
		ATTGCTGCTTCTGCTATATTTGTGATATAGGAATTAAGAG
		GATACACACGTTTGTTTCTTCGTGCCTGTTTTATGTGCAC
		ACATTAGGCATTGAGACTTCAAGCTTTTCTTTTTTTGTCCA
		CGTATCTTTGGGTCTTTGATAAAGAAAAGAATCCCTGTTC
		ATTGTAAGCACTTTTACGGGGGGGGTGGGGAGGGGTGC
		TCTGCTGGTCTTCAATTACCAAGAATTCTCCAAAACAATTT
		TCTGCAGGATGATTGTACAGAATCATTGCTTATGACATGA
		TCGCTTTCTACACTGTATTACATAAATAAATTAAATAAAAT
		AACCCCGGGCAAGACTTTTCTTTGAAGGATGACTACAGA
		CATTAAATAATCGAAGTAATTTTGGGTGGGGAGAAGAGG
		CAGATTCAATTTTCTTTAACCAGTCTGAAGTTTCATTTATG
		ATACAAAAGAAGATGAAAATGGAAGTGGCAATATAAGGG
		GATGAGGAAGGCATGCCTGGACAAACCCTTCTTTTAAGAT
		GTGTCTTCAATTTGTATAAAATGGTGTTTTCATGTAAATAA
		ATACATTCTTGGAGGAGCA
9	ENSP00000350578	>TCONS_00180776|ENST00000357903 SEQ ID NO: 9)
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		AGGCGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCC
		GGGAGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGG
		ACGCGGCGGATCCCACTCGCACAGCAGCGCACTCGGTG
		CCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTG
		CTCCTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGT
		ACCCACTGATGGTAATGCTGGCCTGCTGGCTGAACCCCA
		GATTGCCATGTTCTGTGGCAGACTGAACATGCACATGAAT
		GTCCAGAATGGGAAGTGGGATTCAGATCCATCAGGGACC
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		GCCAAGAAGTCTACCCTGAACTGCAGATCACCAATGTGG
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		ATGCCCTTCTCGTTCCTGACAAGTGCAAATTCTTACACCA
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		CACCGTCGCCAAAGAGACATGCAGTGAGAAGAGTACCAA
		CTTGCATGACTACGGCATGTTGCTGCCCTGCGGAATTGA
		CAAGTTCCGAGGGGTAGAGTTTGTGTGTTGCCCACTGGC
		TGAAGAAAGTGACAATGTGGATTCTGCTGATGCGGAGGA
		GGATGACTCGGATGTCTGGTGGGGCGGAGCAGACACAG
		ACTATGCAGATGGGAGTGAAGACAAAGTAGTAGAAGTAG
		CAGAGGAGGAAGAAGTGGCTGAGGTGGAAGAAGAAGAA
		GCCGATGATGACGAGGACGATGAGGATGGTGATGAGGT
		AGAGGAAGAGGCTGAGGAACCCTACGAAGAAGCCACAG
		AGAGAACCACCAGCATTGCCACCACCACCACCACCACCA
		CAGAGTCTGTGGAAGAGGTGGTTCGAGAGGTGTGCTCTG
		AACAAGCCGAGACGGGGCCGTGCCGAGCAATGATCTCC
		CGCTGGTACTTTGATGTGACTGAAGGGAAGTGTGCCCCA
		TTCTTTTACGGCGGATGTGGCGGCAACCGGAACAACTTT
		GACACAGAAGAGTACTGCATGGCCGTGTGTGGCAGCGC
		CATTCCTACAACAGCAGCCAGTACCCCTGATGCCGTTGA
		CAAGTATCTCGAGACACCTGGGGATGAGAATGAACATGC
		CCATTTCCAGAAAGCCAAAGAGAGGCTTGAGGCCAAGCA
		CCGAGAGAGAATGTCCCAGGTCATGAGAGAATGGGAAGA
		GGCAGAACGTCAAGCAAAGAACTTGCCTAAAGCTGATAA
		GAAGGCAGTTATCCAGCATTTCCAGGAGAAAGTGGAATC
		TTTGGAACAGGAAGCAGCCAACGAGAGACAGCAGCTGGT
		GGAGACACACATGGCCAGAGTGGAAGCCATGCTCAATGA
		CCGCCGCCGCCTGGCCCTGGAGAACTACATCACCGCTCT
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		GCTAAAGAAGTATGTCCGCGCAGAACAGAAGGACAGACA
		GCACACCCTAAAGCATTTCGAGCATGTGCGCATGGTGGA
		TCCCAAGAAAGCCGCTCAGATCCGGTCCCAGGTTATGAC
		ACACCTCCGTGTGATTTATGAGCGCATGAATCAGTCTCTC
		TCCCTGCTCTACAACGTGCCTGCAGTGGCCGAGGAGATT
		CAGGATGAAGTTGATGAGCTGCTTCAGAAAGAGCAAAAC
		TATTCAGATGACGTCTTGGCCAACATGATTAGTGAACCAA
		GGATCAGTTACGGAAACGATGCTCTCATGCCATCTTTGAC
		CGAAACGAAAACCACCGTGGAGCTCCTTCCCGTGAATGG

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		AGAGTTCAGCCTGGACGATCTCCAGCCGTGGCATTCTTT TGGGGCTGACTCTGTGCCAGCCAACACAGAAAACGAAGT TGAGCCTGTTGATGCCCGCCCTGCTGCCGACCGAGGACT GACCACTCGACCAGGTTCTGGGTTGACAAATATCAAGAC GGAGGAGATCTCTGAAGTGAAGATGGATGCAGAATTCCG ACATGACTCAGGATATGAAGTTCATCATCAAAAATTGGTG TTCTTTGCAGAAGATGTGGGTTCAAACAAAGGTGCAATCA TTGGACTCATGGTGGGCGGTGTTGTCATAGCGACAGTGA TCGTCATCACCTTGGTGATGCTGAAGAAGAAACAGTACAC ATCCATTCATCATGGTGTGGTGGAGGTTGACGCCGCTGT CACCCCAGAGGAGCGCCACCTGTCCAAGATGCAGCAGA ACGGCTACGAAAATCCAACCTACAAGTTCTTTGAGCAGAT GCAGAACTAGACCCCCGCCACAGCAGCCTCTGAAGTTGG ACAGCAAAACCATTGCTTCACTACCCATCGGTGTCCATTT ATAGAATAATGTGGGAAGAAACAAACCCGTTTTATGATTT ACTCATTATCGCCTTTTGACAGCTGTGCTGTAACACAAGT AGATGCCTGAACTTGAATTAATCCACACATCAGTAATGTA TTCTATCTCTCTTTACATTTTGGTCTCTATACTACATTATTA ATGGGTTTTGTGTACTGTAAAGAATTTAGCTGTATCAAACT AGTGCATGAATAGATTCTCTCCTGATTATTTATCACATAGC CCCTTAGCCAGTTGTATATTATTCTTGTGGTTTGTGACCC AATTAAGTCCTACTTTACATATGCTTTAAGAATCGATGGG GGATGCTTCATGTGAACGTGGGAGTTCAGCTGCTTCTCTT GCCTAAGTATTCCTTTCCTGATCACTATGCATTTTAAAGTT AAACATTTTTAAGTATTTCAGATGCTTTAGAGAGATTTTTT TTCCATGACTGCATTTTACTGTACAGATTGCTGCTTCTGCT ATATTTGTGATATAGGAATTAAGAGGATACACACGTTTGTT TCTTCGTGCCTGTTTTATGTGCACACATTAGGCATTGAGA CTTCAAGCTTTTCTTTTTTTGTCCACGTATCTTTGGGTCTT TGATAAAGAAAAGAATCCCTGTTCATTGTAAGCACTTTTAC GGGGCGGGTGGGGAGGGGTGCTCTGCTGGTCTTCAATT ACCAAGAATTCTCCAAAACAATTTTCTGCAGGATGATTGT ACAGAATCATTGCTTATGACATGATCGCTTTCTACACTGT ATTACATAAATAAATTAAATAAAATAACCCCGGGCAAGACT TTTCTTTGAAGGATGACTACAGACATTAAATAATCGAAGTA ATTTTGGGTGGGGAGAAGAGGCAGATTCAATTTTCTTTAA CCAGTCTGAAGTTTCATTTATGATACAAAAGAAGATGAAA ATGGAAGTGGCAATATAAGGGGATGAGGAAGGCATGCCT GGACAAACCCTTCTTTTAAGATGTGTCTTCAATTTGTATAA AATGGTGTTTTCATGTAAATAAATACATTCTTGGAGGAGC A
10	ENSP00000350578	>TCONS_00179143|ENST00000357903 (SEQ ID NO: 10) CTTTATCACTTTACTATGCAATTTTTATGACTATGCTTAAG GAGAGTAAATTTTTCGAAGTTATTGAGGCAATGGAGAGTC TTTGGAATGAGGATAATTAGGCCTGAGGACACAGAGGAA TCATGAGGAAGAATTCTCCAGTTTCATTCCTTTTTCTGGG TACAGTTTGTTTCTCCTTCTAAGTAAGTTCCTAGATATAGA ATGAATTGGAAAAAATGAAACGTGAGGTTTGCTACGTCTA TAACAGTATCACATTTCATTTTTTAAAACTGCCAATGCTTT CAGTGAGGACCAGAAAGTACAGTGAGAAAAAAAAATTCCT CAAATATTAGTTTTCATGCTCTTGCACGCATTTTTATAAAG GCAAAAGTCATTCTGGTGCCTGTATACAATCTAAAGGCAT AATCTCCTGGAGCCTTCAGTGCTGGTTTTGGGGTTTTCTG GAGATCAATCCACAGTGTCCCATTTTTTCTGCTGGAGCTC TGAACCCACTAAGAGAGAGCAAGAAGAGATGTAAACCTC TCCTTTGCTTCTGATAAAGCCAAGCCCTTACTAGTCCACA TGATGCTTTCTCTGGGGAGTGAGTCACATACAGGAGACA TGGCTTGTCCAGCTGCGTGCTGGACTGAATTTCAGCTCC AACCTGAACCTTCCAACAGGACAAGGGAGGGAGGAGAAT GGGCCGTAGCA
11	ENSP00000350578	>TCONS_00179153|ENST00000357903 (SEQ ID NO: 11) GTGTGTACCCCTAAACCCAGCTTATTATTTTTTTGACTTTT TGTAGAAACAGGGTCTCCCCATGTTGCCCAGGCTGGTCT TAAACTCCTGGGCTCAAATGATCCTCCTGCCTCAGCCTCC CATAGGGCTAGGATTACAGGTGTGAGCCACCATGCCTGG CCTTTTATACTGTTTATTCCCTTTAGATACAGTTAATGGAC ATTAATAAGCAGTTTATGCCAATCCCTTTTCATAGCTAATA AGAAGTCTTATCTTGGATAAATAAAACCTAGCCACTAATG CTGCCACACCCAAATAAACTCTCTATGCATCTGAACTTCT TGAGGTTAATAATGCTTCATTGTAATATTTTATAAAATCAC CACTTTGGAAGTGAACACCACTAGAAATTCACATGGCCAG

