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Original article

In-silico analysis of phylogenetic relationship and potentially damaging nsSNPs in human SLC2A2 gene

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ABSTRACT

Transport of glucose across the eukaryotic cell membranes is carried out by members of the glucose transporter (GLUT) family which is mainly divided into three classes (I, II and III) on the basis of phylogenetic relationship. In humans, one member of Class I called GLUT2 is encoded by solute carrier family 2, facilitated glucose transporter member 2 (SLC2A2) gene located on third chromosome. Protein mediated glucose movement across cell membranes is made possible through GLUT2 that is a *trans*-membrane carrier protein. It regulates the entry of glucose and secretion of insulin in the pancreatic cell. It has three isoforms and the longest isoform consists of 524 amino acid. There are 13 extracellular, 12 transmembrane and 5 cytoplasmic domains in human GLUT2. The risk of Fanconi-Bickel syndrome (FBS), diabetes, breast cancer (BC) and Alzheimer disease (AD) is associated with improper functioning of GLUT2. The most frequent form of genetic changes is single nucleotide polymorphism (SNPs). Non synonymous SNPs (nsSNPs) can result in alterations of amino acids and subsequent changes in phenotype. In this study, *in-silico* analysis was done to find phylogenetic relationship of human GLUT2 protein and possible deleterious effect of nsSNPs of its coding region. Clustal Omega was used to make phylogenetic tree. SIFT, PolyPhen, PROVEAN and SNPeffect were used to predict deleterious or tolerated SNPs. 167 nsSNPs were predicted to be damaging by SIFT, 65 to be possibly damaging and 77 to be probably damaging by PolyPhen. PROVEAN predicted 162 nsSNPs to be neutral and 138 to be deleterious. 101 SNPs were found to be damaging by three algorithms; SIFT, PolyPhen and PROVEAN.

1. Introduction

Glucose is a major energy source and is an important substrate for both protein and lipid synthesis in mammalian cells. Through glycolysis and the citric acid cycle it supplies energy in the form of adenosine tri phosphate (ATP). In the form of nicotinamide adenine dinucleotide phosphate (NADPH), it provides reducing power through the pentose phosphate shunt. Glucose plays a vital role in retaining cellular homeostasis and metabolic functions. For generating ATP molecules, every vertebrate cell depends on the continuous delivery of glucose (Cant et al., 2002). Glucose transport across the plasma membranes is done by two distinct processes depending on the type of cells and tissues. First is facilitative transport that is interceded by a group of facilitative glucose transporters (GLUT) (Mueckler, 1994; Joost and Thorens, 2001) and the other is sodium dependent transport that is interceded by the Na+/glucose linked transporters (SGLT) (Wright, 2001).

GLUTs are proteins of ~500 amino acids and are estimated to have 12 transmembrane-spanning alpha helices and a single N-linked oligosaccharide. Based on the phylogenetic analysis and sequence similarities 14 members of GLUT family can be divided into three different classes; Class I, II and III (Thorens and Mueckler, 2010; Joost et al., 2002). Class I includes GLUT 1, 2, 3, 4 and 14, class II includes GLUT 5, 7, 9 and 11 while GLUT 6, 8, 10, 12 and 13 are classified as class III (Manolescu et al., 2007). In humans the solute carrier family 2 (facilitated glucose transporter), member 2 (SLC2A2) gene is located on q26.2 of chromo-

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some 3 (Fig. 1) which encodes GLUT2 protein. There are three isoforms of GLUT2; NP_000331.1, NP_001265587.1 and NP_001265588.1.

The GLUT2 is a transmembrane carrier protein and it permits protein facilitated glucose movement across cell membranes. GLUT2 is involved in discharge of absorbed or reabsorbed glucose and is mainly expressed in the kidney and intestinal absorptive epithelial cells of basolateral membrane (Wright et al., 2003; Kellett and Brot-Laroche, 2005). GLUT2 is also present in the liver, brain and pancreas. It serves as major glucose transporter for the islet cells. As GLUT2 is a high capacity transporter, the concentration of glucose in the cell is directly proportional to the extracellular level of glucose. Enhanced level of intracellular glucose is supposed to increase the ATP/ADP ratio which will shut ATP sensitive potassium channels, depolarize the cells and secrete insulin (Schuit et al., 2001).

In hepatocytes, as a result of gluconeogenesis, GLUT2 supports the uptake of glucose into the blood. It also yields insulin secretion as glucose-sensing functions in the pancreatic β-cell and hypothalamus as low level of glucose stimulated insulin was described in GLUT2 knockout mice (Guillam et al., 1997; Burcelin et al., 2001; Bady et al., 2006). In β-cells of pancreatic islets and hepatocytes, the major glucose transporter is GLUT2. In both cell types, GLUT2 helps the facilitated diffusion of glucose across the cell membranes, and then intracellular glucose metabolism is initiated by the glucose-phosphorylating enzyme, hexokinase IV or glucokinase. In the β-cells, the rate of glucose metabolism controls insulin secretion, whereas in the liver, glucose metabolism and transport are essential to subsequent glycogen synthesis and gluconeogenesis (Meglasson et al., 1986; Thorens et al., 1988).

Fanconi Bickel Syndrome (FBS) is an autosomal recessive disease of glucose metabolism characterized by accumulation of hepatorenal glycogen, Fanconi nephropathy, and impaired use of glucose and galactose (Fanconi, 1949; Santer et al., 1998). The risk of diabetes has been found to be associated with SNPs of SLC2A2 gene in some (Barroso et al., 2003; Alcolado and Alcolado, 1991) but not in other studies (Matsutani et al.,1990). Globally, breast cancer (BC) is the most frequent cancer among women (Ilahi et al., 2016; Noreen et al., 2015a, 2015b). One way to stimulate growth of cancer cells may be fructose metabolism and the expression of GLUT5 and GLUT2 in BC is elevated and helpful in fructose metabolism (Godoy et al., 2006). The increased level of GLUT2 was observed in patients of Alzheimer disease (AD) (Liu et al., 2008).

Diseases susceptibility and development is affected by presence of genetic variations, one very common type of which is single nucleotide polymorphism or SNPs. In DNA, SNPs are found in both exonic and intronic regions (Noreen et al. 2012). Non synonymous SNPs (nsSNPs) residing in exonic region of protein involve amino acid substitution which can result in alteration of structure and functioning of the protein. Thus nsSNPs can play more significant role in diseases development. In this study we predicted the structural and functional effect of potential genetic variations of human SLC2A2 gene by using some sequence and structural homology based algorithms.

2. Materials and methods

2.1. Dataset compilation

National centre for biological information; NCBI (http://www.ncbi. nlm.nih.gov) was accessed. Protein and nucleotide sequences were acquired in FASTA format. Public SNP database named as dbSNP (http://www. ncbi.nlm.nih.gov/SNP), Gene Cards (http://www.genecards.org/) and UniProt (http://www.uniprot.org) were searched to assemble information related to longest isoform of GLUT2 regarding protein sequence. (GLUT2 gene ID: 6514 SNPs NCBI Reference Sequence: NP_000331). The coding region nsSNPs were screened and were subjected to further computational analysis.

2.2. Phylogenetic analysis

To carry out phylogenetic analysis, protein sequence of human GLUT2 (GenBank Accession Number: NP 000331.1) along other 9 species of Hominidae family; *Gorilla gorillagorilla* (XP_004038053.1), *Pongo abelli* (XP_002814322.1), *Rhinopithecus roxellana* (XP_010359570.1), *Microcebus murinus* (XP_012591846.1), *Bos taurus* (DAA33241.1), *Myotis brandtii* (XP_005886638.1), *Neomonachus schauinsland* (XP_021558267.1), *Galeopterus variegates* (XP_008586350.1) and *Ailuropoda melanoleuca* (XP_002920886.1) were retrieved from the NCBI. Protein sequence in FASTA format of all 10 species was obtained and saved. Protein sequence alignment was performed using Clustal Omega (https://www.ebi.ac.uk/Tools/msa/clustalo/). In Clustal Omega, output format "ClustalW with charater counts" was chosen and option of phylogenetic tree was clicked.

2.3. Membrane topology

The number of machine learning algorithms wre used to align the set of protein sequences and clustering of topological data. These approaches or algorithms are transmembrane helices prediction (PHDhtm) (Rost et al. 1996), statistical algorithm TMAP (Persson and Argos 1994) and Hidden Markov models (HMMs) (HMMTOP (Tusnady and Simon, 1998, 2001); TMHMM (Sonnhammer et al., 1998; Krogh et al., 2001). The membrane topology of GLUT2 protein was predicted with the TMHMM program, server 2.0 (http://www.cbs.dtu.dk/services/TMHMM-2.0/).

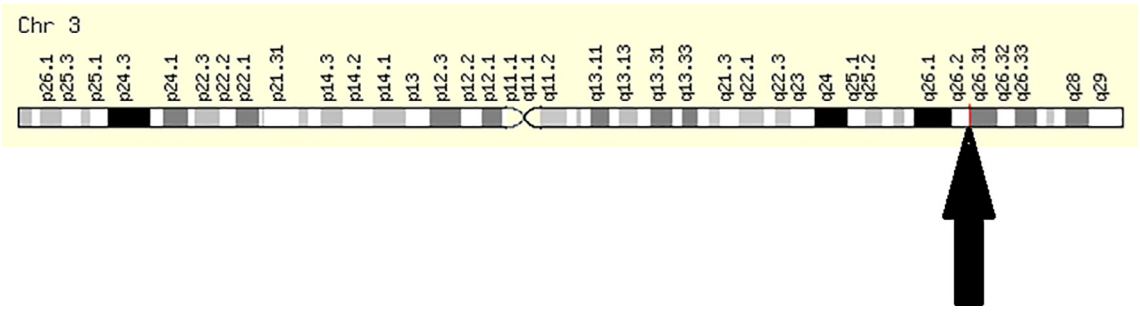

Fig. 1. Location of GLUT2 on human chromosome. Arrow head shows that GLUT2 occupies 3q26.2 on third human chromosome. (https://www.genecards.org/cgi-bin/carddisp.pl?gene=SLC2A2).

2.4. Analysis of nsSNPs by SIFT

Sorting Intolerant from Tolerant (SIFT) is an algorithm that forecasts whether substitution of an amino acid influences protein function or not. It is based on the principle that essential amino acids in a protein family remain conserved, and any replacement at these positions is deleterious, which influences function/activity of protein. Protein sequence in FASTA format along substitution of amino acids was used as input at (http://www.blocks.fhcrc.org/sift/SIFT.html). It then considered the normalized probability for the provided substitution at the related position in the alignment. Substitutions with the normalized probability i.e. Tolerance Index (TI) less than 0.05 were forecasted to be intolerant or harmful whereas substitutions with TI higher than 0.05 were predicted to be tolerant (Adzhubei et al., 2010).

2.5. Analysis of nsSNPs by using PolyPhen

PolyPhen-2 is a tool for forecasting of the feasible impact of an amino acid substitution on the protein structure and function (Adzhubei et al., 2010). Automated divinations of this type are vital for interpreting rare genetic variants, which may have potential approach in recent research of human genetics. Its importance in modern research involves identification of rare alleles that generate Mendelian disease (Bamshad et al., 2011), scanning for medically important alleles in an individual's genome (Ashley *et al*., 2010), and profiling the spectrum of rare variation uncovered by deep sequencing of large populations (Tennessen et al., 2012).

PolyPhen (http://genetics.bwh.harvard.edu/pph2) utilizes UniProtKB database which is used as source of reference. Protein sequence of GLUT2 in FASTA format and position of protein sequence was entered. AA1 wild type (query sequence) as well as substitution reside AA2 were selected. Two pair's datasets were used. First pair of HumDiv and the second pair; HumVar were compiled in UniProt database.

2.6. Analysis of nsSNPs by using PROVEAN

PROVEAN is not only effective to predict single amino acid change but it can also perform task for other changes in the protein sequence including indels (deletion and insertion) (Choi et al., 2012). The PROVEAN web server (http://provean.jcvi.org) gives online approach for the functioning of distribution for the software package of stand-alone. Its major role is to give divination from any of organism's protein sequence. It takes the sequence of protein and variation of amino acid as input. BLAST search was done to recognize the homologous sequence and produce the PROVEAN result. Generally the BLAST search took 10–20 min to produce the divination for a provided protein query. Sequence identifiers list for supporting sequences and clustering data was stored in database. Focused on sequence of query protein consecutive prediction data for supporting sequences were indexed.