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		TTTATAGATGGGGACTGGGGGAAGCAGGGAGGATCTCTG CAATCCAGTAGTTAGGCTCTGCCAGAATGTATTTAGAGTT GTCTCTAAATACATTCTGAGTCTCTGCTTCATTTTTTTTTTC AATGAAAATGACAATGTCTGTCATCCCATGTTCAAGACAA ATATAACAAGTTTCTAAGAATCCTTATATTTTTGTTATTGCA TATAAGCATGAGTTTTAAAAACCTCTGAATGTTTAAAGGAT CACCTGGGGGAATAAGAAAAATGCAGATCTCTGTAGGTC TGAGGTAGAGCCCAAGAATCTGTATTTTTAACTAGAATTC CTCTAAATTACTGTGCTTCACTTGGCCCCAATTACACATTA GGAGACAATGATTTCAGGATGACAATCAGCCTTTTCCATC CAAGGACTTAAAGCAGCTAAACCGAAGACACCGACAAAT ACCAGATACTTTTCTCAGTCTACTGGCTGATGGCACAAAA GTGCAGAAGTCACGTAGGGC
12	ENSP00000350578	>TCONS_00179154|ENST00000357903 (SEQ ID NO: 12) CATGAGGAACTCCTTGGGCCTTGACCATTTTTAGCACTTT CACAGTTTCTGATTTTGATCAAGCCACTTAATCACCCAGG ATTCTGAATCTGAAAACCAGGAGGGTTTAATTCCACTTTC ATGTTCCCTTGAGGAGCTGTTGGCAGCAGGATGAAGGCA GGTCCATACAGAACATGGGAAGGAAGCCAGGAAGCCAG CTTTTCCTTTCACATCAAAGAGATCTAGAAAGCAAAACCT GTCTCACATTTGCATACAATATTAGACTTACATATGGATGC CATGTCTGTCAAAAGACAGGCTAATTAGGGCATTAGTTTC TTTAATGGTTGCGATTTAGTAATTCACAAATAGTCCCACTT AATTTTTCATCCTATACCTAAAGGATCTACTTCACACTTGA AGTTTAAGAAGGCTTCTCCCTTAAGATAGAAAGAAGGCAT TCAAGTATCAAAATACTGGTTTCCTGCCAAAAAATAAGGG ATGAGAAAAAGCAGACACTTAGCTTATCAATCAAAATGCT GGCAGGGAAAGACTACTGGATTACCAAGTTCATTCCCCT AGCCTGCACTGATTCCTCTTTTTCTCTAAAGTTTCTTATTT TTTCAGTTTTTCTCATGATACTGACATTGCCAACCAGCAG TCTGGAAACTGTTCAGGTTGATTCTTAGCAGAAAATCGAG GGGCTCTCCTGTTACTGTTAATATCCTTAAAACACTTAAAT TTGGTTAGTTTGCTTCAAGCATTCTCAGTATATTACAAAAA AAAAAAGTACTCAAGAATTTCTAGACTTTATTTTGACTGAC ATCAGCTACCCTAATGAACAGGAGGGGACAACAGCAAGG TATATTAGGAGCATCTCCTTCCTTTTTAATCAGAATTATAT AGGAATTAAGAACTCTAAGGCCACAGTAGAGTATAGTATC TTGGAAGAAGAAAGCGGAGAATGTCTGACATTTTCACTGA TCGTTTAGGCTGATGGCTTAAACCATTTCCACCCAAGTTT CTTACAAGTTAGCATTTCCAGCCAACATTACCTACTGCAA TTTCTCTATAATCTTAAGGGTATTGAGCCCCCAAATGAGA GAGAGAAAAGAGATGTAAACTAAACAGGAGTCAGAGAAG GGGAAACTGAGTCTGTTGCACATCATTTACCCTTTAACAT GATTTTAAAGGTAATAATGCTTATAAAAATATTAGTAGTAG TAAGGGATATCAGGTGACAAGCAGAAGTGCCCCTCTCCA CAGATATGCCAGTGTATCTGTAGAAATACGGTGCTAAAAT TAGAAAAGACTGAACATTTTAATTTATTAGGTAGACCC
13	ENSP00000351796	>TCONS_00180770|ENST00000358918 (SEQ ID NO: 13) CGCCGCGCTCGGGCTCCGTCAGTTTCCTCGGCAGCGGT AGGCGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCC GGGAGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGG ACGCGGCGGATCCCACTCGCACAGCAGCGCACTCGGTG CCCCGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTG CTCCTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGT ACCCACTGATGGTAATGCTGGCCTGCTGGCTGAACCCCA GATTGCCATGTTCTGTGGCAGACTGAACATGCACATGAAT GTCCAGAATGGGAAGTGGGATTCAGATCCATCAGGGACC AAAACCTGCATTGATACCAAGGAAGGCATCCTGCAGTATT GCCAAGAAGTCTACCCTGAACTGCAGATCACCAATGTGG TAGAAGCCAACCAACCAGTGACCATCCAGAACTGGTGCA AGCGGGGCCGCAAGCAGTGCAAGACCCATCCCCACTTT GTGATTCCCTACCGCTGCTTAGTTGGTGAGTTTGTAAGTG ATGCCCTTCTCGTTCCTGACAAGTGCAAATTCTTACACCA GGAGAGGATGGATGTTTGCGAAACTCATCTTCACTGGCA CACCGTCGCCAAAGAGACATGCAGTGAGAAGAGTACCAA CTTGCATGACTACGGCATGTTGCTGCCCTGCGGAATTGA CAAGTTCCGAGGGGTAGAGTTTGTGTGTTGCCCACTGGC TGAAGAAAGTGACAATGTGGATTCTGCTGATGCGGAGGA GGATGACTCGGATGTCTGGTGGGGCGGAGCAGACACAG ACTATGCAGATGGGAGTGAAGACAAAGTAGTAGAAGTAG CAGAGGAGGAAGAAGTGGCTGAGGTGGAAGAAGAAGAA

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		GCCGATGATGACGAGGACGATGAGGATGGTGATGAGGT AGAGGAAGAGGCTGAGGAACCCTACGAAGAAGCCACAG AGAGAACCACCAGCATTGCCACCACCACCACCACCACCA CAGAGTCTGTGGAAGAGGTGGTTCGAGAGGTGTGCTCTG AACAAGCCGAGACGGGGCCGTGCCGAGCAATGATCTCC CGCTGGTACTTTGATGTGACTGAAGGGAAGTGTGCCCCA TTCTTTTACGGCGGATGTGGCGGCAACCGGAACAACTTT GACACAGAAGAGTACTGCATGGCCGTGTGTGGCAGCGC CATGTCCCAAAGTTTACTCAAGACTACCCAGGAACCTCTT GCCCGAGATCCTGTTAAACTTCCTACAACAGCAGCCAGT ACCCCTGATGCCGTTGACAAGTATCTCGAGACACCTGGG GATGAGAATGAACATGCCCATTTCCAGAAAGCCAAAGAG AGGCTTGAGGCCAAGCACCGAGAGAGAATGTCCCAGGT CATGAGAGAATGGGAAGAGGCAGAACGTCAAGCAAAGAA CTTGCCTAAAGCTGATAAGAAGGCAGTTATCCAGCATTTC CAGGAGAAAGTGGAATCTTTGGAACAGGAAGCAGCCAAC GAGAGACAGCAGCTGGTGGAGACACACATGGCCAGAGT GGAAGCCATGCTCAATGACCGCCGCCGCCTGGCCCTGG AGAACTACATCACCGCTCTGCAGGCTGTTCCTCCTCGGC CTCGTCACGTGTTCAATATGCTAAAGAAGTATGTCCGCGC AGAACAGAAGGACAGACAGCACACCCTAAAGCATTTCGA GCATGTGCGCATGGTGGATCCCAAGAAAGCCGCTCAGAT CCGGTCCCAGGTTATGACACACCTCCGTGTGATTTATGA GCGCATGAATCAGTCTCTCTCCCTGCTCTACAACGTGCCT GCAGTGGCCGAGGAGATTCAGGATGAAGTTGATGAGCTG CTTCAGAAAGAGCAAAACTATTCAGATGACGTCTTGGCCA ACATGATTAGTGAACCAAGGATCAGTTACGGAAACGATG CTCTCATGCCATCTTTGACCGAAACGAAAACCACCGTGG AGCTCCTTCCCGTGAATGGAGAGTTCAGCCTGGACGATC TCCAGCCGTGGCATTCTTTTGGGGCTGACTCTGTGCCAG CCAACACAGAAAACGAAGGTTCTGGGTTGACAAATATCAA GACGGAGGAGATCTCTGAAGTGAAGATGGATGCAGAATT CCGACATGACTCAGGATATGAAGTTCATCATCAAAAATTG GTGTTCTTTGCAGAAGATGTGGGTTCAAACAAAGGTGCAA TCATTGGACTCATGGTGGGCGGTGTTGTCATAGCGACAG TGATCGTCATCACCTTGGTGATGCTGAAGAAGAAACAGTA CACATCCATTCATCATGGTGTGGTGGAGGTTGACGCCGC TGTCACCCCAGAGGAGCGCCACCTGTCCAAGATGCAGCA GAACGGCTACGAAAATCCAACCTACAAGTTCTTTGAGCAG ATGCAGAACTAGACCCCCGCCACAGCAGCCTCTGAAGTT GGACAGCAAAACCATTGCTTCACTACCCATCGGTGTCCAT TTATAGAATAATGTGGGAAGAAACAAACCCGTTTTATGAT TTACTCATTATCGCCTTTTGACAGCTGTGCTGTAACACAA GTAGATGCCTGAACTTGAATTAATCCACACATCAGTAATG TATTCTATCTCTCTTTACATTTTGGTCTCTATACTACATTAT TAATGGGTTTTGTGTACTGTAAAGAATTTAGCTGTATCAAA CTAGTGCATGAATAGATTCTCTCCTGATTATTTATCACATA GCCCCTTAGCCAGTTGTATATTATTCTTGTGGTTTGTGAC CCAATTAAGTCCTACTTTACATATGCTTTAAGAATCGATGG GGGATGCTTCATGTGAACGTGGGAGTTCAGCTGCTTCTC TTGCCTAAGTATTCCTTTCCTGATCACTATGCATTTTAAAG TTAAACATTTTTAAGTATTTCAGATGCTTTAGAGAGATTTT TTTTCCATGACTGCATTTTACTGTACAGATTGCTGCTTCTG CTATATTTGTGATATAGGAATTAAGAGGATACACACGTTT GTTTCTTCGTGCCTGTTTTATGTGCACACATTAGGCATTG AGACTTCAAGCTTTTCTTTTTTTGTCCACGTATCTTTGGGT CTTTGATAAAGAAAAGAATCCCTGTTCATTGTAAGCACTTT TACGGGGCGGGTGGGGAGGGGTGCTCTGCTGGTCTTCA ATTACCAAGAATTCTCCAAAACAATTTTCTGCAGGATGATT GTACAGAATCATTGCTTATGACATGATCGCTTTCTACACT GTATTACATAAATAAATTAAATAAAATAACCCCGGGCAAG ACTTTTCTTTGAAGGATGACTACAGACATTAAATAATCGAA GTAATTTTGGGTGGGGAGAAGAGGCAGATTCAATTTTCTT TAACCAGTCTGAAGTTTCATTTATGATACAAAAGAAGATG AAAATGGAAGTGGCAATATAAGGGGATGAGGAAGGCATG CCTGGACAAACCCTTCTTTTAAGATGTGTCTTCAATTTGTA TAAAATGGTGTTTTCATGTAAATAAATACATTCTTGGAGGA GCACCATTG
14	ENSP00000351796	>TCONS_00180781|ENST00000358918 (SEQ ID NO: 14) GATCCCACTCGCACAGCAGCGCACTCGGTGCCCCGCGC AGGGTCGCGATGCTGCCCGGTTTGGCACTGCTCCTGCTG GCCGCCTGGACGGCTCGGGCGCTGGAGGTACCCACTGA TGGTAATGCTGGCCTGCTGGCTGAACCCCAGATTGCCAT

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		GTTCTGTGGCAGACTGAACATGCACATGAATGTCCAGAAT GGGAAGTGGGATTCAGATCCATCAGGGACCAAAACCTGC ATTGATACCAAGGAAGGCATCCTGCAGTATTGCCAAGAA GTCTACCCTGAACTGCAGATCACCAATGTGGTAGAAGCC AACCAACCAGTGACCATCCAGAACTGGTGCAAGCGGGGC CGCAAGCAGTGCAAGACCCATCCCCACTTTGTGATTCCC TACCGCTGCTTAGTTGGTGAGTTTGTAAGTGATGCCCTTC TCGTTCCTGACAAGTGCAAATTCTTACACCAGGAGAGGAT GGATGTTTGCGAAACTCATCTTCACTGGCACACCGTCGC CAAAGAGACATGCAGTGAGAAGAGTACCAACTTGCATGA CTACGGCATGTTGCTGCCCTGCGGAATTGACAAGTTCCG AGGGGTAGAGTTTGTGTGTTGCCCACTGGCTGAAGAAAG TGACAATGTGGATTCTGCTGATGCGGAGGAGGATGACTC GGATGTCTGGTGGGGCGGAGCAGACACAGACTATGCAG ATGGGAGTGAAGACAAAGTAGTAGAAGTAGCAGAGGAGG AAGAAGTGGCTGAGGTGGAAGAAGAAGAAGCCGATGATG ACGAGGACGATGAGGATGGTGATGAGGTAGAGGAAGAG GCTGAGGAACCCTACGAAGAAGCCACAGAGAGAACCACC AGCATTGCCACCACCACCACCACCACCACAGAGTCTGTG GAAGAGGTGGTTCGAGAGGTGTGCTCTGAACAAGCCGA GACGGGGCCGTGCCGAGCAATGATCTCCCGCTGGTACTT TGATGTGACTGAAGGGAAGTGTGCCCCATTCTTTTACGG CGGATGTGGCGGCAACCGGAACAACTTTGACACAGAAGA GTACTGCATGGCCGTGTGTGGCAGCGCCATGTCCCAAAG TTTACTCAAGACTACCCAGGAACCTCTTGCCCGAGATCCT GTTAAACTTCCTACAACAGCAGCCAGTACCCCTGATGCC GTTGACAAGTATCTCGAGACACCTGGGGATGAGAATGAA CATGCCCATTTCCAGAAAGCCAAAGAGAGGCTTGAGGCC AAGCACCGAGAGAGAATGTCCCAGGTCATGAGAGAATGG GAAGAGGCAGAACGTCAAGCAAAGAACTTGCCTAAAGCT GATAAGAAGGCAGTTATCCAGCATTTCCAGGAGAAAGTG GAATCTTTGGAACAGGAAGCAGCCAACGAGAGACAGCAG CTGGTGGAGACACACATGGCCAGAGTGGAAGCCATGCTC AATGACCGCCGCCGCCTGGCCCTGGAGAACTACATCACC GCTCTGCAGGCTGTTCCTCCTCGGCCTCGTCACGTGTTC AATATGCTAAAGAAGTATGTCCGCGCAGAACAGAAGGAC AGACAGCACACCCTAAAGCATTTCGAGCATGTGCGCATG GTGGATCCCAAGAAAGCCGCTCAGATCCGGTCCCAGGTT ATGACACACCTCCGTGTGATTTATGAGCGCATGAATCAGT CTCTCTCCCTGCTCTACAACGTGCCTGCAGTGGCCGAGG AGATTCAGGATGAAGTTGATGAGCTGCTTCAGAAAGAGC AAAACTATTCAGATGACGTCTTGGCCAACATGATTAGTGA ACCAAGGATCAGTTACGGAAACGATGCTCTCATGCCATCT TTGACCGAAACGAAAACCACCGTGGAGCTCCTTCCCGTG AATGGAGAGTTCAGCCTGGACGATCTCCAGCCGTGGCAT TCTTTTGGGGCTGACTCTGTGCCAGCCAACACAGAAAAC GAAGGTTCTGGGTTGACAAATATCAAGACGGAGGAGATC TCTGAAGTGAAGATGGATGCAGAATTCCGACATGACTCA GGATATGAAGTTCATCATCAAAAATTGGTGTTCTTTGCAG AAGATGTGGGTTCAAACAAAGGTGCAATCATTGGACTCAT GGTGGGCGGTGTTGTCATAGCGACAGTGATCGTCATCAC CTTGGTGATGCTGAAGAAGAAACAGTACACATCCATTCAT CATGGTGTGGTGGAGGTTGACGCCGCTGTCACCCCAGA GGAGCGCCACCTGTCCAAGATGCAGCAGAACGGCTACG AAAATCCAACCTACAAGTTCTTTGAGCAGATGCAGAACTA GACCCCCGCCACAGCAGCCTCTGAAGTTGGACAGCAAAA CCATTGCTTCACTACCCATCGG
15	ENSP00000352760	>TCONS_00180777|ENST00000359726 (SEQ ID NO: 15) GTCGGATGATTCAAGCTCACGGGGACGAGCAGGAGCGC TCTCGACTTTTCTAGAGCCTCAGCGTCCTAGGACTCACCT TTCCCTGATCCTGCACCGTCCCTCTCCTGGCCCCAGACT CTCCCTCCCACTGTTCACGAAGCCCAGGTACCCACTGAT GGTAATGCTGGCCTGCTGGCTGAACCCCAGATTGCCATG TTCTGTGGCAGACTGAACATGCACATGAATGTCCAGAATG GGAAGTGGGATTCAGATCCATCAGGGACCAAAACCTGCA TTGATACCAAGGAAGGCATCCTGCAGTATTGCCAAGAAG TCTACCCTGAACTGCAGATCACCAATGTGGTAGAAGCCA ACCAACCAGTGACCATCCAGAACTGGTGCAAGCGGGGC CGCAAGCAGTGCAAGACCCATCCCCACTTTGTGATTCCC TACCGCTGCTTAGTTGGTGAGTTTGTAAGTGATGCCCTTC TCGTTCCTGACAAGTGCAAATTCTTACACCAGGAGAGGAT GGATGTTTGCGAAACTCATCTTCACTGGCACACCGTCGC CAAAGAGACATGCAGTGAGAAGAGTACCAACTTGCATGA