2.7. Analysis of nsSNPs by using SNPeffect

SNPeffect (De Baets et al., 2012) was used to predict the molecular phenotypic influence of nsSNPs lying in coding region of GLUT2 protein. It works beyond the scores got on conservational basis and mainly emphasizes to map the effect of SNPs on the capability of cells to uphold suitable concentration of the properly folded proteins in appropriate cellular region i.e. protein homeostasis landscape (Powers et al., 2009). For this assessment, wild type protein sequence in FASTA format along with each of its variants was given to the SNPeffect server (http://snpeffect.switchlab.org) for analysis. Homology threshold was fixed to 90%. It uses TANGO (Fernandez-Escamilla et al., 2004) which forecasts the regions in given protein sequence that are prone to aggregation and calculated TANGO score with wild and variant amino acid. On the basis of TANGO score difference (dTANGO), the server assesses effect of these variants on protein aggregation. Aggregate morphology is more distinctively evaluated by WALTZ server (Maurer-Stroh et al., 2010) that forecasts amyloid-forming regions in given protein sequence with accuracy and specificity on basis of dWALTZ score. Chaperone binding propensity is forecasted by LIMBO (Van Durme et al., 2009) for the Hsp70 chaperones and effect of variant is determined by dLIMBO score. SNPeffect also uses high resolution crystal structure of proteins from Protein Data Bank (PDB) (Deshpande et al., 2005) and models the variants using the empirical force field FoldX (version 2.5) (Schymkowitz et al., 2005) to determine possible effects on stability and binding properties of given protein.

3. Results

3.1. Phylogenetic analysis

Evolutionary relationship of GLUT2 protein among 10 different species of primates was carried out using human GLUT2 protein as a reference sequence (Fig. 2). The phylogenetic tree generated from Clustal Omega helps to understand the evolutionary relationship of GLUT2 among different species. Evolutionary tree demonstrates that GLUT2 of human and *Pongo abelli* lie close to each other whereas that of *Bos taurus*is most distant from human.

3.2. Membrane topology

A significant server TMHMM was used to predict the significant features of helices in transmembrane protein and GLUT2 was found to comprise of 12 predicted transmembrane helices with intracellular amino (N-terminal) and carboxyl (C-termini) in cytosol. It also contains extracellular and intracellular loops which are located between the segments of 1st and 2nd transmembrane domains and between 6th and 7th transmembrane segments (Fig. 3). While, the remaining transmembrane segments from seven to twelve have ability to perform transportation of fructose and glucose to the membrane.

3.3. Distribution of SNPs in GLUT2 protein

In the human SLC2A2 gene the non coding region of gene contains 6,628 SNPs in which 83 SNPs were near 3′gene, 340 in 3′UTR, 427 SNPs in 5′ near gene, 62 in 5′UTR and in the intron 5716 SNPs were found (Fig. 4). While the coding region contained 484 SNPs in which 137 SNPs were synonymous, 293 were nsSNPs, 21 were frameshifts; (rs766082034), (rs1447936042), (rs769888108), (rs1255595607), (rs776307487), (rs1162215911), (rs771361095), (rs1326032349), (rs1350704340), (rs1290975016), (rs765132996), (rs1181030797), (rs771799491), (rs746178753), (rs1316522125), (rs748296868), (rs34066960), (rs1174349159), (rs1384674663),(rs1386374799) and (rs1290412048). 11 were

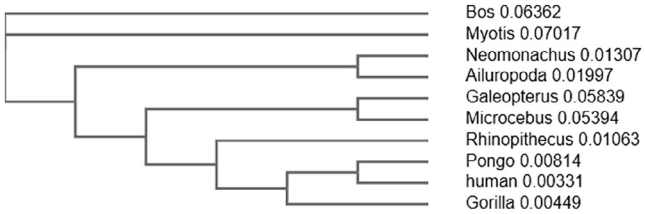

Fig. 2. Phylogenetic analysis of human GLUT2 protein. A phylogenetic tree of the amino acid sequences of GLUT2 protein was constructed using the Clustal Omega.

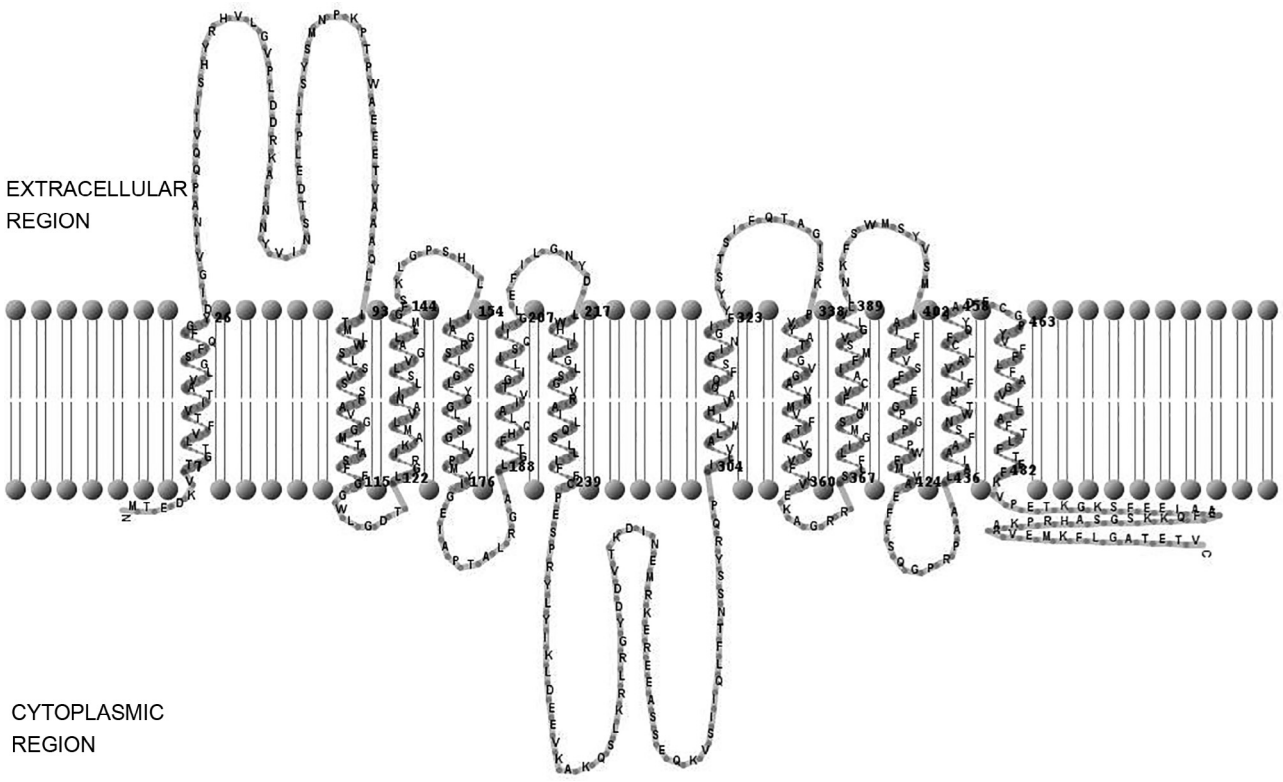

Fig. 3. Toplogy prediction of human GLUT2 protein. The human GLUT2 protein comprises of 12 predicted transmembrane helices with intracellular amino (N-terminal) and carboxyl (C-termini) in cytosol. It also contains extracellular and intracellular loops which are located between the segments of 1st and 2nd transmembrane domains and between 6th and 7th transmembrane segments.

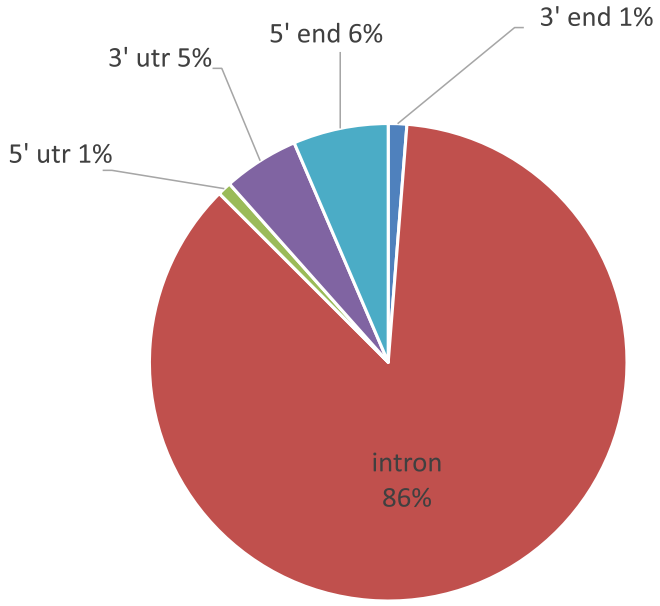

Fig. 4. Distribution of SNPs in human GLUT2 Protein.

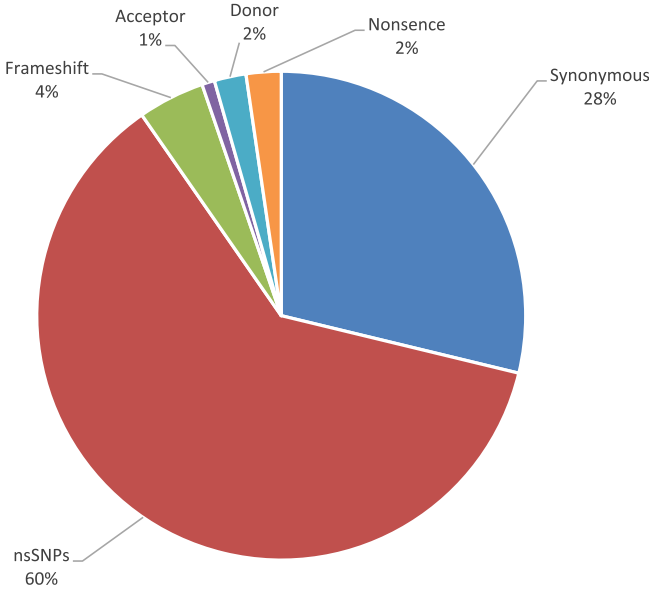

Fig. 5. Distribution of nsSNPs in coding region of GLUT2 protein.

nonsense; (rs774841662), (rs771477447), (rs1475086161), (rs1114167428), (rs753629940), (rs773581866), (rs121909746), (rs121909743), (rs121909742), (rs121909745) and (rs1379944645). Out of 7 SNPs, 4 were inframe deletion; (rs772999215), (rs1169887677), (rs763620441), (rs774721090) and 3 were inframe insertion; (rs1161394690), (rs1463507753) and (rs749789723). 10 (rs1294679246), (rs756163471), (rs371977235), (rs1240053337), (rs756874949), (rs1303795800), (rs1281471314), (rs985090030), (rs757587931), (rs867530965) were donor and 4 (rs754220999), (rs1318756243), (rs776248984), (rs1230247311) were acceptor shown (Fig. 5). (rs749789723) SNPs also contain stop gained. 1 SNPs was stop lost

Table 1
nsSNPs lying in the coding region of human GLUT2.

dbSNP id	Function	dbSNPallele	Codonpos.	mRNApos.	Proteinresidue	Amino acidpos
rs759495940	nsSNPs	G /A	3	312	Met [M]/Ile [I]	1
rs773205789	nsSNPs	A /C	1	313	Thr [T]/Pro [P]	2
rs200073044	nsSNPs	G /C	1	319	Asp [D]/His [H]	4
rs1372689853	nsSNPs	A /G	1	322	Lys [K]/Glu [E]	5
rs767313610	nsSNPs	G /A	1	325	Val [V]/Ile [I]	6
rs369700669	nsSNPs	C /A	2	329	Thr [T]/Asn [N]	7
rs766082034	frame shift	G /-	3	333	Thr [T]/Pro [P]	9
rs766082034	frameshift	G/-	3	333	(Gly)G/(Gly)G	9
rs1181030797	frame shift	G /-	1	340	Val [V]/Phe [F]	11
rs1481905618	nsSNPs	C /A	3	345	Phe [F]/Leu [L]	12
rs1247912820	nsSNPs	C /A	2	347	Thr [T]/Asn [N]	13
rs1247912820	nsSNPs	C /G	2	347	Thr [T]/Ser [S]	13
rs372441014	nsSNPs	G /C	1	349	Val [V]/Leu [L]	14
rs766364438	nsSNPs	T /C	2	353	Ile [I]/Thr [T]	15
rs1463507753	INFRAME INSERTION	TCA	1	355	Ile[I] /IleIle[II]	15
rs867315854	nsSNPs	G /A	1	358	Ala [A]/Thr [T]	17
rs761992056	nsSNPs	G /A	2	368	Gly [G]/Asp [D]	20
rs369781481	nsSNPs	C /A	3	375	Phe [F]/Leu [L]	22
rs1409436045	nsSNPs	T /A	2	380	Phe [F]/Tyr [Y]	24
rs1049223265	nsSNPs	T /C	2	392	Ile [I]/Thr [T]	28
rs1437312005	nsSNPs	G /A	1	394	Gly [G]/Ser [S]	29
rs1437312005	nsSNPs	G /C	1	394	Gly [G]/Arg [R]	29
rs775531825	nsSNPs	A /G	2	404	Asn [N]/Ser [S]	32
rs143528640	nsSNPs	G /A	1	406	Ala [A]/Thr [T]	33
rs746158263	nsSNPs	C /A	1	409	Pro [P]/Thr [T]	34
rs774841662	nonsense	C/ T	1	412	Gln [Q]/	35
rs1158195535	nsSNPs	C /A	1	415	Gln [Q]/Lys [K]	36
rs1158195535	nsSNPs	C /G	1	415	Gln [Q]/Glu [E]	36
rs1451394300	nsSNPs	G /A	1	418	Val [V]/Ile [I]	37
rs1477523180	nsSNPs	A /C	1	421	Ile [I]/Leu [L]	38
rs1360464436	nsSNPs	T /A	2	422	Ile [I]/Lys [K]	38
rs1176350402	nsSNPs	T /C	2	425	Ile [I]/Thr [T]	39
rs772999215	Inframe Deletion	II [ATA] > I []	1	424	IleIle[II] / Ile [I]	39
rs758670698	nsSNPs	G /T	2	437	Arg [R]/Ile [I]	43
rs760618624	nsSNPs	C /T	1	439	His [H]/Tyr [Y]	44
rs775791143	nsSNPs	G /A	1	442	Val [V]/Ile [I]	45
rs149108283	nsSNPs	T /A	2	443	Val [V]/Asp [D]	45
rs149108283	nsSNPs	T /C	2	443	Val [V]/Ala [A]	45
rs1159338702	nsSNPs	G /A	1	448	Gly [G]/Ser [S]	47
rs561765982	nsSNPs	G /A	1	451	Val [V]/Ile [I]	48
rs983907950	nsSNPs	C /T	1	454	Pro [P]/Ser [S]	49
rs1211075508	nsSNPs	T /C	2	458	Leu [L]/Pro [P]	50
rs1311902495	nsSNPs	G /A	1	463	Asp [D]/Asn [N]	52
rs1311902495	nsSNPs	G /T	1	463	Asp [D]/Tyr [Y]	52
rs771477447	nonsense	C /T	1	466	Arg [R]/	53
rs771477447	nsSNPs	C /G	1	466	Arg [R]/Gly [G]	53
rs145210664	nsSNPs	G /A	2	467	Arg [R]/Gln [Q]	53
rs546539032	nsSNPs	A /C	3	471	Lys [K]/Asn [N]	54
rs747555903	nsSNPs	G /A	1	487	Val [V]/Ile [I]	60
rs1447936042	frame shift	- /(26 bp)	1	490	Ile [I]/Thr [T]	61
rs977284195	nsSNPs	T /C	2	491	Ile [I]/Thr [T]	61
rs780903829	nsSNPs	C /G	3	492	Ile [I]/Met [M]	61
rs1373290524	nsSNPs	G /C	2	497	Ser [S]/Thr [T]	63
rs1310901426	nsSNPs	A /G	1	499	Thr [T]/Ala [A]	64
rs1169887677	Inframe Deletion	INS [ATCA] / [ACA]	2	491	INS (IleAsnSer) / ()	61
rs1354126805	nsSNPs	C /G	2	500	Thr [T]/Arg [R]	64
rs754585542	nsSNPs	G /A	1	502	Asp [D]/Asn [N]	65
rs1217666649	nsSNPs	T /A	3	504	Asp [D]/Glu [E]	65
rs1391257598	nsSNPs	C /A	1	511	Pro [P]/Thr [T]	68
rs7637863	nsSNPs	C /T	2	512	Pro [P]/Leu [L]	68
rs779977931	nsSNPs	C /A	2	515	Thr [T]/Lys [K]	69
rs1182852354	nsSNPs	A /G	1	517	Ile [I]/Val [V]	70
rs750405382	nsSNPs	A /G	1	529	Met [M]/Val [V]	74
rs1207297111	nsSNPs	A /G	1	532	Asn [N]/Asp [D]	75
rs1342979475	nsSNPs	A /C	2	533	Asn [N]/Thr [T]	75
rs1274084408	nsSNPs	C /G	1	535	Pro [P]/Ala [A]	76
rs778655073	nsSNPs	C /T	2	542	Pro [P]/Leu [L]	78
rs769888108	frame shift	C /-	2	548	Pro [P]/Leu [L]	80
rs549263048	nsSNPs	T /C	1	550	Trp [W]/Arg [R]	81
rs531049536	nsSNPs	G /T	3	552	Trp [W]/Cys [C]	81
rs150851401	nsSNPs	G /A	1	556	Glu [E]/Lys [K]	83
rs766762468	nsSNPs	C /G	2	566	Thr [T]/Ser [S]	86
rs766762468	nsSNPs	C/T	2	566	T (Thr) > I (Ile)	86
rs763255363	nsSNPs	G /T	1	571	Ala [A]/Ser [S]	88

(*continued on next page*)

Table 1 (*continued*)

dbSNP id	Function	dbSNPallele	Codonpos.	mRNApos.	Proteinresidue	Amino acidpos
rs144715667	nsSNPs	A /G	1	586	Ile [I]/Val [V]	93
rs1415169647	nsSNPs	T /G	2	593	Met [M]/Arg [R]	95
rs1407375423	nsSNPs	G /T	3	600	Trp [W]/Cys [C]	97
rs1800572	nsSNPs	G /A	1	610	Val [V]/Ile [I]	101
rs1800572	nsSNPs	G/C	1	610	Val [V] / Leu [L]	101
rs770135219	nsSNPs	T /C	2	611	Val [V]/Ala [A]	101
rs1399091893	nsSNPs	C /T	2	623	Ala [A]/Val [V]	105
rs1332764085	nsSNPs	G /A	1	625	Val [V]/Ile [I]	106
rs5400	nsSNPs	C /T	2	638	Thr [T]/Ile [I]	110
rs377238940	nsSNPs	G /C	1	640	Ala [A]/Pro [P]	111
rs1475086161	nonsense	C /G	2	644	Ser [S]/	112
rs1255595607	frame shift	C /-	3	648	Phe [F]/Leu [L]	114
rs1255595607	frame shift	C /-	3	648	Phe [F]/ Phe [F]	114
rs768407637	nsSNPs	G /T	2	656	Gly [G]/Val [V]	116
rs753980727	nsSNPs	G /T	3	660	Trp [W]/Cys [C]	117
rs746632604	nsSNPs	G /C	2	665	Gly [G]/Ala [A]	119
rs772002572	nsSNPs	C /T	2	671	Thr [T]/Ile [I]	121
rs1476520648	nsSNPs	T /A	2	683	Ile [I]/Asn [N]	125
rs760201098	nsSNPs	C /A	2	689	Ala [A]/Asp [D]	127
rs1267904495	nsSNPs	T /C	2	692	Met [M]/Thr [T]	128
rs1212980167	nsSNPs	G /C	3	693	Met [M]/Ile [I]	128
rs367856967	nsSNPs	T /C	2	698	Val [V]/Ala [A]	130
rs970550665	nsSNPs	C /G	2	701	Ala [A]/Gly [G]	131
rs775283150	nsSNPs	A /T	1	706	Ile [I]/Phe [F]	133
rs913419413	nsSNPs	T /G	2	710	Leu [L]/Arg [R]	134
rs771843187	nsSNPs	T /C	1	712	Ser [S]/Pro [P]	135
rs144125084	nsSNPs	G /C	1	718	Val [V]/Leu [L]	137
rs993833041	nsSNPs	T /C	2	719	Val [V]/Ala [A]	137
rs1300072764	nsSNPs	G /A	2	722	Gly [G]/Glu [E]	138
rs778548964	nsSNPs	C /T	1	727	Leu [L]/Phe [F]	140
rs776307487	frame shift	T /-	2	728	Leu [L]/Pro [P]	140
rs1016384738	nsSNPs	T /A	2	734	Met [M]/Lys [K]	142
rs770941010	nsSNPs	G /C	1	736	Gly [G]/Arg [R]	143
rs777718289	nsSNPs	G /A	2	752	Gly [G]/Glu [E]	148
rs777718289	nsSNPs	G /T	2	752	Gly [G]/Val [V]	148
rs372621339	nsSNPs	C /G	2	755	Pro [P]/Arg [R]	149
rs747025551	nsSNPs	T /C	2	764	Ile [I]/Thr [T]	152
rs376064965	nsSNPs	C /T	1	766	Leu [L]/Phe [F]	153
rs1188886679	nsSNPs	A /C	1	769	Ile [I]/Leu [L]	154
rs1188886679	nsSNPs	A /G	1	769	Ile [I]/Val [V]	154
rs192720796	nsSNPs	T /A	2	770	Ile [I]/Lys [K]	154
rs763620441	INFRAME DELETION	ILI [CTTATA] / I []	1	766	IleLeuIle [ILI] / Ile [I]	153
rs910976682	nsSNPs	C /T	2	776	Ala [A]/Val [V]	156
rs750836049	nsSNPs	G /C	1	778	Gly [G]/Arg [R]	157
rs1278964539	nsSNPs	G /A	2	782	Arg [R]/Lys [K]	158
rs1231468128	nsSNPs	T /A	2	797	Leu [L]/Gln [Q]	163
rs1445887606	nsSNPs	T /C	1	799	Tyr [Y]/His [H]	164
rs1271546287	nsSNPs	T /C	2	812	Ile [I]/Thr [T]	168
rs760095835	nsSNPs	G /A	2	818	Gly [G]/Asp [D]	170
rs1335888503	nsSNPs	G /C	1	823	Val [V]/Leu [L]	172
rs1293130515	nsSNPs	T /C	2	830	Met [M]/Thr [T]	174
rs1019696977	nsSNPs	A /G	1	835	Ile [I]/Val [V]	176
rs144822218	nsSNPs	G /A	1	838	Gly [G]/Ser [S]	177
rs759047405	nsSNPs	G /A	2	839	Gly [G]/Asp [D]	177
rs1441606652	nsSNPs	C /T	2	848	Ala [A]/Val [V]	180
rs368626129	nsSNPs	G /A	1	856	Ala [A]/Thr [T]	183
rs368626129	nsSNPs	G /T	1	856	Ala [A]/Ser [S]	183
rs771799491	frame shift	G /-	2	866	Gly [G]/Glu [E]	186
rs200213178	nsSNPs	G /A	1	868	Ala [A]/Thr [T]	187
rs200213178	nsSNPs	G /C	1	868	Ala [A]/Pro [P]	187
rs748052042	nsSNPs	C /T	1	871	Leu [L]/Phe [F]	188
rs1412289847	nsSNPs	G /A	1	874	Gly [G]/Ser [S]	189
rs776498787	nsSNPs	G /A	2	875	Gly [G]/Asp [D]	189
rs779065938	nsSNPs	C /G	1	889	Leu [L]/Val [V]	194
rs1469335096	nsSNPs	G /A	1	892	Ala [A]/Thr [T]	195
rs771182536	nsSNPs	T /A	2	896	Ile [I]/Asn [N]	196
rs771182536	nsSNPs	T /C	2	896	Ile [I]/Thr [T]	196
rs121909741	nsSNPs	G /A	1	898	Val [V]/Ile [I]	197
rs149460434	nsSNPs	C /A	2	902	Thr [T]/Lys [K]	198
rs149460434	nsSNPs	C /T	2	902	Thr [T]/Met [M]	198
rs1276756236	nsSNPs	C /A	1	910	Leu [L]/Ile [I]	201
rs779591826	nsSNPs	T /G	3	924	Ile [I]/Met [M]	205
rs1262860274	nsSNPs	T /C	2	926	Ile [I]/Thr [T]	206
rs1186359171	nsSNPs	G /A	1	928	Gly [G]/Ser [S]	207
rs1114167428	nonsense	G /T	1	934	Glu [E]/	209