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		CTACGGCATGTTGCTGCCCTGCGGAATTGACAAGTTCCG
		AGGGGTAGAGTTTGTGTGTTGCCCACTGGCTGAAGAAAG
		TGACAATGTGGATTCTGCTGATGCGGAGGAGGATGACTC
		GGATGTCTGGTGGGGCGGAGCAGACACAGACTATGCAG
		ATGGGAGTGAAGACAAAGTAGTAGAAGTAGCAGAGGAGG
		AAGAAGTGGCTGAGGTGGAAGAAGAAGAAGCCGATGATG
		ACGAGGACGATGAGGATGGTGATGAGGTAGAGGAAGAG
		GCTGAGGAACCCTACGAAGAAGCCACAGAGAGAACCACC
		AGCATTGCCACCACCACCACCACCACCACAGAGTCTGTG
		GAAGAGGTGGTTCGAGTTCCTACAACAGCAGCCAGTACC
		CCTGATGCCGTTGACAAGTATCTCGAGACACCTGGGGAT
		GAGAATGAACATGCCCATTTCCAGAAAGCCAAAGAGAGG
		CTTGAGGCCAAGCACCGAGAGAGAATGTCCCAGGTCATG
		AGAGAATGGGAAGAGGCAGAACGTCAAGCAAAGAACTTG
		CCTAAAGCTGATAAGAAGGCAGTTATCCAGCATTTCCAGG
		AGAAAGTGGAATCTTTGGAACAGGAAGCAGCCAACGAGA
		GACAGCAGCTGGTGGAGACACACATGGCCAGAGTGGAA
		GCCATGCTCAATGACCGCCGCCGCCTGGCCCTGGAGAA
		CTACATCACCGCTCTGCAGGCTGTTCCTCCTCGGCCTCG
		TCACGTGTTCAATATGCTAAAGAAGTATGTCCGCGCAGAA
		CAGAAGGACAGACAGCACACCCTAAAGCATTTCGAGCAT
		GTGCGCATGGTGGATCCCAAGAAAGCCGCTCAGATCCG
		GTCCCAGGTTATGACACACCTCCGTGTGATTTATGAGCG
		CATGAATCAGTCTCTCTCCCTGCTCTACAACGTGCCTGCA
		GTGGCCGAGGAGATTCAGGATGAAGTTGATGAGCTGCTT
		CAGAAAGAGCAAAACTATTCAGATGACGTCTTGGCCAACA
		TGATTAGTGAACCAAGGATCAGTTACGGAAACGATGCTCT
		CATGCCATCTTTGACCGAAACGAAAACCACCGTGGAGCT
		CCTTCCCGTGAATGGAGAGTTCAGCCTGGACGATCTCCA
		GCCGTGGCATTCTTTTGGGGCTGACTCTGTGCCAGCCAA
		CACAGAAAACGAAGTTGAGCCTGTTGATGCCCGCCCTGC
		TGCCGACCGAGGACTGACCACTCGACCAGGTTCTGGGTT
		GACAAATATCAAGACGGAGGAGATCTCTGAAGTGAAGAT
		GGATGCAGAATTCCGACATGACTCAGGATATGAAGTTCAT
		CATCAAAAATTGGTGTTCTTTGCAGAAGATGTGGGTTCAA
		ACAAAGGTGCAATCATTGGACTCATGGTGGGCGGTGTTG
		TCATAGCGACAGTGATCGTCATCACCTTGGTGATGCTGAA
		GAAGAAACAGTACACATCCATTCATCATGGTGTGGTGGA
		GGTTGACGCCGCTGTCACCCCAGAGGAGCGCCACCTGT
		CCAAGATGCAGCAGAACGGCTACGAAAATCCAACCTACA
		AGTTCTTTGAGCAGATGCAGAACTAGACCCCCGCCACAG
		CAGCCTCTGAAGTTGGACAGCAAAACCATTGCTTCACTAC
		CCATCGGTGTCCATTTATAGAATAATGTGGGAAGAAACAA
		ACCCGTTTTATGATTTACTCATTATCGCCTTTTGACAGCTG
		TGCTGTAACACAAGTAGATGCCTGAACTTGAATTAATCCA
		CACATCAGTAATGTATTCTATCTCTCTTTACATTTTGGTCT
		CTATACTACATTATTAATGGGTTTTGTGTACTGTAAAGAAT
		TTAGCTGTATCAAACTAGTGCATGAATAGATTCTCTCCTG
		ATTATTTATCACATAGCCCCTTAGCCAGTTGTATATTATTC
		TTGTGGTTTGTGACCCAATTAAGTCCTACTTTACATATGCT
		TTAAGAATCGATGGGGGATGCTTCATGTGAACGTGGGAG
		TTCAGCTGCTTCTCTTGCCTAAGTATTCCTTTCCTGATCAC
		TATGCATTTTAAAGTTAAACATTTTTAAGTATTTCAGATGC
		TTTAGAGAGATTTTTTTTCCATGACTGCATTTTACTGTACA
		GATTGCTGCTTCTGCTATATTTGTGATATAGGAATTAAGA
		GGATACACACGTTTGTTTCTTCGTGCCTGTTTTATGTGCA
		CACATTAGGCATTGAGACTTCAAGCTTTTCTTTTTTTGTCC
		ACGTATCTTTGGGTCTTTGATAAAGAAAAGAATCCCTGTT
		CATTGTAAGCACTTTTACGGGGGGGGTGGGGAGGGGTG
		CTCTGCTGGTCTTCAATTACCAAGAATTCTCCAAAACAATT
		TTCTGCAGGATGATTGTACAGAATCATTGCTTATGACATG
		ATCGCTTTCTACACTGTATTACATAAATAAATTAAATAAAA
		TAACCCCGGGCAAGACTTTTCTTTGAAGGATGACTACAGA
		CATTAAATAATCGAAGTAATTTTGGGTGGGGAGAAGAGG
		CAGATTCAATTTTCTTTAACCAGTCTGAAGTTTCATTTATG
		ATACAAAAGAAGATGAAAATGGAAGTGGCAATATAAGGG
		GATGAGGAAGGCATGCCTGGACAAACCCTTCTTTTAAGAT
		GTGTCTTCAATTTGTATAAAATGGTGTTTTCATGTAAATAA
		ATACATTCTTGGAGGAGC
16	ENSP00000387483	>TCONS_00180766|ENST00000440126 (SEQ ID NO: 16)
		AGAGTTCCGGAGGCTTTGGTTGTCCATTGTTAGCTTAGAA
		GTTGGCGCAGTGTGCGTGTGATCCACGCCTAAATAGCAC
		AGCCTTGCTGTGCGTGGTAGAAGTTGGGTTAGTGTTGAC

TABLE 3-continued

APP_transcrips_final	
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
		ATGCTGTTGACTCACCCTCCCGAGGATGGAAGCTCTGGC
		CTGGGTCAAGTTGTGGTCACTGCAGTTAACAGTTTGTTGA
		TCTCAGGGAGTATTCCACAGTTGCTGATGTAATTGACAAT
		GATTGGAGCCAGCTCTTCCCCAGATTCAAATGGACCAATT
		AGAGGACTTGTTGGTTCTGTTTATCAACTATGTACCCACT
		GATGGTAATGCTGGCCTGCTGGCTGAACCCCAGATTGCC
		ATGTTCTGTGGCAGACTGAACATGCACATGAATGTCCAGA
		ATGGGAAGTGGGATTCAGATCCATCAGGGACCAAAACCT
		GCATTGATACCAAGGAAGGCATCCTGCAGTATTGCCAAG
		AAGTCTACCCTGAACTGCAGATCACCAATGTGGTAGAAG
		CCAACCAACCAGTGACCATCCAGAACTGGTGCAAGCGGG
		GCCGCAAGCAGTGCAAGACCCATCCCCACTTTGTGATTC
		CCTACCGCTGCTTAGTTGGTGAGTTTGTAAGTGATGCCCT
		TCTCGTTCCTGACAAGTGCAAATTCTTACACCAGGAGAGG
		ATGGATGTTTGCGAAACTCATCTTCACTGGCACACCGTCG
		CCAAAGAGACATGCAGTGAGAAGAGTACCAACTTGCATG
		ACTACGGCATGTTGCTGCCCTGCGGAATTGACAAGTTCC
		GAGGGGTAGAGTTTGTGTGTTGCCCACTGGCTGAAGAAA
		GTGACAATGTGGATTCTGCTGATGCGGAGGAGGATGACT
		CGGATGTCTGGTGGGGCGGAGCAGACACAGACTATGCA
		GATGGGAGTGAAGACAAAGTAGTAGAAGTAGCAGAGGAG
		GAAGAAGTGGCTGAGGTGGAAGAAGAAGAAGCCGATGAT
		GACGAGGACGATGAGGATGGTGATGAGGTAGAGGAAGA
		GGCTGAGGAACCCTACGAAGAAGCCACAGAGAGAACCA
		CCAGCATTGCCACCACCACCACCACCACCACAGAGTCTG
		TGGAAGAGGTGGTTCGAGAGGTGTGCTCTGAACAAGCCG
		AGACGGGGCCGTGCCGAGCAATGATCTCCCGCTGGTAC
		TTTGATGTGACTGAAGGGAAGTGTGCCCCATTCTTTTACG
		GCGGATGTGGCGGCAACCGGAACAACTTTGACACAGAAG
		AGTACTGCATGGCCGTGTGTGGCAGCGCCATTCCTACAA
		CAGCAGCCAGTACCCCTGATGCCGTTGACAAGTATCTCG
		AGACACCTGGGGATGAGAATGAACATGCCCATTTCCAGA
		AAGCCAAAGAGAGGCTTGAGGCCAAGCACCGAGAGAGA
		ATGTCCCAGGTCATGAGAGAATGGGAAGAGGCAGAACGT
		CAAGCAAAGAACTTGCCTAAAGCTGATAAGAAGGCAGTTA
		TCCAGCATTTCCAGGAGAAAGTGGAATCTTTGGAACAGG
		AAGCAGCCAACGAGAGACAGCAGCTGGTGGAGACACAC
		ATGGCCAGAGTGGAAGCCATGCTCAATGACCGCCGCCG
		CCTGGCCCTGGAGAACTACATCACCGCTCTGCAGGCTGT
		TCCTCCTCGGCCTCGTCACGTGTTCAATATGCTAAAGAAG
		TATGTCCGCGCAGAACAGAAGGACAGACAGCACACCCTA
		AAGCATTTCGAGCATGTGCGCATGGTGGATCCCAAGAAA
		GCCGCTCAGATCCGGTCCCAGGTTATGACACACCTCCGT
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		ACAACGTGCCTGCAGTGGCCGAGGAGATTCAGGATGAAG
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		CGTCTTGGCCAACATGATTAGTGAACCAAGGATCAGTTAC
		GGAAACGATGCTCTCATGCCATCTTTGACCGAAACGAAAA
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		CTGTGCCAGCCAACACAGAAAACGAAGTTGAGCCTGTTG
		ATGCCCGCCCTGCTGCCGACCGAGGACTGACCACTCGA
		CCAGGTTCTGGGTTGACAAATATCAAGACGGAGGAGATC
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		GGATATGAAGTTCATCATCAAAAATTGGTGTTCTTTGCAG
		AAGATGTGGGTTCAAACAAAGGTGCAATCATTGGACTCAT
		GGTGGGCGGTGTTGTCATAGCGACAGTGATCGTCATCAC
		CTTGGTGATGCTGAAGAAGAAACAGTACACATCCATTCAT
		CATGGTGTGGTGGAGGTTGACGCCGCTGTCACCCCAGA
		GGAGCGCCACCTGTCCAAGATGCAGCAGAACGGCTACG
		AAAATCCAACCTACAAGTTCTTTGAGCAGATGCAGAACTA
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		TGTGGGAAGAAACAAACCCGTTTTATGATTTACTCATTAT
		CGCCTTTTGACAGCTGTGCTGTAACACAAGTAGATGCCT
		GAACTTGAATTAATCCACACATCAGTAATGTATTCTATCTC
		TCTTTACATTTTGGTCTCTATACTACATTATTAATGGGTTTT
		GTGTACTGTAAAGAATTTAGCTGTATCAAACTAGTGCATG
		AATAGATTCTCTCCTGATTATTTATCACATAGCCCCTTAGC
		CAGTTGTATATTATTCTTGTGGTTTGTGACCCAATTAAGTC
		CTACTTTACATATGCTTTAAGAATCGATGGGGGATGCTTC
		ATGTGAACGTGGGAGTTCAGCTGCTTCTCTTGCCTAAGTA
		TTCCTTTCCTGATCACTATGCATTTTAAAGTTAAACATTTTT
		AAGTATTTCAGATGCTTTAGAGAGATTTTTTTTCCATGACT
		GCATTTTACTGTACAGATTGCTGCTTCTGCTATATTTGTGA

TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
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17	ENSP00000387483	>TCONS_00180778|ENST00000440126 (SEQ ID NO: 17) AGAGTTCCGGAGGCTTTGGTTGTCCATTGTTAGCTTAGAA GTTGGCGCAGTGTGCGTGTGATCCACGCCTAAATAGCAC AGCCTTGCTGTGCGTGGTAGAAGTTGGGTTAGTGTTGAC ATGCTGTTGACTCACCCTCCCGAGGATGGAAGCTCTGGC CTGGGTCAAGTTGTGGTCACTGCAGTTAACAGTTTGTTGA TCTCAGGGAGTATTCCACAGTTGCTGATGTAATTGACAAT GATTGGAGCCAGCTCTTCCCCAGATTCAAATGGACCAATT AGAGGACTTGTTGGTTCTGTTTATCAACTATGTACCCACT GATGGTAATGCTGGCCTGCTGGCTGAACCCCAGATTGCC ATGTTCTGTGGCAGACTGAACATGCACATGAATGTCCAGA ATGGGAAGTGGGATTCAGATCCATCAGGGACCAAAACCT GCATTGATACCAAGGAAGGCATCCTGCAGTATTGCCAAG AAGTCTACCCTGAACTGCAGATCACCAATGTGGTAGAAG CCAACCAACCAGTGACCATCCAGAACTGGTGCAAGCGGG GCCGCAAGCAGTGCAAGACCCATCCCCACTTTGTGATTC CCTACCGCTGCTTAGTTGGTGAGTTTGTAAGTGATGCCCT TCTCGTTCCTGACAAGTGCAAATTCTTACACCAGGAGAGG ATGGATGTTTGCGAAACTCATCTTCACTGGCACACCGTCG CCAAAGAGACATGCAGTGAGAAGAGTACCAACTTGCATG ACTACGGCATGTTGCTGCCCTGCGGAATTGACAAGTTCC GAGGGGTAGAGTTTGTGTGTTGCCCACTGGCTGAAGAAA GTGACAATGTGGATTCTGCTGATGCGGAGGAGGATGACT CGGATGTCTGGTGGGGCGGAGCAGACACAGACTATGCA GATGGGAGTGAAGACAAAGTAGTAGAAGTAGCAGAGGAG GAAGAAGTGGCTGAGGTGGAAGAAGAAGAAGCCGATGAT GACGAGGACGATGAGGATGGTGATGAGGTAGAGGAAGA GGCTGAGGAACCCTACGAAGAAGCCACAGAGAGAACCA CCAGCATTGCCACCACCACCACCACCACCACAGAGTCTG TGGAAGAGGTGGTTCGAGAGGTGTGCTCTGAACAAGCCG AGACGGGGCCGTGCCGAGCAATGATCTCCCGCTGGTAC TTTGATGTGACTGAAGGGAAGTGTGCCCCATTCTTTTACG GCGGATGTGGCGGCAACCGGAACAACTTTGACACAGAAG AGTACTGCATGGCCGTGTGTGGCAGCGCCATTCCTACAA CAGCAGCCAGTACCCCTGATGCCGTTGACAAGTATCTCG AGACACCTGGGGATGAGAATGAACATGCCCATTTCCAGA AAGCCAAAGAGAGGCTTGAGGCCAAGCACCGAGAGAGA ATGTCCCAGGTCATGAGAGAATGGGAAGAGGCAGAACGT CAAGCAAAGAACTTGCCTAAAGCTGATAAGAAGGCAGTTA TCCAGCATTTCCAGGAGAAAGTGGAATCTTTGGAACAGG AAGCAGCCAACGAGAGACAGCAGCTGGTGGAGACACAC ATGGCCAGAGTGGAAGCCATGCTCAATGACCGCCGCCG CCTGGCCCTGGAGAACTACATCACCGCTCTGCAGGCTGT TCCTCCTCGGCCTCGTCACGTGTTCAATATGCTAAAGAAG TATGTCCGCGCAGAACAGAAGGACAGACAGCACACCCTA AAGCATTTCGAGCATGTGCGCATGGTGGATCCCAAGAAA GCCGCTCAGATCCGGTCCCAGGTTATGACACACCTCCGT GTGATTTATGAGCGCATGAATCAGTCTCTCTCCCTGCTCT ACAACGTGCCTGCAGTGGCCGAGGAGATTCAGGATGAAG TTGATGAGCTGCTTCAGAAAGAGCAAAACTATTCAGATGA CGTCTTGGCCAACATGATTAGTGAACCAAGGATCAGTTAC GGAAACGATGCTCTCATGCCATCTTTGACCGAAACGAAAA CCACCGTGGAGCTCCTTCCCGTGAATGGAGAGTTCAGCC TGGACGATCTCCAGCCGTGGCATTCTTTTGGGGCTGACT CTGTGCCAGCCAACACAGAAAACGAAGTTGAGCCTGTTG ATGCCCGCCCTGCTGCCGACCGAGGACTGACCACTCGA CCAGGTTCTGGGTTGACAAATATCAAGACGGAGGAGATC TCTGAAGTGAAGATGGATGCAGAATTCCGACATGACTCA GGATATGAAGTTCATCATCAAAAATTGGTGTTCTTTGCAG

TABLE 3-continued

APP_transcrips_final		
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18	ENSP00000396923	>TCONS_00180783|ENST00000448850 (SEQ ID NO: 18) ACTGCAGATCACCAATGTGGTAGAAGCCAACCAACCAGT GACCATCCAGAACTGGTGCAAGCGGGGCCGCAAGCAGT GCAAGACCCATCCCCACTTTGTGATTCCCTACCGCTGCTT AGTTGGTGAGTTTGTAAGTGATGCCCTTCTCGTTCCTGAC AAGTGCAAATTCTTACACCAGGAGAGGATGGATGTTTGC GAAACTCATCTTCACTGGCACACCGTCGCCAAAGAGACA TGCAGTGAGAAGAGTACCAACTTGCATGACTACGGCATG TTGCTGCCCTGCGGAATTGACAAGTTCCGAGGGGTAGAG TTTGTGTGTTGCCCACTGGCTGAAGAAAGTGACAATGTG GATTCTGCTGATGCGGAGGAGGATGACTCGGATGTCTGG TGGGGCGGAGCAGACACAGACTATGCAGATGGGAGTGA AGACAAAGTAGTAGAAGTAGCAGAGGAGGAAGAAGTGGC TGAGGTGGAAGAAGAAGAAGCCGATGATGACGAGGACG ATGAGGATGGTGATGAGGTAGAGGAAGAGGCTGAGGAA CCCTACGAAGAAGCCACAGAGAGAACCACCAGCATTGCC ACCACCACCACCACCACCACAGAGTCTGTGGAAGAGGTG GTTCGAGAGGTGTGCTCTGAACAAGCCGAGACGGGGCC GTGCCGAGCAATGATCTCCCGCTGGTACTTTGATGTGAC TGAAGGGAAGTGTGCCCCATTCTTTTACGGCGGATGTGG CGGCAACCGGAACAACTTTGACACAGAAGAGTACTGCAT GGCCGTGTGTGGCAGCGCCATTCCTACAACAGCAGCCA GTACCCCTGATGCCGTTGACAAGTATCTCGAGACACCTG GGGATGAGAATGAACATGCCCATTTCCAGAAAGCCAAAG AGAGGCTTGAGGCCAAGCACCGAGAGAGAATGTCCCAG GTCATGAGAGAATGGGAAGAGGCAGAACGTCAAGCAAAG AACTTGCCTAAAGCTGATAAGAAGGCAGTTATCCAGCATT TCCAGGAGAAAGTGGAATCTTTGGAACAGGAAGCAGCCA ACGAGAGACAGCAGCTGGTGGAGACACACATGGCCAGA GTGGAAGCCATGCTCAATGACCGCCGCCGCCTGGCCCT GGAGAACTACATCACCGCTCTGCAGGCTGTTCCTCCTCG GCCTCGTCACGTGTTCAATATGCTAAAGAAGTATGTCCGC GCAGAACAGAAGGACAGACAGCACACCCTAAAGCATTTC GAGCATGTGCGCATGGTGGATCCCAAGAAAGCCGCTCAG ATCCGGTCCCAGGTTATGACACACCTCCGTGTGATTTATG AGCGCATGAATCAGTCTCTCTCCCTGCTCTACAACGTGC CTGCAGTGGCCGAGGAGATTCAGGATGAAGTTGGTGCAG TGGCTCATGCCTGTAATTCCAGCATTTTGGGAGGCCAAG GTGGGCAGATGACTTGAGCCCAGAAGTTCAAGACCAGAA TGGGAAACATGGCAAGACCACATTTCTACAAAAAAATTAT CCAGGCATGATAACATCTATTTGTAGTCCCAGCTACTCAG GAGGCTGTGGTGGGAGGATCTCCTGAGCCTGGGGTGGC TGAGGCTGCAGTGAGCCTTGATCACGCCACCTGGGCAAT AGAGCAAGACCCTGTCTCAAAAAAAGGAAGAAAAAGACT ATTATTTCCCCCATTGAATGGTCTTGGCACTATTACACAAA ATCAATTGTCCATAGATAATATGGGTTTATTTCTTAATTCT TAGTTCTTTTCTTTGATCTGTGTGCCTGTGCTTACTGTAGT ACCACACTGTTTTGATTATTGTAGCTTTGTAGTAAATTTTG AAATCAGC
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TABLE 3-continued

APP_transcrips_final		
Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
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20	ENSP00000406539	>TCONS_00180784|ENST00000415997 (SEQ ID NO: 20) GGGCGGAGCAGACACAGACTATGCAGATGGGAGTGAAG ACAAAGTAGTAGAAGTAGCAGAGGAGGAAGAAGTGGCTG AGGTGGAAGAAGAAGAAGCCGATGATGACGAGGACGAT GAGGATGGTGATGAGGTAGAGGAAGAGGCTGAGGAACC CTACGAAGAAGCCACAGAGAGAACCACCAGCATTGCCAC CACCACCACCACCACCACAGAGTCTGTGGAAGAGGTGGT TCGAGTGTCCCAAAGTTTACTCAAGACTACCCAGGAACCT CTTGCCCGAGATCCTGTTAAACTTCCTACAACAGCAGCCA GTACCCCTGATGCCGTTGACAAGTATCTCGAGACACCTG GGGATGAGAATGAACATGCCCATTTCCAGAAAGCCAAAG AGAGGCTTGAGGCCAAGCACCGAGAGAGAATGTCCCAG GTCATGAGAGAATGGGAAGAGGCAGAACGTCAAGCAAAG