Table 1 (*continued*)

dbSNP id	Function	dbSNPallele	Codonpos.	mRNApos.	Proteinresidue	Amino acidpos
rs1215469128	nsSNPs	T /C	2	944	Leu [L]/Ser [S]	212
rs1347267249	nsSNPs	A /C	1	949	Asn [N]/His [H]	214
rs573292685	nsSNPs	A /G	2	950	Asn [N]/Ser [S]	214
rs764799427	nsSNPs	A /T	2	956	Asp [D]/Val [V]	216
rs753629940	nonsense	G /A	3	963	Trp [W]/	218
rs1380319602	nsSNPs	T /A	2	968	Ile [I]/Asn [N]	220
rs760641937	nsSNPs	G /C	2	977	Gly [G]/Ala [A]	223
rs1413841367	nsSNPs	T /C	2	980	Leu [L]/Pro [P]	224
rs771075989	nsSNPs	G /A	1	988	Val [V]/Met [M]	227
rs773581866	nonsense	C /T	1	991	Arg [R]/	228
rs773581866	nsSNPs	C /G	1	991	Arg [R]/Gly [G]	228
rs770126214	nsSNPs	C /A	1	1000	Leu [L]/Ile [I]	231
rs1374154306	nsSNPs	T /A	2	1013	Leu [L]/Gln [Q]	235
rs748588515	nsSNPs	C /T	1	1015	Leu [L]/Phe [F]	236
rs1162215911	frame shift	CT /-	3	1017	Phe [F]/Leu [L]	238
rs1162215911	frame shift	CT /-	3	1017	Leu [L] /Leu[L]	238
rs757087261	nsSNPs	T /A	1	1021	Phe [F]/Ile [I]	238
rs777020657	nsSNPs	T /G	2	1022	Phe [F]/Cys [C]	238
rs777020657	nsSNPs	T/C	2	1022	Phe [F] /Ser[S]	238
rs769089021	nsSNPs	G /A	2	1034	Ser [S]/Asn [N]	242
rs780381836	nsSNPs	A /G	1	1039	Arg [R]/Gly [G]	244
rs1480881050	nsSNPs	T /C	1	1042	Tyr [Y]/His [H]	245
rs1250722271	nsSNPs	T /C	1	1048	Tyr [Y]/His [H]	247
rs1158317020	nsSNPs	A /T	2	1049	Tyr [Y]/Phe [F]	247
rs867996396	nsSNPs	T /A	2	1052	Ile [I]/Asn [N]	248
rs867996396	nsSNPs	T/C	2	1052	Ile [I] / Thr [T]	248
rs536261161	nsSNPs	G /C	3	1056	Lys [K]/Asn [N]	249
rs745373269	nsSNPs	G /A	1	1060	Asp [D]/Asn [N]	251
rs745373269	nsSNPs	G /C	1	1060	Asp [D]/His [H]	251
rs1367431424	nsSNPs	A /C	2	1064	Glu [E]/Ala [A]	252
rs865881030	nsSNPs	G /A	1	1066	Glu [E]/Lys [K]	253
rs778607566	nsSNPs	A /G	2	1067	Glu [E]/Gly [G]	253
rs1309254226	nsSNPs	A /C	3	1068	Glu [E]/Asp [D]	253
rs777225980	nsSNPs	C /A	3	1086	Ser [S]/Arg [R]	259
rs76026576	nsSNPs	G /T	3	1089	Leu [L]/Phe [F]	260
rs746178753	frame shift	AG /-	3	1101	Gly [G]/Ile [I]	265
rs746178753	frame shift	AG /-	3	1101	Arg [R]/ Arg[R]	265
rs1490504926	nsSNPs	G /A	1	1108	Asp [D]/Asn [N]	267
rs935009475	nsSNPs	T /A	3	1113	Asp [D]/Glu [E]	268
rs774721090	Inframe Deletion	DD [GATG] / D [GTC]	2	1112	AspAsp[DD]/ Asp [D]	268
rs140285191	nsSNPs	G /A	1	1123	Asp [D]/Asn [N]	272
rs140285191	nsSNPs	G /T	1	1123	Asp [D]/Tyr [Y]	272
rs754932741	nsSNPs	G /A	3	1137	Met [M]/Ile [I]	276
rs750579210	nsSNPs	A /G	1	1138	Arg [R]/Gly [G]	277
rs1304842107	nsSNPs	A /C	1	1141	Lys [K]/Gln [Q]	278
rs765426962	nsSNPs	A /C	2	1142	Lys [K]/Thr [T]	278
rs761756532	nsSNPs	A /C	3	1143	Lys [K]/Asn [N]	278
rs771361095	frame shift	-/A	1	1147	Arg [R]/Lys [K]	280
rs1329237779	nsSNPs	G /A	1	1153	Glu [E]/Lys [K]	282
rs1384542256	nsSNPs	A /C	2	1154	Glu [E]/Ala [A]	282
rs776912318	nsSNPs	A /C	1	1162	Ser [S]/Arg [R]	285
rs776912318	nsSNPs	A /T	1	1162	Ser [S]/Cys [C]	285
rs121909746	nonsense	C /T	1	1168	Gln [Q]/	287
rs764161243	nsSNPs	A /C	2	1172	Lys [K]/Thr [T]	288
rs780873643	nsSNPs	T /G	2	1175	Val [V]/Gly [G]	289
rs775691314	nsSNPs	C /G	2	1178	Ser [S]/Cys [C]	290
rs772619265	nsSNPs	A /G	1	1180	Ile [I]/Val [V]	291
rs760061096	nsSNPs	T /A	2	1181	Ile [I]/Lys [K]	291
rs749789723	inframe insertion/stop gained	TTT	2	1181	Leu [L]	291
rs1205719797	nsSNPs	T /A	2	1190	Leu [L]/His [H]	294
rs1364855365	nsSNPs	C /G	2	1196	Thr [T]/Ser [S]	296
rs368432491	nsSNPs	A /G	2	1199	Asn [N]/Ser [S]	297
rs182778895	nsSNPs	T /C	1	1201	Ser [S]/Pro [P]	298
rs777540740	nsSNPs	A /T	1	1204	Ser [S]/Cys [C]	299
rs769325995	nsSNPs	T /C	1	1207	Tyr [Y]/His [H]	300
rs121909743	nonsense	C /T	1	1210	Arg [R]/	301
rs374492763	nsSNPs	G /A	2	1211	Arg [R]/Gln [Q]	301
rs374492763	nsSNPs	G /T	2	1211	Arg [R]/Leu [L]	301
rs1326032349	frame shift	-/TTGG	3	1212	Gln [Q]/Leu [L]	302
rs1316522125	frame shift	C /-	2	1217	Pro [P]/Leu [L]	303
rs938526894	nsSNPs	T /C	2	1223	Leu [L]/Pro [P]	305
rs1312418962	nsSNPs	T /C	2	1235	Met [M]/Thr [T]	309
rs1421580115	nsSNPs	G /A	1	1243	Val [V]/Met [M]	312
rs1324205444	nsSNPs	G /A	1	1246	Ala [A]/Thr [T]	313
rs1324205444	nsSNPs	G /T	1	1246	Ala [A]/Ser [S]	313

(*continued on next page*)

Table 1 (*continued*)

dbSNP id	Function	dbSNPallele	Codonpos.	mRNApos.	Proteinresidue	Amino acidpos
rs780067980	nsSNPs	G /A	1	1261	Gly [G]/Arg [R]	318
rs369101584	nsSNPs	A /G	2	1268	Asn [N]/Ser [S]	320
rs757366672	nsSNPs	G /T	1	1270	Gly [G]/Cys [C]	321
rs767670296	nsSNPs	T /A	2	1274	Ile [I]/Asn [N]	322
rs1272816101	nsSNPs	T /G	3	1275	Ile [I]/Met [M]	322
rs759952425	nsSNPs	T /C	1	1282	Tyr [Y]/His [H]	325
rs751917665	nsSNPs	C /T	2	1304	Thr [T]/Met [M]	332
rs1441375275	nsSNPs	G /A	1	1306	Ala [A]/Thr [T]	333
rs763345848	nsSNPs	G /A	2	1310	Gly [G]/Asp [D]	334
rs748296868	frame shift	G /-	2	1310	Gly [G]/Val [V]	334
rs1461795294	nsSNPs	A /G	1	1315	Ser [S]/Gly [G]	336
rs773717998	nsSNPs	C /A	2	1334	Thr [T]/Asn [N]	342
rs1162318193	nsSNPs	T /C	2	1337	Ile [I]/Thr [T]	343
rs1050103029	nsSNPs	T /C	2	1343	Val [V]/Ala [A]	345
rs764683908	nsSNPs	G /A	2	1346	Gly [G]/Asp [D]	346
rs776435170	nsSNPs	G /A	1	1348	Ala [A]/Thr [T]	347
rs1236921754	nsSNPs	C /T	2	1349	Ala [A]/Val [V]	347
rs746863503	nsSNPs	T /G	2	1358	Met [M]/Arg [R]	350
rs775407568	nsSNPs	G /C	3	1359	Met [M]/Ile [I]	350
rs771855037	nsSNPs	G /A	1	1369	Ala [A]/Thr [T]	354
rs140815551	nsSNPs	G /A	1	1372	Val [V]/Ile [I]	355
rs1348497054	nsSNPs	C /G	2	1376	Ser [S]/Cys [C]	356
rs1469035471	nsSNPs	G /C	1	1378	Val [V]/Leu [L]	357
rs372845210	nsSNPs	C /A	1	1384	Leu [L]/Ile [I]	359
rs372845210	nsSNPs	C /T	1	1384	Leu [L]/Phe [F]	359
rs1380054283	nsSNPs	G /C	1	1390	Glu [E]/Gln [Q]	361
rs999185720	nsSNPs	G /T	3	1392	Glu [E]/Asp [D]	361
rs745619267	nsSNPs	G /C	3	1395	Lys [K]/Asn [N]	362
rs76362149	nsSNPs	G /T	1	1396	Ala [A]/Ser [S]	363
rs121909742	nonsense	C /T	1	1402	Arg [R]/	365
rs34066960	frame shift	-/C	3	1401	Arg [R]/Pro [P]	365
rs781225543	nsSNPs	G /A	2	1403	Arg [R]/Gln [Q]	365
rs1321655963	nsSNPs	C /T	1	1405	Arg [R]/Cys [C]	366
rs755000812	nsSNPs	G /A	2	1406	Arg [R]/His [H]	366
rs1174349159	frame shift	CT /-	3	1413	Phe [F]/Ser [S]	369
rs1223071449	nsSNPs	T /A	3	1416	Phe [F]/Leu [L]	369
rs1430684701	nsSNPs	T /C	2	1418	Leu [L]/Pro [P]	370
rs747262541	nsSNPs	G /A	2	1430	Ser [S]/Asn [N]	374
rs868182136	nsSNPs	G /A	2	1433	Gly [G]/Glu [E]	375
rs780255530	nsSNPs	A /G	1	1435	Met [M]/Val [V]	376
rs758699271	nsSNPs	G /A	3	1437	Met [M]/Ile [I]	376
rs946622803	nsSNPs	T /C	1	1438	Phe [F]/Leu [L]	377
rs1381085405	nsSNPs	T /A	2	1439	Phe [F]/Tyr [Y]	377
rs1381085405	nsSNPs	T /C	2	1439	Phe [F]/Ser [S]	377
rs1384674663	frame shift	TTGT /-	3	1443	Cys [C]/Pro [P]	379
rs750782646	nsSNPs	T /A	2	1451	Ile [I]/Asn [N]	381
rs765728439	nsSNPs	T /C	2	1457	Met [M]/Thr [T]	383
rs757805176	nsSNPs	G /A	1	1465	Gly [G]/Arg [R]	386
rs757805176	nsSNPs	G /C	1	1465	Gly [G]/Arg [R]	386
rs1199637811	nsSNPs	T /G	2	1472	Val [V]/Gly [G]	388
rs121909747	nsSNPs	T /G	2	1475	Leu [L]/Arg [R]	389
rs 121,909,747	nsSNPs	T/C	2	1475	L (Leu) > P (Pro)	389
rs760200790	nsSNPs	T /G	2	1478	Leu [L]/Arg [R]	390
rs766191732	nsSNPs	C /A	3	1488	Phe [F]/Leu [L]	393
rs1464417991	nsSNPs	T /C	1	1489	Ser [S]/Pro [P]	394
rs762668792	nsSNPs	T /A	2	1505	Val [V]/Glu [E]	399
rs1457657980	nsSNPs	A /G	1	1510	Met [M]/Val [V]	401
rs374702599	nsSNPs	T /C	2	1514	Ile [I]/Thr [T]	402
rs1161394690	inframe insertion	GAT	2	1514	Met [M]/ MetMet [MM]	401
rs1419532672	nsSNPs	A /G	1	1519	Ile [I]/Val [V]	404
rs2229608	nsSNPs	T /C	2	1520	Ile [I]/Thr [T]	404
rs760729620	nsSNPs	T /C	2	1529	Phe [F]/Ser [S]	407
rs140791627	nsSNPs	A /T	1	1534	Ser [S]/Cys [C]	409
rs746136121	nsSNPs	T /C	1	1537	Phe [F]/Leu [L]	410
rs1353890919	nsSNPs	T /G	2	1541	Phe [F]/Cys [C]	411
rs966424064	nsSNPs	T/ C	2	1547	Ile [I]/Thr [T]	413
rs779212294	nsSNPs	T /G	3	1548	Ile [I]/Met [M]	413
rs121909744	nsSNPs	C /G	2	1559	Pro [P]/Arg [R]	417
rs121909744	nsSNPs	C /T	2	1559	Pro [P]/Leu [L]	417
rs1309197020	nsSNPs	C /G	3	1563	Ile [I]/Met [M]	418
rs1309197020	nsSNPs	C/A	3	1563	Ile [I] / Ile [I]	418
rs121909745	nonsense	G /A	2	1568	Trp [W]/	420
rs749661374	nsSNPs	A /G	1	1573	Met [M]/Val [V]	422
rs778490867	nsSNPs	T /C	2	1574	Met [M]/Thr [T]	422
rs28928874	nsSNPs	T /A	2	1577	Val [V]/Glu [E]	423

Table 1 (*continued*)

dbSNP id	Function	dbSNPallele	Codonpos.	mRNApos.	Proteinresidue	Amino acidpos
rs1386374799	frame shift	T /-	2	1589	Phe [F]/Ser [S]	427
rs367980651	nsSNPs	C /T	1	1603	Arg [R]/Cys [C]	432
rs75144723	nsSNPs	G /A	2	1604	Arg [R]/His [H]	432
rs754405476	nsSNPs	G /A	1	1612	Ala [A]/Thr [T]	435
rs1379813904	nsSNPs	C /A	2	1619	Ala [A]/Glu [E]	437
rs751226875	nsSNPs	T /C	2	1622	Ile [I]/Thr [T]	438
rs762675284	nsSNPs	G /T	1	1624	Ala [A]/Ser [S]	439
rs1262058831	nsSNPs	C /T	2	1625	Ala [A]/Val [V]	439
rs758246412	nsSNPs	C /A	2	1628	Ala [A]/Glu [E]	440
rs1203908311	nsSNPs	A /G	2	1637	Asn [N]/Ser [S]	443
rs765196886	nsSNPs	A /C	1	1654	Ile [I]/Leu [L]	449
rs761784655	nsSNPs	T /C	2	1655	Ile [I]/Thr [T]	449
rs776395971	nsSNPs	T /C	2	1658	Val [V]/Ala [A]	450
rs1238600269	nsSNPs	G /A	1	1660	Ala [A]/Thr [T]	451
rs1418589512	nsSNPs	T /C	1	1666	Cys [C]/Arg [R]	453
rs1350704340	frame shift	-/G	3	1665	Cys [C]/Val [V]	453
rs759480075	nsSNPs	T /C	1	1675	Tyr [Y]/His [H]	456
rs771274850	nsSNPs	T /C	2	1679	Ile [I]/Thr [T]	457
rs749710583	nsSNPs	C /A	2	1682	Ala [A]/Glu [E]	458
rs749710583	nsSNPs	C /T	2	1682	Ala [A]/Val [V]	458
rs1290975016	frame shift	-/T	2	1688	Cys [C]/Leu [L]	461
rs774542648	nsSNPs	G /A	1	1693	Gly [G]/Arg [R]	462
rs765132996	frame shift	G /-	2	1694	Gly [G]/Asp [D]	462
rs1272353608	nsSNPs	C /A	2	1697	Pro [P]/His [H]	463
rs1381049817	nsSNPs	A /G	2	1700	Tyr [Y]/Cys [C]	464
rs1336322605	nsSNPs	T /C	1	1708	Phe [F]/Leu [L]	467
rs140138702	nsSNPs	C /G	1	1711	Leu [L]/Val [V]	468
rs770197371	nsSNPs	T /G	2	1712	Leu [L]/Arg [R]	468
rs748401954	nsSNPs	T /C	2	1715	Phe [F]/Ser [S]	469
rs1290412048	frame shift	TT /-	2	1715	Phe [F]/Cys [C]	469
rs374342938	nsSNPs	G /C	2	1721	Gly [G]/Ala [A]	471
rs769037887	nsSNPs	G /A	1	1723	Val [V]/Met [M]	472
rs556023421	nsSNPs	T /C	1	1735	Phe [F]/Leu [L]	476
rs5397	nsSNPs	C /G	1	1741	Leu [L]/Val [V]	478
rs5398	nsSNPs	C /A	3	1746	Phe [F]/Leu [L]	479
rs757137603	nsSNPs	C /T	2	1748	Thr [T]/Ile [I]	480
rs1441249949	nsSNPs	T /A	1	1750	Phe [F]/ Ile [I]	481
rs1195253424	nsSNPs	G /A	1	1759	Val [V]/Ile [I]	484
rs753575081	nsSNPs	C /A	1	1762	Pro [P]/Thr [T]	485
rs777806589	nsSNPs	A /G	2	1772	Lys [K]/Arg [R]	488
rs766600474	nsSNPs	T /A	1	1780	Ser [S]/Thr [T]	491
rs766600474	nsSNPs	T /G	1	1780	Ser [S]/Ala [A]	491
rs1379944645	nonsense	G /T	1	1786	Glu [E]/	493
rs1379944645	nsSNPs	G /A	1	1786	Glu [E]/Lys [K]	493
rs1353603250	nsSNPs	G /C	1	1789	Glu [E]/Gln [Q]	494
rs1446857276	nsSNPs	A /T	3	1791	Glu [E]/Asp [D]	494
rs1283734332	nsSNPs	T /C	2	1793	Ile [I]/Thr [T]	495
rs1445660295	nsSNPs	C /T	2	1796	Ala [A]/Val [V]	496
rs201797691	nsSNPs	G /A	1	1798	Ala [A]/Thr [T]	497
rs201797691	nsSNPs	G /C	1	1798	Ala [A]/Pro [P]	497
rs200160167	nsSNPs	C /A	2	1799	Ala [A]/Glu [E]	497
rs200160167	nsSNPs	C /T	2	1799	Ala [A]/Val [V]	497
rs762305192	nsSNPs	T /C	1	1804	Phe [F]/Leu [L]	499
rs776826621	nsSNPs	G /C	3	1812	Lys [K]/Asn [N]	501
rs5399	nsSNPs	G /C	3	1815	Lys [K]/Asn [N]	502
rs1412427073	nsSNPs	G /A	1	1819	Gly [G]/Ser [S]	504
rs966895511	nsSNPs	G /T	1	1825	Ala [A]/Ser [S]	506
rs1199349184	nsSNPs	C /T	2	1826	Ala [A]/Val [V]	506
rs374630641	nsSNPs	G /C	3	1833	Arg [R]/Ser [S]	508
rs771586150	nsSNPs	C /A	2	1835	Pro [P]/Gln [Q]	509
rs776597156	nsSNPs	A /C	3	1839	Lys [K]/Asn[N]	510
rs770462591	nsSNPs	C /A	2	1841	Ala [A]/Asp [D]	511
rs770462591	nsSNPs	C /T	2	1841	Ala [A]/Val [V]	511
rs141574520	nsSNPs	T /A	2	1859	Phe [F]/Tyr [Y]	517
rs147959014	nsSNPs	G /A	2	1865	Gly [G]/Glu [E]	519
rs752687355	nsSNPs	A /G	2	1874	Glu [E]/Gly[G]	522
rs781215842	nsSNPs	A /T	1	1876	Thr [T]/Ser [S]	523
rs758607933	nsSNPs	G/ A	1	1879	Val[V]/Met[M]	524
rs750463981	stop lost	T /C	1	1882	(Ter) /Gln[Q]	525

(rs750463981). 10 additional SNPs were detected by dbSNP in which 4 SNPs; (rs766082034), (rs1255595607), (rs1162215911), (rs746178753) were frameshifts and 6; (rs766762468), (rs1800572), (rs777020657), (rs867996396), (rs121909747), (rs1309197020) were nsSNPs (Table 1)

3.4. Analysis of nsSNPS using SIFT

SIFT forecasts whether amino acid substitution in protein has phenotypic effect or not. Alignment also gave forecasted changes of all amino acid locations. The SIFT intolerance index starting point was 0.05. The color code of non polar, basic, uncharged polar and acidic amino acids were shown by black, red, green and blue color respectively. On the other hand, the amino acid alignment is shown by capital letter while the results of prediction are shown by small letter. 'Seq Rep' was the proportion of sequences that has one of the important amino acids. The position either severely gapped or unalignable was determined by low fraction and it has little information which has poor prediction. Its prediction score ranges from 0 to 1. On phenotypic substitution by aligning orthologous and paralogous protein sequence, this study mainly considers the physical properties of amino acids, effect of natural nsSNPs and alignment of homologous sequences (Noreen et al., 2015a, 2015b). For positions 1–524 of amino acids, the prediction of possible substitutions was made (Figure 6). It was used to predict damaging and tolerated effect of 293 nsSNPs that occurs in coding region of GLUT2 protein. As a consequence, 167 were predicted to be damaging (Table 2).

3.5. Analysis of nsSNPS using PolyPhen

To forecast the effects of function and structure 293 nsSNPs lying in the coding region of GLUT2 protein, PolyPhen-2 server was used. It permits three types of prediction score which is based on a "Sensitivity" as well as "Specificity". Three prediction types are given by PolyPhen benign, possibly damaging or probably damaging. Out of 293 nsSNPs, 165 were considered to be benign. 65 were predicted to be possibly damaging and 77 were considered to be probably damaging (Table 2).

3.6. Analysis of SNPs using PROVEAN

PROVEAN gave score to predict neutral and deleterious effect of 293 nsSNPs present in coding region of GLUT2 protein. Score equal to or below −2.5 was considered as deleterious and above −2.5, as neutral. Out of 293 nsSNPs, 162 were predicted to be neutral and 138 were considered to be deleterious. It also gave the results of inframe deletion and insertion. Out of 4 inframe deletion 2 (rs772999215 and rs774721090) were shown to be deleterious 3 SNPs were inframe insertion (rs1161394690), (rs1463507753), (rs749789723) and no results were found for them (Table 2).

3.7. Analysis of nsSNPS using SNPeffect

The SNPeffect server was used to predict the effect of molecular phenotype of nsSNPs found in coding region of GLUT2 protein. Effect of 293 nsSNPs on aggregation tendency, amyloid propensity and chaperon binding tendency was specified by dTANGO, dWALTZ and dLIMBO score. Two significant effects, intrinsic aggregation propensity and protein stability were shown. In a protein sequence, aggregation propensity was identified by dTANGO. Out of 293 nsSNPs, 61 were detected to decrease the aggregation propensity, 27 to increase the aggregation propensity while 211 had no effect on aggregation propensity. dWALTZ indicated the score of amyloid propensity. 23 nsSNPs were shown to increase the amyloid propensity, 16 decreased the amyloid propensity and 257 had no effect on the amyloid propensity. According to dLIMBO, the chaperon binding tendency was given. None of them had any effect on chaperon binding tendency (Table 3).

4. Discussion

For most living cells, glucose is a vital energy source and an important substrate for biochemical reaction. There are two types of glucose transporters. GLUTs and SGLTs. SGLT family members consist of 580–718 amino acids and 60–80-kDa weight. GLUTs are proteins containing 12 membrane-spanning regions with intracellularl carboxyl and amino terminals. The sequence of GLUT proteins has been known to show 28–65% resemblance with GLUT1. The GLUTs symport glucose by facilitated diffusion mechanism across the plasma membrane (Navale and Paranjape, 2016). On the basis of phylogenetic relationship, 14 human GLUT proteins are grouped into three classes. Class I includes GLUT 1–4 and 14, in class II has GLUT 5,9,7, 11 and class III contains GLUT 6,13,8,12,10 (Manolescu et al., 2007). GLUT2 is a low affinity glucose transporter with affinity of Km of ~ 17 mM, fructose (~76 mM), galactose (~92 mM) and mannose (~125 mM) but high affinity glucosamine transporter (Km= ~0.8 mM). The amino acid sequence of GLUT2 shows 81% resemblance among the human, rat and mouse.

In this study, a phylogenetic tree of 10 species of hominidae family including human was constructed using NCBI and Clustal Omega. Evolutionary tree shows that human GLUT2 is most closely related to that of *Pongo abelli* whereas is least related to GLUT2 of *Bos Taurus* among these ten members (Fig. 2). GLUT2 was predicted to have 12 transmembrane helices with intracellular amino and carboxyl termini in cytosol. It was also found to contain extracellular and intracellular loops which are located between the segments of 1st and 2nd transmembrane domains and between 6th and 7th transmembrane segments (Fig. 3)

The human genome consists of three billion base pairs. The SNPs neither cause disease nor indicate the sign of disease progression, but they can facilitate to establish the possibility that someone has acquired a specific disease. The SNPs build up approximately 90% of all genetic variations of human and take place every 100–300 bases on the genome (Noreen and Arshad, 2015). On a large scale genotyping and genome sequencing projects are producing huge data for the sequencing of diseased and healthy individuals. In human beings as well as in the model organisms the sequence variants are present in the genome of protein non-coding and coding regions. In non-coding regions, variants usually have no effect on gene expression and a regular function (Noreen et al., 2021). Association of molecular epidemiological studies is mainly concerned with non synonymous single nucleotide polymorphism (nsSNPs) that resides in exonic regions of gene (Savas et al., 2004; Zhu et al., 2004). Studying the structural as well as functional effect of nsSNPs on protein can facilitate in chosing nsSNPs which are functionally important. The activity and functioning of proteins are affected mainly by the coding variants in which truncation or frame shift, insertion or amino acids deletion or switching are included. There are so many variants, thus it is matter of great challenge to recognize important variants for disease. More than a dozen algorithms have been developed for resolving this issue. Some recent predicted algorithms are developed which utilize some score approaches that are alignment focused such as PolyPhen (Adzhubei et al., 2010), SIFT etc. In this study some sequences as well as structural homology focused algorithms were used to screen those SNPs which can play fundamental role in structural and functional changes in GLUT2.