TABLE 3-continued

APP_transcrips_final

Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
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21	Uniprot_id: P05067	>TCONS_00180780|ENST00000464867 (SEQ ID NO: 21) ATCCTTGCCAACCTCTCAACCAGGATTTAACTTCTGCTTTT CCCCCATTTTCAAAAATTATAGCATGTATTTAAAGGCAGC AGAAGCCTTACTTTCAGGTTTCCCTTACCCTTTCATTTCTT TTTGTTCAAAATAGGTAGTAATTGAAGTTTTAAATATAGGG TATCATTTTTCTTTAAGAGTCATTTATCAATTTTCTTCTAAC TTCAGGCCTAGAAAGAAGTTTTGGGTAGGCTTTGTCTTAC AGTGTTATTATTTATGAGTAAAACTAATTGGTTGTCCTGCA TACTTTAATTATGATGTAATACAGGTTCTGGGTTGACAAAT ATCAAGACGGAGGAGATCTCTGAAGTGAAGATGGATGCA GAATTCCGACATGACTCAGGATATGAAGTTCATCATCAAA AATTGGTGTTCTTTGCAGAAGATGTGGGTTCAAACAAAGG TGCAATCATTGGACTCATGGTGGGCGGTGTTGTCATAGC GACAGTGATCGTCATCACCTTGGTGATGCTGAAGAAGAA ACAGTACACATCCATTCATCATGGTGTGGTGGAGGTTGA CGCCGCTGTCACCCCAGAGGAGCGCCACCTGTCCAAGA TGCAGCAGAACGGCTACGAAAATCCAACCTACAAGTTCTT TGAGCAGATGCAGAACTAGACCCCCGCCACAGCAGCCTC TGAAGTTGGACAGCAAAACCATTGCTTCACTACCCATCGG TGTCCATTTATAGAATAATGTGGGAAGAAACAAACCCGTT TTATGATTTACTCATTATCGCCTTTTGACAGCTGTGCTGTA ACACAAGTAGATGCC
22	Uniprot_id: P05067	>TCONS_00180785|ENST00000491395 (SEQ ID NO: 22) CAGACTATGCAGATGGGAGTGAAGACAAAGTAGTAGAAG TAGCAGAGGAGGAAGAAGTGGCTGAGGTGGAAGAAGAA GAAGCCGATGATGACGAGGACGATGAGGATGGTGATGA GGTAGAGGAAGAGGCTGAGGAACCCTACGAAGAAGCCA CAGAGAGAACCACCAGCATTGCCACCACCACCACCACCA CCACAGAGTCTGTGGAAGAGGTGGTTCGAGAGGTGTGCT CTGAACAAGCCGAGACGGGGCCGTGCCGAGCAATGATC TCCCGCTGGTACTTTGATGTGACTGAAGGGAAGTGTGCC CCATTCTTTTACGGCGGATGTGGCGGCAACCGGAACAAC TTTGACACAGAAGAGTACTGCATGGCCGTGTGTGGCAGC GCCATGTCCCAAAGTTTACTCAAGACTACCCAGGAACCTC TTGCCCGAGATCCTGTTAAACGTACGTTGTCATTCACCTG AGGGAAGGGAAGAGGGGAGGAGGATGCTGCTTGGTTCA CATAACTCCAGCATCATCACCTTCTTTGCATGGTTTTGTG TTTCTTGAACACCTGTCTTAGTAAAATGTTTCTTCCCATTA CCTTGCTTGTAATTACATCTGATTTTGCCAGACA
23	Uniprot_id: P05067	>TCONS_00180786|ENST00000474136 (SEQ ID NO: 23) CGAGAGCACGCGGAGGAGCGTGCGCGGGGGCCCCGGG AGACGGCGGCGGTGGCGGCGCGGGCAGAGCAAGGACG CGGCGGATCCCACTCGCACAGCAGCGCACTCGGTGCCC CGCGCAGGGTCGCGATGCTGCCCGGTTTGGCACTGCTC CTGCTGGCCGCCTGGACGGCTCGGGCGCTGGAGGTACC CACTGATGGTAATGCTGGCCTGCTGGCTGAACCCCAGAT TGCCATGTTCTGTGGCAGACTGAACATGCACATGAATGTC CAGAATGGGAAGTGGGATTCAGATCCATCAGGGACCAAA ACCTGCATTGATACCAAGGAAGGCATCCTGCAGTATTGC CAAGAAGTCTACCCTGAACTGCAGATCACCAATGTGGTA GAAGCCAACCAACCAGTGACCATCCAGAACTGGTGCAAG CGGGGCCGCAAGCAGTGCAAGACCCATCCCCACTTTGTG ATTCCCTACCGCTGCTTAGTTGGTGAGTTTGTAAGTGATG CCCTTCTCGTTCCTGACAAGTGCAAATTCTTACACCAGGA GAGGATGGATGTTTGCGAAACTCATCTTCACTGGCACAC CGTCGCCAAAGAGACATGCAGTGAGAAGAGTACCAACTT GCATGACTACGGCATGTTGCTGCCCTGCGGAATTGACAA GTTCCGAGGGGTAGAGTTTGTGTGTTGCCCACTGGCTGA AGAAAGTGACAATGTGGATTCTGCTGATGCGGAGGAGGA TGACTCGGATGTCTGGTGGGGCGGAGCAGACACAGACT ATGCAGATGGGAGTGAAGACAAAGTAGTAGAAGTAGCAG AGGAGGAAGAAGTGGCTGAGGTGGAAGAAGAAGAAGCC GATGATGACGAGGACGATGAGGATGGTGATGAGGTAGA GGAAGAGGCTGAGGAACCCTACGAAGAAGCCACAGAGA GAACCACCAGCATTGCCACCACCACCACCACCACCACAG AGTCTGTGGAAGAGGTGGTTCGAGAGAAGTGGTATAAGG AAGTACATTCTGGCCAGGCACGATGGCTCATGCTGTAAT

TABLE 3-continued

APP_transcrips_final

Number of variants	Ensembl_protein_id/ UniProt_id	Fasta_Formatted_DNA_sequences_with_cufflinks_ transcript_ids_and_corres-ponding_Ensembl_ids
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24	Uniprot_id: P05067	>TCONS_00180787|ENST00000463070 (SEQ ID NO: 24) GTAACATTCTAAAGGTAGTAGGGTCTTGATTGGGTTGCTT AGGCATTAAAAGGCTGTTTAACTTGTCTTGAAGTCTATCTT TCCTTGATGTCTTCTGCGGTAAGAACACTGTGATACAGAT GGAATGACGGGAAGTGGTTTTCCTTTCTTTCAGTTGGTGA GTTTGTAAGTGATGCCCTTCTCGTTCCTGACAAGTGCAAA TTCTTACACCAGGAGAGGATGGATGTTTGCGAAACTCATC TTCACTGGCACACCGTCGCCAAAGAGACATGCAGTGAGA AGAGTACCAACTTGCATGACTACGGCATGTTGCTGCCCT GCGGAATTGACAAGTTCCGAGGGGTAGAGTTTGTGTGTT GCCCACTGGCTGAAGAAAGTGACAATGTGGATTCTGCTG ATGCGGAGGAGGATGACTCGGATGTCTGGTGGGGCGGA GCAGACACAGACTATGCAGATGGGAGTGAAGACAAAGTA GTAGAAGTAGCAGAGGAGGAAGAAGTGGCTGAGGTGGA AGAAGAAGAAGCCGATGATGACGAGGACGATGAGGATG GTGATGAGGTAGAGGAAGAGGCTGAGGAACCC
25	Uniprot_id: P05067	>TCONS_00180788|ENST00000548570 (SEQ ID NO: 25) ACTGGAGGGCTGAGAAGAGACTGATGGCATTTGTTGTTC TTGACCTTGAAAGAAGAGTTGCAGATTGTTGGAGCAAGG CCAGATGGTAATAGGTTGGAAAGAACAAGTGAGGGGCGT GAGAGTGACAGTCTACAACCCCGTTAAGAAGTTATCTGTG AAAATGCCTCTTCCTGTCTTGATTATAGCCTCCCTCGCAC ATGGCTTTCTGAGTATGTTGGTGAGTTTGTAAGTGATGCC CTTCTCGTTCCTGACAAGTGCAAATTCTTACACCAGGAGA GGATGGATGTTTGCGAAACTCATCTTCACTGGCACACCG TCGCCAAAGAGACATGCAGTGAGAAGAGTACCAACTTGC ATGACT
26	Uniprot_id: P05067	>TCONS_00180789|ENST00000462267 (SEQ ID NO: 26) CTGAACATGCACATGAATGTCCAGAATGGGAAGTGGGAT TCAGATCCATCAGGGACCAAAACCTGCATTGATACCAAG GAAGGCATCCTGCAGTATTGCCAAGAAGTCTACCCTGAA CTGCAGATCACCAATGTGGTAGAAGCCAACCAACCAGTG ACCATCCAGAACTGGTGCAAGCGGGGCCGCAAGCAGTG CAAGACCCATCCCCACTTTGTGATTCCCTACCGCTGCTTA GGTGAGCCGGCCGGCCGTGGGGCTGGTGTTGATTGGGG GCCTGGTCTTGAGGGAAGAAAAAGAGGATGCTCCTGTTA GGTCACATACACAGACTTGTTCTTCAGCACATTGCCACTC TGTGTTGTACTGTGTTTTGGACTCTTGCAGTTACATTCTGT GCACTGACCCTATAGGAGCAGTATTTTTGAGTTCCCTGCC TCAGAATGAATTTACCCAGGGTGTATATTGAAATTACAAAT TCCTGGGCCAGTTCCAGGACTCCTGAATGAAAAATGCCT ATAGTAGCGGATCCGGGAATTCTTATTTTACCGTATCGCA TAGATGATTCTCATGAACAGGGGCCTTGTGTGTTTCTTCA CATAGACTTTCTAGAAGAAAGAATCTAATGTGAAGCTGCA GCATTTTGTTAATTTCTAAAAAAAAAAAAAAAAAA
27	Uniprot_id: P05067	>TCONS_00180790|ENST00000466453 (SEQ ID NO: 27) GGCGCGGCCTCTTCCCTGGCAGCTCTGGGGACTCTGGT TTAGTTCCCCTGGGGGCACAGGATGCTGGGGAGGGTCC GAAGGGTCTTTTTTTTTAGGGTGCAGATAAAAGGATCGAAT TGAGTGAAGATTAAGACGGAGAAGATGGCGCCTCTGCAG TGCAGCAAAGAAAAGCTGTGTGGAGGCTGCAGCCTAGTG AAATCCACCCACCACTAGGTACCCACTGATGGTAATGCT GGCCTGCTGGCTGAACCCCAGATTGCCATGTTCTGTGGC AGACTGAACATGCACATGAATGTCCAGAATGGGAAGTGG GATTCAGATCCATCAGGGACCAAAACCTGCATTGATACCA AGGAAGGCATCCTGCAGTATTGC

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8. Picelli S, Faridani O R, Bjorklund A K, Winberg G, Sagasser S, Sandberg R. Full-length RNA-seq from single cells using Smart-seq2. Nature protocols. 2014; 9 (1): 171-81.

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<400> SEQUENCE: 1

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caaaacctgc attgatacca aggaaggcat cctgcagtat tgccaagaag tctaccctga 180

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<210> SEQ ID NO 2
<211> LENGTH: 3423
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 2

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<210> SEQ ID NO 3
<211> LENGTH: 3204
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 3

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<210> SEQ ID NO 4
<211> LENGTH: 3495
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 4

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<210> SEQ ID NO 5
<211> LENGTH: 3254
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 5

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gatcccactc gcacagcagc gcactcggtg ccccgcgcag ggtcgcgatg ctgcccggtt 180

tggcactgct cctgctggcc gcctggacgg ctcgggcgct ggaggtaccc actgatggta 240

atgctggcct gctggctgaa ccccagattg ccatgttctg tggcagactg aacatgcaca 300

tgaatgtcca gaatgggaag tgggattcag atccatcagg gaccaaaacc tgcattgata 360

ccaaggaagg catcctgcag tattgccaag aagtctaccc tgaactgcag atcaccaatg 420

tggtagaagc caaccaacca gtgaccatcc agaactggtg caagcggggc cgcaagcagt 480

gcaagaccca tccccacttt gtgattccct accgctgctt agttggtgag tttgtaagtg 540

atgcccttct cgttcctgac aagtgcaaat tcttacacca ggagaggatg gatgtttgcg 600

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agaagaggca gattcaattt tctttaacca gtctgaagtt tcatttatga tacaaaagaa 3120

gatgaaaatg gaagtggcaa tataagggga tgaggaaggc atgcctggac aaacccttct 3180

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gaggagcacc attg 3254

<210> SEQ ID NO 6
<211> LENGTH: 3467
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 6

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ggctgaaccc cagattgcca tgttctgtgg cagactgaac atgcacatga atgtccagaa 180

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cctgcagtat tgccaagaag tctaccctga actgcagatc accaatgtgg tagaagccaa 300

ccaaccagtg accatccaga actggtgcaa gcggggccgc aagcagtgca agacccatcc 360

ccactttgtg attccctacc gctgcttagt tggtgagttt gtaagtgatg cccttctcgt 420

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agaggaggaa gaagtggctg aggtggaaga agaagaagcc gatgatgacg aggacgatga 780

ggatggtgat gaggtagagg aagaggctga ggaaccctac gaagaagcca cagagagaac 840

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ataaggggat gaggaaggca tgcctggaca aacccttctt ttaagatgtg tcttcaattt 3420

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<210> SEQ ID NO 7
<211> LENGTH: 3355
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 7

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gcactcggtg ccccgcgcag ggtcgcgatg ctgcccggtt tggcactgct cctgctggcc 180

gcctggacgg ctcgggcgct ggaggtaccc actgatggta atgctggcct gctggctgaa 240

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tattgccaag aagtctaccc tgaactgcag atcaccaatg tggtagaagc caaccaacca 420

gtgaccatcc agaactggtg caagcggggc cgcaagcagt gcaagaccca tccccacttt 480

gtgattccct accgctgctt agttggtgag tttgtaagtg atgcccttct cgttcctgac 540

aagtgcaaat tcttacacca ggagaggatg gatgtttgcg aaactcatct tcactggcac 600

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<210> SEQ ID NO 8
<211> LENGTH: 3167
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 8