The SIFT is a tool that was used to predict tolerant and intolerant amino acid substitution effect on protein function (Ng and

Table 2
SIFT, PolyPhen and PROVEAN analysis of nsSNPs in coding region of human GLUT2 protein.

dbSNP id	Proteinresidue	SIFT score	SIFTprediction	PolyPhenscore	PolyPhenprediction	PROVEANscore	PROVEAN prediction
rs759495940	Met [M]/Ile [I]	0.02	Intolerant	0.016	Benign	−1.576	Neutral
rs773205789	Thr [T]/Pro [P]	0.08	Tolerant	0.003	Benign	−0.251	Neutral
rs200073044	Asp [D]/His [H]	0.16	Tolerant	0.001	Benign	−1.256	Neutral
rs1372689853	Lys [K]/Glu [E]	0.27	Tolerant	0.009	Benign	−1.503	Neutral
rs767313610	Val [V]/Ile [I]	0.24	Tolerant	0.003	Benign	0.189	Neutral
rs369700669	Thr [T]/Asn [N]	0.05	Tolerant	0.505	Possibly damaging	−4.345	Deleterious
rs1481905618	Phe [F]/Leu [L]	1	Tolerant	0.002	Benign	−1.974	Neutral
rs1247912820	Thr [T]/Asn [N]	0	Intolerant	0.255	Benign	−1.769	Neutral
rs1247912820	Thr [T]/Ser [S]	0.37	Tolerant	0.007	Benign	0.439	Neutral
rs372441014	Val [V]/Leu [L]	0.04	Intolerant	0.534	Possibly damaging	−2.404	Neutral
rs766364438	Ile [I]/Thr [T]	0.48	Tolerant	0.007	Benign	−0.108	Neutral
rs1463507753	I (Ile) > II (IleIle)	–	–	–	–	–	–
rs867315854	Ala [A]/Thr [T]	0	Intolerant	0.951	Probably damaging	−3.332	Deleterious
rs761992056	Gly [G]/Asp [D]	0	Intolerant	0.967	Probably damaging	−5.211	Deleterious
rs369781481	Phe [F]/Leu [L]	1	Tolerant	0.253	Benign	−0.832	Neutral
rs1409436045	Phe [F]/Tyr [Y]	0.08	Tolerant	0.582	Possibly damaging	−1.774	Neutral
rs1049223265	Ile [I]/Thr [T]	0.61	Tolerant	0.041	Benign	−0.47	Neutral
rs1437312005	Gly [G]/Ser [S]	0	Intolerant	0.996	Probably damaging	−5.242	Deleterious
rs1437312005	Gly [G]/Arg [R]	0	Intolerant	1	Probably damaging	−6.99	Deleterious
rs775531825	Asn [N]/Ser [S]	0	Intolerant	0.979	Probably damaging	−4.384	Deleterious
rs143528640	Ala [A]/Thr [T]	0.05	Tolerant	0.934	Probably damaging	−3.505	Deleterious
rs746158263	Pro [P]/Thr [T]	0	Intolerant	0.999	Probably damaging	−7.021	Deleterious
rs1158195535	Gln [Q]/Lys [K]	1	Tolerant	0.004	Benign	0.622	Neutral
rs1158195535	Gln [Q]/Glu [E]	0.14	Tolerant	0.002	Benign	−0.245	Neutral
rs1451394300	Val [V]/Ile [I]	0.59	Tolerant	0.006	Benign	−0.067	Neutral
rs1477523180	Ile [I]/Leu [L]	0.16	Tolerant	0.437	Benign	−1.338	Neutral
rs1360464436	Ile [I]/Lys [K]	0	Intolerant	0.977	Probably damaging	−4.893	Deleterious
rs1176350402	Ile [I]/Thr [T]	0.02	Intolerant	0.012	Benign	0.3	Neutral
rs772999215	II (IleIle) > I (Ile)	–	–	–	–	−4.083	Deleterious
rs758670698	Arg [R]/Ile [I]	0.14	Tolerant	0.016	Benign	−2.042	Neutral
rs760618624	His [H]/Tyr [Y]	0.04	Intolerant	0	Benign	−1.705	Neutral
rs775791143	Val [V]/Ile [I]	0.09	Tolerant	0.098	Benign	−0.283	Neutral
rs149108283	Val [V]/Asp [D]	0.02	Intolerant	0.689	Possibly damaging	−2.294	Neutral
rs149108283	Val [V]/Ala [A]	0.14	Tolerant	0.034	Benign	−1.116	Neutral
rs1159338702	Gly [G]/Ser [S]	0.01	Intolerant	0.653	Possibly damaging	−1.878	Neutral
rs561765982	Val [V]/Ile [I]	0.11	Tolerant	0.006	Benign	−0.204	Neutral
rs983907950	Pro [P]/Ser [S]	0.41	Tolerant	0.004	Benign	−1.397	Neutral
rs1211075508	Leu [L]/Pro [P]	0.32	Tolerant	0.01	Benign	−1.458	Neutral
rs1311902495	Asp [D]/Asn[N]	0.34	Tolerant	0.493	Possibly damaging	−0.762	Neutral
rs1311902495	Asp [D]/Tyr [Y]	0.01	Intolerant	0.873	Possibly damaging	−2.194	Neutral
rs771477447	Arg [R]/Gly [G]	0.05	Tolerant	0.013	Benign	−1.477	Neutral
rs145210664	Arg [R]/Gln [Q]	0.18	Tolerant	0.039	Benign	−0.58	Neutral
rs546539032	Lys [K]/Asn [N]	0.48	Tolerant	0.038	Benign	−0.733	Neutral
rs747555903	Val [V]/Ile [I]	0.43	Tolerant	0.006	Benign	−0.048	Neutral
rs977284195	Ile [I]/Thr [T]	0.65	Tolerant	0.003	Benign	−0.17	Neutral
rs780903829	Ile [I]/Met [M]	0.17	Tolerant	0.006	Benign	−0.304	Neutral
rs1169887677	INS (IleAsnSer) > ()	–	–	–	–	–	–
rs1373290524	Ser [S]/Thr [T]	0.61	Tolerant	0.005	Benign	−0.656	Neutral
rs1310901426	Thr [T]/Ala [A]	0.78	Tolerant	0.484	Possibly damaging	−1.49	Neutral
rs1354126805	Thr [T]/Arg [R]	0.53	Tolerant	0.93	Probably damaging	−1.61	Neutral
rs754585542	Asp [D]/Asn[N]	0.6	Tolerant	0.003	Benign	−0.514	Neutral
rs1217666649	Asp [D]/Glu [E]	1	Tolerant	0.001	Benign	−0.257	Neutral
rs1391257598	Pro [P]/Thr [T]	0.01	Intolerant	0.005	Benign	−0.821	Neutral
rs7637863	Pro [P]/Leu [L]	0.05	Intolerant	0.005	Benign	−0.881	Neutral
rs779977931	Thr [T]/Lys [K]	0.16	Tolerant	0.037	Benign	−0.951	Neutral
rs1182852354	Ile [I]/Val [V]	0.67	Tolerant	0.001	Benign	0.053	Neutral
rs750405382	Met [M]/Val[V]	0.6	Tolerant	0.001	Benign	0.191	Neutral
rs1207297111	Asn [N]/Asp[D]	0.84	Tolerant	0.001	Benign	−0.029	Neutral
rs1342979475	Asn [N]/Thr [T]	0.69	Tolerant	0	Benign	0.053	Neutral
rs1274084408	Pro [P]/Ala [A]	0.73	Tolerant	0.01	Benign	−0.158	Neutral
rs778655073	Pro [P]/Leu [L]	0.01	Intolerant	0.258	Benign	−1.466	Neutral
rs549263048	Trp [W]/Arg [R]	0.07	Tolerant	0	Benign	−1.382	Neutral
rs531049536	Trp [W]/Cys [C]	0.03	Intolerant	0.069	Benign	−1.624	Neutral
rs150851401	Glu [E]/Lys [K]	0.03	Intolerant	0.004	Benign	−0.777	Neutral
rs766762468	Thr [T]/Ser [S]	0.71	Tolerant	0.004	Benign	−0.271	Neutral
rs766762468	Thr (T)/ Ile (I)	0.18	Tolerant	0.039	Benign	−0.862	Neutral
rs763255363	Ala [A]/Ser [S]	0.74	Tolerant	0.016	Benign	0.281	Neutral
rs144715667	Ile [I]/Val [V]	0.53	Tolerant	0.002	Benign	−0.043	Neutral
rs1415169647	Met [M]/Arg[R]	0.07	Tolerant	0.179	Benign	−2.363	Neutral
rs1407375423	Trp [W]/Cys [C]	0	Intolerant	0.999	Probably damaging	−11.435	Deleterious
rs1800572	Val [V]/Ile [I]	0	Intolerant	0.997	Probably damaging	−0.887	Neutral
rs1800572	Val [V] / Leu[L]	0	Intolerant	0.996	Probably damaging	−2.66	Deleterious
rs770135219	Val [V]/Ala [A]	0	Intolerant	0.991	Probably damaging	−3.541	Deleterious
rs1399091893	Ala [A]/Val [V]	0	Intolerant	0.542	Possibly damaging	−2.559	Deleterious

(*continued on next page*)

Table 2 (*continued*)

dbSNP id	Proteinresidue	SIFT score	SIFTprediction	PolyPhenscore	PolyPhenprediction	PROVEANscore	PROVEAN prediction
rs1332764085	Val [V]/Ile [I]	0.39	Tolerant	0.026	Benign	−0.536	Neutral
rs5400	Thr [T]/Ile [I]	1	Tolerant	0	Benign	3.394	Neutral
rs377238940	Ala [A]/Pro [P]	0.01	Intolerant	0.808	Possibly damaging	−2.114	Neutral
rs768407637	Gly [G]/Val [V]	0	Intolerant	0.996	Probably damaging	−6.815	Deleterious
rs753980727	Trp [W]/Cys [C]	0.01	Intolerant	0.704	Possibly damaging	−2.72	Deleterious
rs746632604	Gly [G]/Ala [A]	1	Tolerant	0.011	Benign	−0.025	Neutral
rs772002572	Thr [T]/Ile [I]	0.02	Intolerant	0.003	Benign	−1.408	Neutral
rs1476520648	Ile [I]/Asn [N]	0.09	Tolerant	0.18	Benign	−0.471	Neutral
rs760201098	Ala [A]/Asp [D]	0.03	Intolerant	0.616	Possibly damaging	−2.467	Neutral
rs1267904495	Met [M]/Thr [T]	0	Intolerant	0.799	Possibly damaging	−5.134	Deleterious
rs1212980167	Met [M]/Ile [I]	0	Intolerant	0.175	Benign	−3.41	Deleterious
rs367856967	Val [V]/Ala [A]	0.27	Tolerant	0.004	Benign	−1.196	Neutral
rs970550665	Ala [A]/Gly [G]	0.53	Tolerant	0.526	Possibly damaging	−1.704	Neutral
rs775283150	Ile [I]/Phe [F]	0.05	Tolerant	0.082	Benign	−2.379	Neutral
rs913419413	Leu [L]/Arg [R]	0	Intolerant	0.954	Probably damaging	−4.778	Deleterious
rs771843187	Ser [S]/Pro [P]	0	Intolerant	0.82	Possibly damaging	−2.268	Neutral
rs144125084	Val [V]/Leu [L]	0.75	Tolerant	0.006	Benign	−0.509	Neutral
rs993833041	Val [V]/Ala [A]	0.6	Tolerant	0.004	Benign	−1.391	Neutral
rs1300072764	Gly [G]/Glu [E]	0	Intolerant	0.991	Probably damaging	−5.45	Deleterious
rs778548964	Leu [L]/Phe [F]	0.65	Tolerant	0.125	Benign	−1.799	Neutral
rs1016384738	Met [M]/Lys[K]	0	Intolerant	0.979	Probably damaging	−5.027	Deleterious
rs770941010	Gly [G]/Arg [R]	0	Intolerant	0.89	Possibly damaging	−5.634	Deleterious
rs777718289	Gly [G]/Glu [E]	0.02	Intolerant	0.588	Possibly damaging	−3.269	Deleterious
rs777718289	Gly [G]/Val [V]	0.04	Intolerant	0.065	Benign	−3.177	Deleterious
rs372621339	Pro [P]/Arg [R]	0.54	Tolerant	0.017	Benign	−0.696	Neutral
rs747025551	Ile [I]/Thr [T]	0.14	Tolerant	0.158	Benign	0.37	Neutral
rs376064965	Leu [L]/Phe [F]	0	Intolerant	0.114	Benign	−2.421	Neutral
rs763620441	ILI (IleLeuIle) /I(Ile)	–	–	–	–	–	–
rs1188886679	Ile [I]/Leu [L]	1	Tolerant	0.006	Benign	−0.029	Neutral
rs1188886679	Ile [I]/Val [V]	0.28	Tolerant	0.02	Benign	−0.518	Neutral
rs192720796	Ile [I]/Lys [K]	0	Intolerant	0.616	Possibly damaging	−4.296	Deleterious
rs910976682	Ala [A]/Val [V]	0.24	Tolerant	0.007	Benign	0.447	Neutral
rs750836049	Gly [G]/Arg [R]	0	Intolerant	0.996	Probably damaging	−7.236	Deleterious
rs1278964539	Arg [R]/Lys [K]	0	Intolerant	0.999	Probably damaging	−2.714	Deleterious
rs1231468128	Leu [L]/Gln [Q]	0	Intolerant	0.951	Probably damaging	−4.187	Deleterious
rs1445887606	Tyr [Y]/His [H]	0.08	Tolerant	0.319	Benign	−3.492	Deleterious
rs1271546287	Ile [I]/Thr [T]	1	Tolerant	0.007	Benign	0.249	Neutral
rs760095835	Gly [G]/Asp [D]	0	Intolerant	0.998	Probably damaging	−6.71	Deleterious
rs1335888503	Val [V]/Leu [L]	0	Intolerant	0.48	Possibly damaging	−2.654	Deleterious
rs1293130515	Met [M]/Thr [T]	0	Intolerant	0.792	Possibly damaging	−5.465	Deleterious
rs1019696977	Ile [I]/Val [V]	1	Tolerant	0.014	Benign	−0.016	Neutral
rs144822218	Gly [G]/Ser [S]	0.19	Tolerant	0.153	Benign	−4.8	Deleterious
rs759047405	Gly [G]/Asp [D]	0	Intolerant	0.275	Benign	−6.064	Deleterious
rs1441606652	Ala [A]/Val [V]	0	Intolerant	0.93	Probably damaging	−3.261	Deleterious
rs368626129	Ala [A]/Thr [T]	0.8	Tolerant	0.015	Benign	−0.903	Neutral
rs368626129	Ala [A]/Ser [S]	0.86	Tolerant	0.012	Benign	−0.098	Neutral
rs200213178	Ala [A]/Thr [T]	0	Intolerant	0.838	Possibly damaging	−3.928	Deleterious
rs200213178	Ala [A]/Pro [P]	0	Intolerant	0.996	Probably damaging	−4.91	Deleterious
rs748052042	Leu [L]/Phe [F]	0.31	Tolerant	0.044	Benign	−1.051	Neutral
rs1412289847	Gly [G]/Ser [S]	0	Intolerant	0.994	Probably damaging	−5.883	Deleterious
rs776498787	Gly [G]/Asp [D]	0	Intolerant	0.999	Probably damaging	−6.867	Deleterious
rs779065938	Leu [L]/Val [V]	0.03	Intolerant	0.951	Probably damaging	−2.948	Deleterious
rs1469335096	Ala [A]/Thr [T]	0.01	Intolerant	0.688	Possibly damaging	−2.844	Deleterious
rs771182536	Ile [I]/Asn [N]	0	Intolerant	0.961	Probably damaging	−6.383	Deleterious
rs771182536	Ile [I]/Thr [T]	0.02	Intolerant	0.517	Possibly damaging	−4.26	Deleterious
rs121909741	Val [V]/Ile [I]	0.01	Intolerant	0.846	Possibly damaging	−0.978	Neutral
rs149460434	Thr [T]/Lys [K]	0	Intolerant	0.665	Possibly damaging	−3.176	Deleterious
rs149460434	Thr [T]/Met[M]	0.01	Intolerant	0.166	Benign	−0.836	Neutral
rs1276756236	Leu [L]/Ile [I]	0	Intolerant	0.967	Probably damaging	−1.897	Neutral
rs779591826	Ile [I]/Met [M]	0	Intolerant	0.973	Probably damaging	−2.473	Neutral
rs1262860274	Ile [I]/Thr [T]	0.01	Intolerant	0.102	Benign	−2.589	Deleterious
rs1186359171	Gly [G]/Ser [S]	0	Intolerant	0.982	Probably damaging	−5.869	Deleterious
rs1215469128	Leu [L]/Ser [S]	0	Intolerant	0.993	Probably damaging	−4.95	Deleterious
rs1347267249	Asn [N]/His [H]	0.01	Intolerant	0.413	Benign	−3.346	Deleterious
rs573292685	Asn [N]/Ser [S]	0.88	Tolerant	0.048	Benign	−1.171	Neutral
rs764799427	Asp [D]/Val [V]	0.08	Tolerant	0.027	Benign	−3.592	Deleterious
rs1380319602	Ile [I]/Asn [N]	0	Intolerant	0.863	Possibly damaging	−5.167	Deleterious
rs760641937	Gly [G]/Ala [A]	0.26	Tolerant	0.401	Benign	−3.395	Deleterious
rs1413841367	Leu [L]/Pro [P]	0	Intolerant	0.996	Probably damaging	−5.774	Deleterious
rs771075989	Val [V]/Met [M]	0.02	Intolerant	0.863	Possibly damaging	−1.251	Neutral
rs773581866	Arg [R]/Gly [G]	0	Intolerant	0.008	Benign	−0.341	Neutral
rs770126214	Leu [L]/Ile [I]	0.09	Tolerant	0.032	Benign	−1.069	Neutral
rs1374154306	Leu [L]/Gln [Q]	0	Intolerant	0.853	Possibly damaging	−4.116	Deleterious
rs748588515	Leu [L]/Phe [F]	0	Intolerant	0.914	Probably damaging	−3.922	Deleterious
rs757087261	Phe [F]/Ile [I]	0.08	Tolerant	0.219	Benign	−4.242	Deleterious

Table 2 (*continued*)

dbSNP id	Proteinresidue	SIFT score	SIFTprediction	PolyPhenscore	PolyPhenprediction	PROVEANscore	PROVEAN prediction
rs777020657	Phe [F]/Cys [C]	0.03	Intolerant	0.359	Benign	−6.281	Deleterious
rs777020657	F (Phe) > S (Ser)	0	Intolerant	0.936	Probably damaging	−6.607	Deleterious
rs769089021	Ser [S]/Asn [N]	0	Intolerant	0.999	Probably damaging	−2.946	Deleterious
rs780381836	Arg [R]/Gly [G]	0.01	Intolerant	0.548	Possibly damaging	−6.565	Deleterious
rs1480881050	Tyr [Y]/His [H]	0	Intolerant	0.903	Possibly damaging	−4.446	Deleterious
rs1250722271	Tyr [Y]/His [H]	0	Intolerant	0.928	Probably damaging	−3.256	Deleterious
rs1158317020	Tyr [Y]/Phe [F]	0.06	Tolerant	0.02	Benign	−1.172	Neutral
rs867996396	Ile [I]/Asn [N]	0	Intolerant	0.958	Probably damaging	−6.497	Deleterious
rs867996396	Ile [I] / Thr [T]	0	Intolerant	0.925	Probably damaging	−4.799	Deleterious
rs536261161	Lys [K]/Asn [N]	1	Tolerant	0.004	Benign	0.309	Neutral
rs745373269	Asp [D]/Asn [N]	1	Tolerant	0.003	Benign	0.872	Neutral
rs745373269	Asp [D]/His [H]	0.05	Tolerant	0.637	Possibly damaging	−1.072	Neutral
rs1367431424	Glu [E]/Ala [A]	0.2	Tolerant	0.155	Benign	−3.915	Deleterious
rs865881030	Glu [E]/Lys [K]	0	Intolerant	0.377	Benign	−3.096	Deleterious
rs778607566	Glu [E]/Gly [G]	0	Intolerant	0.944	Probably damaging	−5.575	Deleterious
rs1309254226	Glu [E]/Asp [D]	0.03	Intolerant	0.247	Benign	−2.277	Neutral
rs777225980	Ser [S]/Arg [R]	0.07	Tolerant	0.689	Possibly damaging	−2.569	Deleterious
rs76026576	Leu [L]/Phe [F]	0	Intolerant	0.998	Probably damaging	−3.757	Deleterious
rs1490504926	Asp [D]/Asn[N]	0.51	Tolerant	0.005	Benign	−0.126	Neutral
rs935009475	Asp [D]/Glu [E]	0.06	Tolerant	0.434	Benign	−3.438	Deleterious
rs774721090	DD (AspAsp) / D (Asp)	–	–	–	–	−6.952	Deleterious
rs140285191	Asp [D]/Asn[N]	0	Intolerant	0.516	Possibly damaging	−4.047	Deleterious
rs140285191	Asp [D]/Tyr [Y]	0	Intolerant	0.981	Probably damaging	−7.312	Deleterious
rs754932741	Met [M]/Ile [I]	0	Intolerant	0.17	Benign	−3.506	Deleterious
rs750579210	Arg [R]/Gly [G]	0	Intolerant	0.579	Possibly damaging	−4.146	Deleterious
rs1304842107	Lys [K]/Gln [Q]	0.07	Tolerant	0.166	Benign	−0.767	Neutral
rs765426962	Lys [K]/Thr [T]	0.13	Tolerant	0.065	Benign	−2.692	Deleterious
rs761756532	Lys [K]/Asn [N]	0.09	Tolerant	0.036	Benign	−1.633	Neutral
rs1329237779	Glu [E]/Lys [K]	1	Tolerant	0.03	Benign	−0.266	Neutral
rs1384542256	Glu [E]/Ala [A]	0.64	Tolerant	0.055	Benign	−3.333	Deleterious
rs776912318	Ser [S]/Arg [R]	1	Tolerant	0.009	Benign	−0.133	Neutral
rs776912318	Ser [S]/Cys [C]	0.02	Intolerant	0.031	Benign	−2.646	Deleterious
rs764161243	Lys [K]/Thr [T]	0.05	Tolerant	0.133	Benign	−4.412	Deleterious
rs780873643	Val [V]/Gly [G]	0	Intolerant	0.943	Probably damaging	−6.041	Deleterious
rs775691314	Ser [S]/Cys [C]	0	Intolerant	0.984	Probably damaging	−3.556	Deleterious
rs772619265	Ile [I]/Val [V]	0.4	Tolerant	0.02	Benign	−0.515	Neutral
rs760061096	Ile [I]/Lys [K]	0	Intolerant	0.824	Possibly damaging	−5.896	Deleterious
rs749789723	Leu [L]	–	–	–	–	–	–
rs1205719797	Leu [L]/His [H]	0	Intolerant	0.999	Probably damaging	−6.482	Deleterious
rs1364855365	Thr [T]/Ser [S]	0.58	Tolerant	0.065	Benign	−0.827	Neutral
rs368432491	Asn [N]/Ser [S]	1	Tolerant	0.006	Benign	1.283	Neutral
rs182778895	Ser [S]/Pro [P]	1	Tolerant	0.004	Benign	1.098	Neutral
rs777540740	Ser [S]/Cys [C]	0.06	Tolerant	0.031	Benign	−2.516	Deleterious
rs769325995	Tyr [Y]/His [H]	0.11	Tolerant	0.32	Benign	−4.3	Deleterious
rs374492763	Arg [R]/Gln [Q]	0.04	Intolerant	0.771	Possibly damaging	−3.702	Deleterious
rs374492763	Arg [R]/Leu [L]	0	Intolerant	0.906	Possibly damaging	−6.535	Deleterious
rs938526894	Leu [L]/Pro [P]	0	Intolerant	0.811	Possibly damaging	−4.885	Deleterious
rs1312418962	Met [M]/Thr [T]	0.03	Intolerant	0.411	Benign	−3.131	Deleterious
rs1421580115	Val [V]/Met [M]	0.04	Intolerant	0.007	Benign	0.763	Neutral
rs1324205444	Ala [A]/Thr [T]	0	Intolerant	0.842	Possibly damaging	−0.976	Neutral
rs1324205444	Ala [A]/Ser [S]	1	Tolerant	0.138	Benign	1.321	Neutral
rs780067980	Gly [G]/Arg [R]	0	Intolerant	1	Probably damaging	−7.439	Deleterious
rs369101584	Asn [N]/Ser [S]	0.01	Intolerant	0.919	Probably damaging	−4.649	Deleterious
rs757366672	Gly [G]/Cys [C]	0	Intolerant	0.507	Possibly damaging	−2.067	Neutral
rs767670296	Ile [I]/Asn [N]	0	Intolerant	0.99	Probably damaging	−6.223	Deleterious
rs1272816101	Ile [I]/Met [M]	0	Intolerant	0.985	Probably damaging	−2.411	Neutral
rs759952425	Tyr [Y]/His [H]	0	Intolerant	0.986	probaly damaging	−4.763	Deleterious
rs751917665	Thr [T]/Met [M]	0.03	Intolerant	0.075	Benign	−2.321	Neutral
rs1441375275	Ala [A]/Thr [T]	0	Intolerant	0.955	Probably damaging	−3.749	Deleterious
rs763345848	Gly [G]/Asp [D]	0	Intolerant	0.96	Probably damaging	−6.283	Deleterious
rs1461795294	Ser [S]/Gly [G]	0.47	Tolerant	0.013	Benign	−1.028	Neutral
rs773717998	Thr [T]/Asn [N]	0	Intolerant	0.986	Probably damaging	−4.736	Deleterious
rs1162318193	Ile [I]/Thr [T]	0	Intolerant	0.775	Possibly damaging	−4.7	Deleterious
rs1050103029	Val [V]/Ala [A]	1	Tolerant	0.071	Benign	0.25	Neutral
rs764683908	Gly [G]/Asp [D]	0	Intolerant	1	Probably damaging	−6.631	Deleterious
rs776435170	Ala [A]/Thr [T]	0.02	Intolerant	0.032	Benign	−0.943	Neutral
rs1236921754	Ala [A]/Val [V]	1	Tolerant	0.006	Benign	1.67	Neutral
rs746863503	Met [M]/Arg[R]	0	Intolerant	0.034	Benign	−1.288	Neutral
rs775407568	Met [M]/Ile [I]	0.06	Tolerant	0.001	Benign	−0.367	Neutral
rs771855037	Ala [A]/Thr [T]	0.01	Intolerant	0.102	Benign	−0.618	Neutral
rs140815551	Val [V]/Ile [I]	0.03	Intolerant	0.047	Benign	−0.733	Neutral
rs1348497054	Ser [S]/Cys [C]	0	Intolerant	0.929	Probably damaging	−4.52	Deleterious
rs1469035471	Val [V]/Leu [L]	1	Tolerant	0.105	Benign	0.367	Neutral
rs372845210	Leu [L]/Ile [I]	0.04	Intolerant	0.817	Possibly damaging	−1.156	Neutral
rs372845210	Leu [L]/Phe [F]	0	Intolerant	0.94	Probably damaging	−3.045	Deleterious