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ggtcgcgatg ctgcccggtt tggcactgct cctgctggcc gcctggacgg ctcgggcgct 180

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gaactagacc cccgccacag cagcctctga agttggacag caaaaccatt gcttcactac 2100

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<210> SEQ ID NO 9
<211> LENGTH: 3543
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 9

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gtgcgcgggg gccccgggag acggcggcgg tggcggcgcg ggcagagcaa ggacgcggcg 120

gatcccactc gcacagcagc gcactcggtg ccccgcgcag ggtcgcgatg ctgcccggtt 180

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tggcactgct cctgctggcc gcctggacgg ctcgggcgct ggaggtaccc actgatggta 240

atgctggcct gctggctgaa ccccagattg ccatgttctg tggcagactg aacatgcaca 300

tgaatgtcca gaatgggaag tgggattcag atccatcagg gaccaaaacc tgcattgata 360

ccaaggaagg catcctgcag tattgccaag aagtctaccc tgaactgcag atcaccaatg 420

tggtagaagc caaccaacca gtgaccatcc agaactggtg caagcggggc cgcaagcagt 480

gcaagaccca tccccacttt gtgattccct accgctgctt agttggtgag tttgtaagtg 540

atgcccttct cgttcctgac aagtgcaaat tcttacacca ggagaggatg gatgtttgcg 600

aaactcatct tcactggcac accgtcgcca aagagacatg cagtgagaag agtaccaact 660

tgcatgacta cggcatgttg ctgccctgcg gaattgacaa gttccgaggg gtagagtttg 720

tgtgttgccc actggctgaa gaaagtgaca atgtggattc tgctgatgcg gaggaggatg 780

actcggatgt ctggtggggc ggagcagaca cagactatgc agatgggagt gaagacaaag 840

tagtagaagt agcagaggag gaagaagtgg ctgaggtgga agaagaagaa gccgatgatg 900

acgaggacga tgaggatggt gatgaggtag aggaagaggc tgaggaaccc tacgaagaag 960

ccacagagag aaccaccagc attgccacca ccaccaccac caccacagag tctgtggaag 1020

aggtggttcg agaggtgtgc tctgaacaag ccgagacggg gccgtgccga gcaatgatct 1080

cccgctggta ctttgatgtg actgaaggga agtgtgcccc attcttttac ggcggatgtg 1140

gcggcaaccg gaacaacttt gacacagaag agtactgcat ggccgtgtgt ggcagcgcca 1200

ttcctacaac agcagccagt acccctgatg ccgttgacaa gtatctcgag acacctgggg 1260

atgagaatga acatgcccat ttccagaaag ccaaagagag gcttgaggcc aagcaccgag 1320

agagaatgtc ccaggtcatg agagaatggg aagaggcaga acgtcaagca aagaacttgc 1380

ctaaagctga taagaaggca gttatccagc atttccagga gaaagtggaa tctttggaac 1440

aggaagcagc caacgagaga cagcagctgg tggagacaca catggccaga gtggaagcca 1500

tgctcaatga ccgccgccgc ctggccctgg agaactacat caccgctctg caggctgttc 1560

ctcctcggcc tcgtcacgtg ttcaatatgc taaagaagta tgtccgcgca gaacagaagg 1620

acagacagca caccctaaag catttcgagc atgtgcgcat ggtggatccc aagaaagccg 1680

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caaggatcag ttacggaaac gatgctctca tgccatcttt gaccgaaacg aaaaccaccg 1920

tggagctcct tcccgtgaat ggagagttca gcctggacga tctccagccg tggcattctt 1980

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ctgctgccga ccgaggactg accactcgac caggttctgg gttgacaaat atcaagacgg 2100

aggagatctc tgaagtgaag atggatgcag aattccgaca tgactcagga tatgaagttc 2160

atcatcaaaa attggtgttc tttgcagaag atgtgggttc aaacaaaggt gcaatcattg 2220

gactcatggt gggcggtgtt gtcatagcga cagtgatcgt catcaccttg gtgatgctga 2280

agaagaaaca gtacacatcc attcatcatg gtgtggtgga ggttgacgcc gctgtcaccc 2340

cagaggagcg ccacctgtcc aagatgcagc agaacggcta cgaaaatcca acctacaagt 2400

tctttgagca gatgcagaac tagacccccg ccacagcagc ctctgaagtt ggacagcaaa 2460

accattgctt cactacccat cggtgtccat ttatagaata atgtgggaag aaacaaaccc 2520

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gttttatgat ttactcatta tcgccttttg acagctgtgc tgtaacacaa gtagatgcct 2580

gaacttgaat taatccacac atcagtaatg tattctatct ctctttacat tttggtctct 2640

atactacatt attaatgggt tttgtgtact gtaaagaatt tagctgtatc aaactagtgc 2700

atgaatagat tctctcctga ttatttatca catagcccct tagccagttg tatattattc 2760

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gcttcatgtg aacgtgggag ttcagctgct tctcttgcct aagtattcct ttcctgatca 2880

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ccatgactgc attttactgt acagattgct gcttctgcta tatttgtgat ataggaatta 3000

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tgttcattgt aagcactttt acggggcggg tggggagggg tgctctgctg gtcttcaatt 3180

accaagaatt ctccaaaaca attttctgca ggatgattgt acagaatcat tgcttatgac 3240

atgatcgctt tctacactgt attacataaa taaattaaat aaaataaccc cgggcaagac 3300

ttttctttga aggatgacta cagacattaa ataatcgaag taattttggg tggggagaag 3360

aggcagattc aattttcttt aaccagtctg aagtttcatt tatgatacaa aagaagatga 3420

aaatggaagt ggcaatataa ggggatgagg aaggcatgcc tggacaaacc cttcttttaa 3480

gatgtgtctt caatttgtat aaaatggtgt tttcatgtaa ataaatacat tcttggagga 3540

gca 3543

<210> SEQ ID NO 10
<211> LENGTH: 690
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 10

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ttattgaggc aatggagagt ctttggaatg aggataatta ggcctgagga cacagaggaa 120

tcatgaggaa gaattctcca gtttcattcc ttttttctggg tacagtttgt ttctccttct 180

aagtaagttc ctagatatag aatgaattgg aaaaaatgaa acgtgaggtt tgctacgtct 240

ataacagtat cacatttcat tttttaaaac tgccaatgct ttcagtgagg accagaaagt 300

acagtgagaa aaaaaaattc ctcaaatatt agttttcatg ctcttgcacg catttttata 360

aaggcaaaag tcattctggt gcctgtatac aatctaaagg cataatctcc tggagccttc 420

agtgctggtt ttggggtttt ctggagatca atccacagtg tcccattttt tctgctggag 480

ctctgaaccc actaagagag agcaagaaga gatgtaaacc tctcctttgc ttctgataaa 540

gccaagccct tactagtcca catgatgctt tctctgggga gtgagtcaca tacaggagac 600

atggcttgtc cagctgcgtg ctggactgaa tttcagctcc aacctgaacc ttccaacagg 660

acaagggagg gaggagaatg ggccgtagca 690

<210> SEQ ID NO 11
<211> LENGTH: 905
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

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<400> SEQUENCE: 11

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catagggcta ggattacagg tgtgagccac catgcctggc cttttatact gtttattccc 180

tttagataca gttaatggac attaataagc agtttatgcc aatccctttt catagctaat 240

aagaagtctt atcttggata aataaaacct agccactaat gctgccacac ccaaataaac 300

tctctatgca tctgaacttc ttgaggttaa taatgcttca ttgtaatatt ttataaaatc 360

accactttgg aagtgaacac cactagaaat tcacatggcc agtttataga tggggactgg 420

gggaagcagg gaggatctct gcaatccagt agttaggctc tgccagaatg tatttagagt 480

tgtctctaaa tacattctga gtctctgctt catttttttt ttcaatgaaa atgacaatgt 540

ctgtcatccc atgttcaaga caaatataac aagtttctaa gaatccttat atttttgtta 600

ttgcatataa gcatgagttt taaaaacctc tgaatgttta aaggatcacc tgggggaata 660

agaaaaatgc agatctctgt aggtctgagg tagagcccaa gaatctgtat ttttaactag 720

aattcctcta aattactgtg cttcacttgg ccccaattac acattaggag acaatgattt 780

caggatgaca atcagccttt tccatccaag gacttaaagc agctaaaccg aagacaccga 840

caaataccag atacttttct cagtctactg gctgatggca caaaagtgca gaagtcacgt 900

agggc 905

<210> SEQ ID NO 12
<211> LENGTH: 1320
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 12

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aagccactta atcacccagg attctgaatc tgaaaaccag gagggtttaa ttccactttc 120

atgttccctt gaggagctgt tggcagcagg atgaaggcag gtccatacag aacatgggaa 180

ggaagccagg aagccagctt ttcctttcac atcaaagaga tctagaaagc aaaacctgtc 240

tcacatttgc atacaatatt agacttacat atggatgcca tgtctgtcaa aagacaggct 300

aattagggca ttagtttctt taatggttgc gatttagtaa ttcacaaata gtcccactta 360

atttttcatc ctatacctaa aggatctact tcacacttga agtttaagaa ggcttctccc 420

ttaagataga aagaaggcat tcaagtatca aaatactggt ttcctgccaa aaaataaggg 480

atgagaaaaa gcagacactt agcttatcaa tcaaaatgct ggcagggaaa gactactgga 540

ttaccaagtt cattccccta gcctgcactg attcctcttt ttctctaaag tttcttattt 600

tttcagtttt tctcatgata ctgacattgc caaccagcag tctggaaact gttcaggttg 660

attcttagca gaaaatcgag gggctctcct gttactgtta atatccttaa aacacttaaa 720

tttggttagt ttgcttcaag cattctcagt atattacaaa aaaaaaaagt actcaagaat 780

ttctagactt tattttgact gacatcagct accctaatga acaggagggg acaacagcaa 840

ggtatattag gagcatctcc ttccttttta atcagaatta tataggaatt aagaactcta 900

aggccacagt agagtatagt atcttggaag aagaaagcgg agaatgtctg acattttcac 960

tgatcgttta ggctgatggc ttaaaccatt tccacccaag tttcttacaa gttagcattt 1020

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ccagccaaca ttacctactg caatttctct ataatcttaa gggtattgag cccccaaatg 1080

agagagagaa aagagatgta aactaaacag gagtcagaga aggggaaact gagtctgttg 1140

cacatcattt acccttaac atgattttaa aggtaataat gcttataaaa atattagtag 1200

tagtaaggga tatcaggtga caagcagaag tgcccctctc cacagatatg ccagtgtatc 1260

tgtagaaata cggtgctaaa attagaaaag actgaacatt ttaatttatt aggtagaccc 1320

<210> SEQ ID NO 13
<211> LENGTH: 3552
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 13

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gatcccactc gcacagcagc gcactcggtg ccccgcgcag ggtcgcgatg ctgcccggtt 180

tggcactgct cctgctggcc gcctggacgg ctcgggcgct ggaggtaccc actgatggta 240

atgctggcct gctggctgaa ccccagattg ccatgttctg tggcagactg aacatgcaca 300

tgaatgtcca gaatgggaag tgggattcag atccatcagg gaccaaaacc tgcattgata 360

ccaaggaagg catcctgcag tattgccaag aagtctaccc tgaactgcag atcaccaatg 420

tggtagaagc caaccaacca gtgaccatcc agaactggtg caagcggggc cgcaagcagt 480

gcaagaccca tccccacttt gtgattccct accgctgctt agttggtgag tttgtaagtg 540

atgcccttct cgttcctgac aagtgcaaat tcttacacca ggagaggatg gatgtttgcg 600

aaactcatct tcactggcac accgtcgcca aagagacatg cagtgagaag agtaccaact 660

tgcatgacta cggcatgttg ctgccctgcg gaattgacaa gttccgaggg gtagagtttg 720

tgtgttgccc actggctgaa gaaagtgaca atgtggattc tgctgatgcg gaggaggatg 780

actcggatgt ctggtggggc ggagcagaca cagactatgc agatgggagt gaagacaaag 840

tagtagaagt agcagaggag gaagaagtgg ctgaggtgga agaagaagaa gccgatgatg 900

acgaggacga tgaggatggt gatgaggtag aggaagaggc tgaggaaccc tacgaagaag 960

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aggtggttcg agaggtgtgc tctgaacaag ccgagacggg gccgtgccga gcaatgatct 1080

cccgctggta ctttgatgtg actgaaggga agtgtgcccc attcttttac ggcggatgtg 1140

gcggcaaccg gaacaacttt gacacagaag agtactgcat ggccgtgtgt ggcagcgcca 1200

tgtcccaaag tttactcaag actacccagg aacctcttgc ccgagatcct gttaaacttc 1260

ctacaacagc agccagtacc cctgatgccg ttgacaagta tctcgagaca cctggggatg 1320

agaatgaaca tgcccatttc cagaaagcca aagagaggct tgaggccaag caccgagaga 1380

gaatgtccca ggtcatgaga gaatgggaag aggcagaacg tcaagcaaag aacttgccta 1440

aagctgataa gaaggcagtt atccagcatt tccaggagaa agtggaatct ttggaacagg 1500

aagcagccaa cgagagacag cagctggtgg agacacacat ggccagagtg gaagccatgc 1560

tcaatgaccg ccgccgcctg gccctggaga actacatcac cgctctgcag gctgttcctc 1620

ctcggcctcg tcacgtgttc aatatgctaa agaagtatgt ccgcgcagaa cagaaggaca 1680

gacagcacac cctaaagcat ttcgagcatg tgcgcatggt ggatcccaag aaagccgctc 1740

agatccggtc ccaggttatg acacacctcc gtgtgattta tgagcgcatg aatcagtctc 1800

tctccctgct ctacaacgtg cctgcagtgg ccgaggagat tcaggatgaa gttgatgagc 1860

tgcttcagaa agagcaaaac tattcagatg acgtcttggc caacatgatt agtgaaccaa 1920

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cggaggagat ctctgaagtg aagatggatg cagaattccg acatgactca ggatatgaag 2160

ttcatcatca aaaattggtg ttctttgcag aagatgtggg ttcaaacaaa ggtgcaatca 2220

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tgaagaagaa acagtacaca tccattcatc atggtgtggt ggaggttgac gccgctgtca 2340

ccccagagga gcgccacctg tccaagatgc agcagaacgg ctacgaaaat ccaacctaca 2400

agttctttga gcagatgcag aactagaccc ccgccacagc agcctctgaa gttggacagc 2460

aaaaccattg cttcactacc catcggtgtc catttataga ataatgtggg aagaaacaaa 2520

cccgttttat gatttactca ttatcgcctt ttgacagctg tgctgtaaca caagtagatg 2580

cctgaacttg aattaatcca cacatcagta atgtattcta tctctcttta cattttggtc 2640

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tcactatgca ttttaaagtt aaacattttt aagtatttca gatgctttag agagattttt 2940

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gacatgatcg ctttctacac tgtattacat aaataaatta aataaaataa ccccgggcaa 3300

gacttttctt tgaaggatga ctacagacat taaataatcg aagtaatttt gggtggggag 3360

aagaggcaga ttcaattttc tttaaccagt ctgaagtttc atttatgata caaaagaaga 3420

tgaaaatgga agtggcaata taaggggatg aggaaggcat gcctggacaa acccttcttt 3480

taagatgtgt cttcaatttg tataaaatgg tgttttcatg taaataaata cattcttgga 3540

ggagcaccat tg 3552

<210> SEQ ID NO 14
<211> LENGTH: 2366
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 14

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tggcactgct cctgctggcc gcctggacgg ctcgggcgct ggaggtaccc actgatggta 120

atgctggcct gctggctgaa ccccagattg ccatgttctg tggcagactg aacatgcaca 180

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tgaatgtcca gaatgggaag tgggattcag atccatcagg gaccaaaacc tgcattgata 240

ccaaggaagg catcctgcag tattgccaag aagtctaccc tgaactgcag atcaccaatg 300

tggtagaagc caaccaacca gtgaccatcc agaactggtg caagcggggc cgcaagcagt 360

gcaagaccca tccccacttt gtgattccct accgctgctt agttggtgag tttgtaagtg 420

atgcccttct cgttcctgac aagtgcaaat tcttacacca ggagaggatg gatgtttgcg 480

aaactcatct tcactggcac accgtcgcca aagagacatg cagtgagaag agtaccaact 540

tgcatgacta cggcatgttg ctgccctgcg gaattgacaa gttccgaggg gtagagtttg 600

tgtgttgccc actggctgaa gaaagtgaca atgtggattc tgctgatgcg gaggaggatg 660

actcggatgt ctggtggggc ggagcagaca cagactatgc agatgggagt gaagacaaag 720

tagtagaagt agcagaggag gaagaagtgg ctgaggtgga agaagaagaa gccgatgatg 780

acgaggacga tgaggatggt gatgaggtag aggaagaggc tgaggaaccc tacgaagaag 840

ccacagagag aaccaccagc attgccacca ccaccaccac caccacagag tctgtggaag 900

aggtggttcg agaggtgtgc tctgaacaag ccgagacggg gccgtgccga gcaatgatct 960

cccgctggta ctttgatgtg actgaaggga agtgtgcccc attcttttac ggcggatgtg 1020

gcggcaaccg gaacaacttt gacacagaag agtactgcat ggccgtgtgt ggcagcgcca 1080

tgtcccaaag tttactcaag actacccagg aacctcttgc ccgagatcct gttaaacttc 1140

ctacaacagc agccagtacc cctgatgccg ttgacaagta tctcgagaca cctggggatg 1200

agaatgaaca tgcccatttc cagaaagcca aagagaggct tgaggccaag caccgagaga 1260

gaatgtccca ggtcatgaga gaatgggaag aggcagaacg tcaagcaaag aacttgccta 1320

aagctgataa gaaggcagtt atccagcatt tccaggagaa agtggaatct ttggaacagg 1380

aagcagccaa cgagagacag cagctggtgg agacacacat ggccagagtg gaagccatgc 1440

tcaatgaccg ccgccgcctg gccctggaga actacatcac cgctctgcag gctgttcctc 1500

ctcggcctcg tcacgtgttc aatatgctaa agaagtatgt ccgcgcagaa cagaaggaca 1560

gacagcacac cctaaagcat ttcgagcatg tgcgcatggt ggatcccaag aaagccgctc 1620

agatccggtc ccaggttatg acacacctcc gtgtgattta tgagcgcatg aatcagtctc 1680

tctccctgct ctacaacgtg cctgcagtgg ccgaggagat tcaggatgaa gttgatgagc 1740

tgcttcagaa agagcaaaac tattcagatg acgtcttggc caacatgatt agtgaaccaa 1800

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agctccttcc cgtgaatgga gagttcagcc tggacgatct ccagccgtgg cattcttttg 1920

gggctgactc tgtgccagcc aacacagaaa acgaaggttc tgggttgaca aatatcaaga 1980

cggaggagat ctctgaagtg aagatggatg cagaattccg acatgactca ggatatgaag 2040

ttcatcatca aaaattggtg ttctttgcag aagatgtggg ttcaaacaaa ggtgcaatca 2100

ttggactcat ggtgggcggt gttgtcatag cgacagtgat cgtcatcacc ttggtgatgc 2160

tgaagaagaa acagtacaca tccattcatc atggtgtggt ggaggttgac gccgctgtca 2220

ccccagagga gcgccacctg tccaagatgc agcagaacgg ctacgaaaat ccaacctaca 2280

agttctttga gcagatgcag aactagaccc ccgccacagc agcctctgaa gttggacagc 2340

aaaaccattg cttcactacc catcgg 2366

<210> SEQ ID NO 15
<211> LENGTH: 3294
<212> TYPE: DNA

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<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 15

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cctcccactg ttcacgaagc ccaggtaccc actgatggta atgctggcct gctggctgaa 180

ccccagattg ccatgttctg tggcagactg aacatgcaca tgaatgtcca gaatgggaag 240

tgggattcag atccatcagg gaccaaaacc tgcattgata ccaaggaagg catcctgcag 300

tattgccaag aagtctaccc tgaactgcag atcaccaatg tggtagaagc caaccaacca 360

gtgaccatcc agaactggtg caagcggggc cgcaagcagt gcaagaccca tccccacttt 420

gtgattccct accgctgctt agttggtgag tttgtaagtg atgcccttct cgttcctgac 480

aagtgcaaat tcttacacca ggagaggatg gatgtttgcg aaactcatct tcactggcac 540

accgtcgcca aagagacatg cagtgagaag agtaccaact tgcatgacta cggcatgttg 600

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gaaagtgaca atgtggattc tgctgatgcg gaggaggatg actcggatgt ctggtggggc 720

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tcaattttct ttaaccagtc tgaagtttca tttatgatac aaaagaagat gaaaatggaa 3180

gtggcaatat aaggggatga ggaaggcatg cctggacaaa cccttctttt aagatgtgtc 3240

ttcaatttgt ataaaatggt gttttcatgt aaataaatac attcttggag gagc 3294

<210> SEQ ID NO 16
<211> LENGTH: 3633
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 16

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gctgttgact caccctcccg aggatggaag ctctggcctg ggtcaagttg tggtcactgc 180

agttaacagt ttgttgatct cagggagtat tccacagttg ctgatgtaat tgacaatgat 240

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tcaactatgt acccactgat ggtaatgctg gcctgctggc tgaaccccag attgccatgt 360

tctgtggcag actgaacatg cacatgaatg tccagaatgg gaagtgggat tcagatccat 420

cagggaccaa aacctgcatt gataccaagg aaggcatcct gcagtattgc caagaagtct 480

accctgaact gcagatcacc aatgtggtag aagccaacca accagtgacc atccagaact 540

ggtgcaagcg gggccgcaag cagtgcaaga cccatcccca ctttgtgatt ccctaccgct 600

gcttagttgg tgagtttgta agtgatgccc ttctcgttcc tgacaagtgc aaattcttac 660

accaggagag gatggatgtt tgcgaaactc atcttcactg gcacaccgtc gccaaagaga 720

catgcagtga gaagagtacc aacttgcatg actacggcat gttgctgccc tgcggaattg 780

acaagttccg aggggtagag tttgtgtgtt gcccactggc tgaagaaagt gacaatgtgg 840

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gtctttgata aagaaaagaa tccctgttca ttgtaagcac ttttacgggg cgggtgggga 3240

ggggtgctct gctggtcttc aattaccaag aattctccaa aacaattttc tgcaggatga 3300

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gaagtaattt tgggtgggga gaagaggcag attcaatttt ctttaaccag tctgaagttt 3480

catttatgat acaaaagaag atgaaaatgg aagtggcaat ataaggggat gaggaaggca 3540

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gtaaataaat acattcttgg aggagcacca ttg 3633

<210> SEQ ID NO 17
<211> LENGTH: 2846
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 17

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gctgttgact caccctcccg aggatggaag ctctggcctg ggtcaagttg tggtcactgc 180

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tctgtggcag actgaacatg cacatgaatg tccagaatgg gaagtgggat tcagatccat 420

cagggaccaa aacctgcatt gataccaagg aaggcatcct gcagtattgc caagaagtct 480

accctgaact gcagatcacc aatgtggtag aagccaacca accagtgacc atccagaact 540

ggtgcaagcg gggccgcaag cagtgcaaga cccatcccca ctttgtgatt ccctaccgct 600

gcttagttgg tgagtttgta agtgatgccc ttctcgttcc tgacaagtgc aaattcttac 660

accaggagag gatggatgtt tgcgaaactc atcttcactg gcacaccgtc gccaaagaga 720

catgcagtga gaagagtacc aacttgcatg actacggcat gttgctgccc tgcggaattg 780

acaagttccg aggggtagag tttgtgtgtt gcccactggc tgaagaaagt gacaatgtgg 840

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cacacatggc cagagtggaa gccatgctca atgaccgccg ccgcctggcc ctggagaact 1620

acatcaccgc tctgcaggct gttcctcctc ggcctcgtca cgtgttcaat atgctaaaga 1680

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agtatgtccg cgcagaacag aaggacagac agcacaccct aaagcatttc gagcatgtgc 1740

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tgatttatga gcgcatgaat cagtctctct ccctgctcta caacgtgcct gcagtggccg 1860

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gtgctgtaac acaagtagat gcctgaactt gaattaatcc acacatcagt aatgtattct 2700

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<210> SEQ ID NO 18
<211> LENGTH: 1846
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 18

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tggtgagttt gtaagtgatg cccttctcgt tcctgacaag tgcaaattct tacaccagga 180

gaggatggat gtttgcgaaa ctcatcttca ctggcacacc gtcgccaaag agacatgcag 240

tgagaagagt accaacttgc atgactacgg catgttgctg ccctgcggaa ttgacaagtt 300

ccgaggggta gagtttgtgt gttgcccact ggctgaagaa agtgacaatg tggattctgc 360

tgatgcggag gaggatgact cggatgtctg gtggggcgga gcagacacag actatgcaga 420

tgggagtgaa gacaaagtag tagaagtagc agaggaggaa gaagtggctg aggtggaaga 480

agaagaagcc gatgatgacg aggacgatga ggatggtgat gaggtagagg aagaggctga 540

ggaaccctac gaagaagcca cagagagaac caccagcatt gccaccacca ccaccaccac 600

cacagagtct gtggaagagg tggttcgaga ggtgtgctct gaacaagccg agacggggcc 660

gtgccgagca atgatctccc gctggtactt tgatgtgact gaagggaagt gtgccccatt 720

cttttacggc ggatgtggcg gcaaccggaa caactttgac acagaagagt actgcatggc 780

cgtgtgtggc agcgccattc ctacaacagc agccagtacc cctgatgccg ttgacaagta 840

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tgggcagatg acttgagccc agaagttcaa gaccagaatg ggaaacatgg caagaccaca 1500

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tcccccattg aatggtcttg gcactattac acaaaatcaa ttgtccatag ataatatggg 1740

tttatttctt aattcttagt tcttttcttt gatctgtgtg cctgtgctta ctgtagtacc 1800

acactgtttt gattattgta gctttgtagt aaattttgaa atcagc 1846

<210> SEQ ID NO 19
<211> LENGTH: 2517
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 19

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ggtagaagcc aaccaaccag tgaccatcca gaactggtgc aagcggggcc gcaagcagtg 180

caagacccat ccccactttg tgattcccta ccgctgctta gttggtgagt ttgtaagtga 240

tgcccttctc gttcctgaca agtgcaaatt cttacaccag gagaggatgg atgtttgcga 300

aactcatctt cactggcaca ccgtcgccaa agagacatgc agtgagaaga gtaccaactt 360

gcatgactac ggcatgttgc tgccctgcgg aattgacaag ttccgagggg tagagtttgt 420

gtgttgccca ctggctgaag aaagtgacaa tgtggattct gctgatgcgg aggaggatga 480

ctcggatgtc tggtggggcg gagcagacac agactatgca gatgggagtg aagacaaagt 540

agtagaagta gcagaggagg aagaagtggc tgaggtggaa gaagaagaag ccgatgatga 600

cgaggacgat gaggatggtg atgaggtaga ggaagaggct gaggaaccct acgaagaagc 660

cacagagaga accaccagca ttgccaccac caccaccacc accacagagt ctgtggaaga 720

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agcagccaac gagagacagc agctggtgga gacacacatg gccagagtgg aagccatgct 1260

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ggagcgccac ctgtccaaga tgcagcagaa cggctacgaa aatccaacct acaagttctt 2160

tgagcagatg cagaactaga cccccgccac agcagcctct gaagttggac agcaaaacca 2220

ttgcttcact acccatcggt gtccatttat agaataatgt gggaagaaac aaacccgttt 2280

tatgatttac tcattatcgc cttttgacag ctgtgctgta acacaagtag atgcctgaac 2340

ttgaattaat ccacacatca gtaatgtatt ctatctctct ttacattttg gtctctatac 2400

tacattatta atgggttttg tgtactgtaa agaatttagc tgtatcaaac tagtgcatga 2460

atagattctc tcctgattat ttatcacata gccccttagc cagttgtata ttattct 2517

<210> SEQ ID NO 20
<211> LENGTH: 541
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 20

gggcggagca gacacagact atgcagatgg gagtgaagac aaagtagtag aagtagcaga 60

ggaggaagaa gtggctgagg tggaagaaga agaagccgat gatgacgagg acgatgagga 120

tggtgatgag gtagaggaag aggctgagga accctacgaa gaagccacag agagaaccac 180

cagcattgcc accaccacca ccaccaccac agagtctgtg gaagaggtgg ttcgagtgtc 240

ccaaagttta ctcaagacta cccaggaacc tcttgcccga gatcctgtta aacttcctac 300

aacagcagcc agtacccctg atgccgttga caagtatctc gagacacctg gggatgagaa 360

tgaacatgcc catttccaga aagccaaaga gaggcttgag gccaagcacc gagagagaat 420

gtcccaggtc atgagagaat gggaagaggc agaacgtcaa gcaaagaact tgcctaaagc 480

tgataagaag gcagttatcc agcatttcca ggagaaagtg gaatctttgg aacaggaagc 540

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a 541

<210> SEQ ID NO 21
<211> LENGTH: 816
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 21

atccttgcca acctctcaac caggatttaa cttctgcttt tcccccattt tcaaaaatta 60

tagcatgtat ttaaaggcag cagaagcctt actttcaggt ttcccttacc ctttcatttc 120

tttttgttca aaataggtag taattgaagt tttaaatata gggtatcatt tttctttaag 180

agtcatttat caatttttctt ctaacttcag gcctagaaag aagttttggg taggctttgt 240

cttacagtgt tattatttat gagtaaaact aattggttgt cctgcatact ttaattatga 300

tgtaatacag gttctgggtt gacaaatatc aagacggagg agatctctga agtgaagatg 360

gatgcagaat tccgacatga ctcaggatat gaagttcatc atcaaaaatt ggtgttcttt 420

gcagaagatg tgggttcaaa caaaggtgca atcattggac tcatggtggg cggtgttgtc 480

atagcgacag tgatcgtcat caccttggtg atgctgaaga agaaacagta cacatccatt 540

catcatggtg tggtggaggt tgacgccgct gtcaccccag aggagcgcca cctgtccaag 600

atgcagcaga acggctacga aaatccaacc tacaagttct ttgagcagat gcagaactag 660

acccccgcca cagcagcctc tgaagttgga cagcaaaacc attgcttcac tacccatcgg 720

tgtccattta tagaataatg tgggaagaaa caaacccgtt ttatgattta ctcattatcg 780

ccttttgaca gctgtgctgt aacacaagta gatgcc 816

<210> SEQ ID NO 22
<211> LENGTH: 619
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 22

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ctgaggtgga agaagaagaa gccgatgatg acgaggacga tgaggatggt gatgaggtag 120

aggaagaggc tgaggaaccc tacgaagaag ccacagagag aaccaccagc attgccacca 180

ccaccaccac caccacagag tctgtggaag aggtggttcg agaggtgtgc tctgaacaag 240

ccgagacggg gccgtgccga gcaatgatct cccgctggta ctttgatgtg actgaaggga 300

agtgtgcccc attcttttac ggcggatgtg gcggcaaccg gaacaacttt gacacagaag 360

agtactgcat ggccgtgtgt ggcagcgcca tgtcccaaag tttactcaag actacccagg 420

aacctcttgc ccgagatcct gttaaacgta cgttgtcatt cacctgaggg aagggaagag 480

gggaggagga tgctgcttgg ttcacataac tccagcatca tcaccttctt tgcatggttt 540

tgtgtttctt gaacacctgt cttagtaaaa tgtttcttcc cattaccttg cttgtaatta 600

catctgattt tgccagaca 619

<210> SEQ ID NO 23
<211> LENGTH: 1309
<212> TYPE: DNA

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<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 23

cgagagcacg cggaggagcg tgcgcggggg ccccgggaga cggcggcggt ggcggcgcgg 60

gcagagcaag gacgcggcgg atcccactcg cacagcagcg cactcggtgc cccgcgcagg 120

gtcgcgatgc tgcccggttt ggcactgctc ctgctggccg cctggacggc tcgggcgctg 180

gaggtaccca ctgatggtaa tgctggcctg ctggctgaac cccagattgc catgttctgt 240

ggcagactga acatgcacat gaatgtccag aatgggaagt gggattcaga tccatcaggg 300

accaaaacct gcattgatac caaggaaggc atcctgcagt attgccaaga agtctaccct 360

gaactgcaga tcaccaatgt ggtagaagcc aaccaaccag tgaccatcca gaactggtgc 420

aagcggggcc gcaagcagtg caagacccat ccccactttg tgattcccta ccgctgctta 480

gttggtgagt ttgtaagtga tgcccttctc gttcctgaca agtgcaaatt cttacaccag 540

gagaggatgg atgtttgcga aactcatctt cactggcaca ccgtcgccaa agagacatgc 600

agtgagaaga gtaccaactt gcatgactac ggcatgttgc tgccctgcgg aattgacaag 660

ttccgagggg tagagtttgt gtgttgccca ctggctgaag aaagtgacaa tgtggattct 720

gctgatgcgg aggaggatga ctcggatgtc tggtggggcg gagcagacac agactatgca 780

gatgggagtg aagacaaagt agtagaagta gcagaggagg aagaagtggc tgaggtggaa 840

gaagaagaag ccgatgatga cgaggacgat gaggatggtg atgaggtaga ggaagaggct 900

gaggaaccct acgaagaagc cacagagaga accaccagca ttgccaccac caccaccacc 960

accacagagt ctgtggaaga ggtggttcga gagaagtggt ataaggaagt acattctggc 1020

caggcacgat ggctcatgct gtaatcccag cactttggga ggccgaggtg ggtgcatcac 1080

ctgaggtcag gagtttgaga ccagcctggc caacatggtg aaacccctcg ctactaaaaa 1140

tacaaaaatt agccgggcgt ggtggcacac acctgtggtc ccagctactc gggaggctga 1200

agcaggagaa tcgcttgaac ccgggagacg gaggttgcag taagccgagt tcactccatt 1260

gtactctagc ctgggtgaca gagcgagatt cgtctcaaaa aaaaaaaaa 1309

<210> SEQ ID NO 24
<211> LENGTH: 582
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 24

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acttgtcttg aagtctatct ttccttgatg tcttctgcgg taagaacact gtgatacaga 120

tggaatgacg ggaagtggtt ttcctttctt tcagttggtg agtttgtaag tgatgccctt 180

ctcgttcctg acaagtgcaa attcttacac caggagagga tggatgtttg cgaaactcat 240

cttcactggc acaccgtcgc caaagagaca tgcagtgaga agagtaccaa cttgcatgac 300

tacggcatgt tgctgccctg cggaattgac aagttccgag gggtagagtt tgtgtgttgc 360

ccactggctg aagaaagtga caatgtggat tctgctgatg cggaggagga tgactcggat 420

gtctggtggg gcggagcaga cacagactat gcagatggga gtgaagacaa agtagtagaa 480

gtagcagagg aggaagaagt ggctgaggtg gaagaagaag aagccgatga tgacgaggac 540

gatgaggatg gtgatgaggt agaggaagag gctgaggaac cc 582

<210> SEQ ID NO 25
<211> LENGTH: 361
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 25

actggagggc tgagaagaga ctgatggcat ttgttgttct tgaccttgaa agaagagttg 60

cagattgttg gagcaaggcc agatggtaat aggttggaaa gaacaagtga ggggcgtgag 120

agtgacagtc tacaaccccg ttaagaagtt atctgtgaaa atgcctcttc ctgtcttgat 180

tatagcctcc ctcgcacatg gctttctgag tatgttggtg agtttgtaag tgatgccctt 240

ctcgttcctg acaagtgcaa attcttacac caggagagga tggatgtttg cgaaactcat 300

cttcactggc acaccgtcgc caaagagaca tgcagtgaga agagtaccaa cttgcatgac 360

t 361

<210> SEQ ID NO 26
<211> LENGTH: 667
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 26

ctgaacatgc acatgaatgt ccagaatggg aagtgggatt cagatccatc agggaccaaa 60

acctgcattg ataccaagga aggcatcctg cagtattgcc aagaagtcta ccctgaactg 120

cagatcacca atgtggtaga agccaaccaa ccagtgacca tccagaactg gtgcaagcgg 180

ggccgcaagc agtgcaagac ccatccccac tttgtgattc cctaccgctg cttaggtgag 240

ccggccggcc gtggggctgg tgttgattgg gggcctggtc ttgagggaag aaaaagagga 300

tgctcctgtt aggtcacata cacagacttg ttcttcagca cattgccact ctgtgttgta 360

ctgtgttttg gactcttgca gttacattct gtgcactgac cctataggag cagtattttt 420

gagttccctg cctcagaatg aatttaccca gggtgtatat tgaaattaca aattcctggg 480

ccagttccag gactcctgaa tgaaaaatgc ctatagtagc ggatccggga attcttattt 540

taccgtatcg catagatgat tctcatgaac aggggccttg tgtgtttctt cacatagact 600

ttctagaaga aagaatctaa tgtgaagctg cagcattttg ttaatttcta aaaaaaaaaa 660

aaaaaaa 667

<210> SEQ ID NO 27
<211> LENGTH: 374
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of sequence: amyloid precursor protein coding sequence

<400> SEQUENCE: 27

ggcgcggcct cttccctggc agctctgggg actctggttt agttcccctg ggggcacagg 60

atgctgggga gggtccgaag ggtctttttt ttagggtgca gataaaagga tcgaattgag 120

tgaagattaa gacggagaag atggcgcctc tgcagtgcag caaagaaaag ctgtgtggag 180

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gctgcagcct agtgaaatcc acccaccact aggtacccac tgatggtaat gctggcctgc 240

tggctgaacc ccagattgcc atgttctgtg gcagactgaa catgcacatg aatgtccaga 300

atgggaagtg ggattcagat ccatcaggga ccaaaacctg cattgatacc aaggaaggca 360

tcctgcagta ttgc 374

What is claimed is:

1. A method for diagnosing biliary atresia (BA) or assessing risk of developing BA in an infant, comprising:

(i) determining expression level of amyloid precursor protein (APP) in a liver sample taken from the infant;

(ii) detecting an increase in the APP expression level from step (i) when compared with a standard control value; and

(iii) determining the infant as having BA or at risk of developing BA.

2. The method of claim **1**, wherein the APP expression level is APP mRNA level.

3. The method of claim **1**, wherein the APP expression level is APP protein level.

4. The method of claim **2**, wherein step (i) comprises a reverse transcription polymerase chain reaction (RT-PCR).

5. The method of claim **3**, wherein step (i) comprises an immunoassay.

6. The method of claim **1**, wherein the liver sample is a liver biopsy.

7. The method of claim **1**, further comprising a step, following step (iii), of performing at least one additional diagnostic test for BA.

8. The method of claim **7**, further comprising a step, following step (iii), of treating the infant with Kasai procedure.

9. A method for assessing effectiveness of Kasai procedure in an infant who has BA and has undergone Kasai procedure, comprising:

(i) determining expression level of amyloid precursor protein (APP) in a liver sample taken from the infant;

(ii) detecting an increase in the APP expression level from step (i) when compared with a standard control value; and

(iii) determining the Kasai procedure as ineffective.

10. The method of claim **9**, wherein the APP expression level is APP mRNA level.

11. The method of claim **9**, wherein the APP expression level is APP protein level.

12. The method of claim **10**, wherein step (i) comprises an RT-PCR.

13. The method of claim **11**, wherein step (i) comprises an immunoassay.

14. The method of claim **9**, wherein the liver sample is a liver biopsy.

15. The method of claim **9**, further comprising a step, following step (iii), of performing liver transplant.

* * * * *