(*continued on next page*)

Table 2 (*continued*)

dbSNP id	Proteinresidue	SIFT score	SIFTprediction	PolyPhenscore	PolyPhenprediction	PROVEANscore	PROVEAN prediction
rs1380054283	Glu [E]/Gln [Q]	0	Intolerant	0.984	Probably damaging	−2.416	Neutral
rs999185720	Glu [E]/Asp [D]	0.31	Tolerant	0.162	Benign	−2.169	Neutral
rs745619267	Lys [K]/Asn [N]	0	Intolerant	0.821	Possibly damaging	−2.418	Neutral
rs76362149	Ala [A]/Ser [S]	0	Intolerant	0.457	Possibly damaging	−2.448	Neutral
rs781225543	Arg [R]/Gln [Q]	0	Intolerant	1	Probably damaging	−3.368	Deleterious
rs1321655963	Arg [R]/Cys [C]	0	Intolerant	0.998	Probably damaging	−6.914	Deleterious
rs755000812	Arg [R]/His [H]	0	Intolerant	0.996	Probably damaging	−4.126	Deleterious
rs1223071449	Phe [F]/Leu [L]	0.14	Tolerant	0.004	Benign	−2.507	Deleterious
rs1430684701	Leu [L]/Pro [P]	0	Intolerant	0.988	Probably damaging	−5.765	Deleterious
rs747262541	Ser [S]/Asn [N]	0.01	Intolerant	0.361	Benign	−1.303	Neutral
rs868182136	Gly [G]/Glu [E]	0	Intolerant	0.99	Probably damaging	−6.873	Deleterious
rs780255530	Met [M]/Val [V]	0	Intolerant	0.491	Possibly damaging	−3.484	Deleterious
rs758699271	Met [M]/Ile [I]	0	Intolerant	0.612	Possibly damaging	−3.451	Deleterious
rs946622803	Phe [F]/Leu [L]	0.49	Tolerant	0.006	Benign	0.13	Neutral
rs1381085405	Phe [F]/Tyr [Y]	0.23	Tolerant	0.652	Possibly damaging	−0.543	Neutral
rs1381085405	Phe [F]/Ser [S]	0.41	Tolerant	0.063	Benign	0.376	Neutral
rs750782646	Ile [I]/Asn [N]	0	Intolerant	0.811	Possibly damaging	−4.874	Deleterious
rs765728439	Met [M]/Thr [T]	0	Intolerant	0.403	Benign	−5.185	Deleterious
rs757805176	Gly [G]/Arg [R]	0	Intolerant	0.752	Possibly damaging	−2.96	Deleterious
rs757805176	Gly [G]/Arg [R]	0	Intolerant	0.752	Possibly damaging	−2.96	Deleterious
rs1199637811	Val [V]/Gly [G]	0.19	Tolerant	0.027	Benign	−2.318	Neutral
rs121909747	Leu [L]/Arg [R]	0	Intolerant	0.947	Probably damaging	−4.842	Deleterious
rs 121,909,747	Leu [L] / Pro [P]	0.01	Intolerant	0.618	Possibly damaging	−5.813	Deleterious
rs760200790	Leu [L]/Arg [R]	0.6	Tolerant	0.139	Benign	−1.45	Neutral
rs766191732	Phe [F]/Leu [L]	0.69	Tolerant	0.002	Benign	−1.523	Neutral
rs1464417991	Ser [S]/Pro [P]	1	Tolerant	0.005	Benign	−0.341	Neutral
rs762668792	Val [V]/Glu [E]	0	Intolerant	0.866	Possibly damaging	−5.082	Deleterious
rs1457657980	Met [M]/Val [V]	0.27	Tolerant	0.03	Benign	−0.744	Neutral
rs1161394690	M (Met) > MM(MetMet)	–	–	–	–	–	–
rs374702599	Ile [I]/Thr [T]	0.18	Tolerant	0.002	Benign	−0.852	Neutral
rs1419532672	Ile [I]/Val [V]	0.19	Tolerant	0.139	Benign	−0.555	Neutral
rs2229608	Ile [I]/Thr [T]	0.21	Tolerant	0.401	Benign	−3.639	Deleterious
rs760729620	Phe [F]/Ser [S]	0	Intolerant	0.861	Possibly damaging	−7.529	Deleterious
rs140791627	Ser [S]/Cys [C]	0.05	Tolerant	0.082	Benign	−2.035	Neutral
rs746136121	Phe [F]/Leu [L]	0.06	Tolerant	0.38	Benign	−3.987	Deleterious
rs1353890919	Phe [F]/Cys [C]	0	Intolerant	1	Probably damaging	−7.57	Deleterious
rs966424064	Ile [I]/Thr [T]	0	Intolerant	0.206	Benign	−4.159	Deleterious
rs779212294	Ile [I]/Met [M]	0.08	Tolerant	0.643	Possibly damaging	−2.032	Neutral
rs121909744	Pro [P]/Arg [R]	0	Intolerant	0.998	Probably damaging	−8.516	Deleterious
rs121909744	Pro [P]/Leu [L]	0	Intolerant	0.994	Probably damaging	−9.463	Deleterious
rs1309197020	Ile [I]/Met [M]	0	Intolerant	1	Probably damaging	−2.838	Deleterious
rs1309197020	I (Ile) / I (Ile)	1	Tolerant	–	–	0	Neutral
rs749661374	Met [M]/Val [V]	0.01	Intolerant	0.004	Benign	0.655	Neutral
rs778490867	Met [M]/Thr [T]	0	Intolerant	0.016	Benign	−2.558	Deleterious
rs28928874	Val [V]/Glu [E]	0	Intolerant	0.976	Probably damaging	−5.619	Deleterious
rs367980651	Arg [R]/Cys [C]	0	Intolerant	0.983	Probably damaging	−7.42	Deleterious
rs75144723	Arg [R]/His [H]	0	Intolerant	0.986	Probably damaging	−4.632	Deleterious
rs754405476	Ala [A]/Thr [T]	0	Intolerant	0.992	Probably damaging	−3.706	Deleterious
rs1379813904	Ala [A]/Glu [E]	0	Intolerant	0.987	Probably damaging	−4.592	Deleterious
rs751226875	Ile [I]/Thr [T]	0	Intolerant	0.678	Possibly damaging	−3.063	Deleterious
rs762675284	Ala [A]/Ser [S]	0.07	Tolerant	0.665	Possibly damaging	−1.839	Neutral
rs1262058831	Ala [A]/Val [V]	0	Intolerant	0.99	Probably damaging	−3.433	Deleterious
rs758246412	Ala [A]/Glu [E]	0.02	Intolerant	0.515	Possibly damaging	−2.432	Neutral
rs1203908311	Asn [N]/Ser [S]	0	Intolerant	0.992	Probably damaging	−4.589	Deleterious
rs765196886	Ile [I]/Leu [L]	0.59	Tolerant	0.009	Benign	−0.308	Neutral
rs761784655	Ile [I]/Thr [T]	0	Intolerant	0.213	Benign	−3.564	Deleterious
rs776395971	Val [V]/Ala [A]	0	Intolerant	0.895	Possibly damaging	−3.625	Deleterious
rs1238600269	Ala [A]/Thr [T]	0	Intolerant	0.219	Benign	−2.469	Neutral
rs1418589512	Cys [C]/Arg [R]	0.13	Tolerant	0.532	Possibly damaging	−4.842	Deleterious
rs759480075	Tyr [Y]/His [H]	0.15	Tolerant	0.976	Probably damaging	−3.381	Deleterious
rs771274850	Ile [I]/Thr [T]	0.01	Intolerant	0.653	Possibly damaging	−2.456	Neutral
rs749710583	Ala [A]/Glu [E]	0.75	Tolerant	0.025	Benign	−1.512	Neutral
rs749710583	Ala [A]/Val [V]	0.18	Tolerant	0.025	Benign	−2.403	Neutral
rs774542648	Gly [G]/Arg [R]	0	Intolerant	0.734	Possibly damaging	−7.25	Deleterious
rs1272353608	Pro [P]/His [H]	0	Intolerant	0.598	Possibly damaging	−5.957	Deleterious
rs1381049817	Tyr [Y]/Cys [C]	0	Intolerant	0.439	Benign	−8.015	Deleterious
rs1336322605	Phe [F]/Leu [L]	0.67	Tolerant	0.002	Benign	1.022	Neutral
rs140138702	Leu [L]/Val [V]	0.26	Tolerant	0.085	Benign	−0.015	Neutral
rs770197371	Leu [L]/Arg [R]	0	Intolerant	0.944	Probably damaging	−4.636	Deleterious
rs748401954	Phe [F]/Ser [S]	0	Intolerant	0.999	Probably damaging	−7.315	Deleterious
rs374342938	Gly [G]/Ala [A]	0.15	Tolerant	0.02	Benign	0.329	Neutral
rs769037887	Val [V]/Met [M]	0.01	Intolerant	0.216	Benign	0.077	Neutral
rs556023421	Phe [F]/Leu [L]	0	Intolerant	0.919	Probably damaging	−5.436	Deleterious
rs5397	Leu [L]/Val [V]	0.41	Tolerant	0.04	Benign	−0.284	Neutral
rs5398	Phe [F]/Leu [L]	0	Intolerant	0.424	Benign	−5.276	Deleterious

Table 2 (*continued*)

dbSNP id	Proteinresidue	SIFT score	SIFTprediction	PolyPhenscore	PolyPhenprediction	PROVEANscore	PROVEAN prediction
rs757137603	Thr [T]/Ile [I]	0.09	Tolerant	0.12	Benign	−4.225	Deleterious
rs1441249949	Phe [F]/ Ile [I]	0	Intolerant	0.616	Possibly damaging	−4.39	Deleterious
rs1195253424	Val [V]/Ile [I]	0	Intolerant	0.971	Probably damaging	−0.908	Neutral
rs753575081	Pro [P]/Thr [T]	0	Intolerant	0.994	Probably damaging	−7.274	Deleterious
rs777806589	Lys [K]/Arg [R]	0.38	Tolerant	0.601	Possibly damaging	−1.518	Neutral
rs766600474	Ser [S]/Thr [T]	1	Tolerant	0.104	Benign	1.006	Neutral
rs766600474	Ser [S]/Ala [A]	0	Intolerant	0.304	Benign	−1.65	Neutral
rs1379944645	Glu [E]/Lys [K]	0.04	Intolerant	0.279	Benign	−3.223	Deleterious
rs1353603250	Glu [E]/Gln [Q]	0.19	Tolerant	0.759	Possibly damaging	−2.031	Neutral
rs1446857276	Glu [E]/Asp [D]	0.31	Tolerant	0.405	Benign	−0.5	Neutral
rs1283734332	Ile [I]/Thr [T]	0	Intolerant	0.999	Probably damaging	−4.518	Deleterious
rs1445660295	Ala [A]/Val [V]	0.02	Intolerant	0.444	Benign	−3.184	Deleterious
rs201797691	Ala [A]/Thr [T]	0.06	Tolerant	0.566	Possibly damaging	−1.562	Neutral
rs201797691	Ala [A]/Pro [P]	0.03	Intolerant	0.979	Probably damaging	−2.518	Deleterious
rs200160167	Ala [A]/Glu [E]	0.05	Tolerant	0.302	Benign	−1.482	Neutral
rs200160167	Ala [A]/Val [V]	0.03	Intolerant	0.566	Possibly damaging	−2.596	Deleterious
rs762305192	Phe [F]/Leu [L]	0	Intolerant	0.866	Possibly damaging	−5.144	Deleterious
rs776826621	Lys [K]/Asn [N]	0.2	Tolerant	0.005	Benign	−1.549	Neutral
rs5399	Lys [K]/Asn [N]	0.41	Tolerant	0.004	Benign	−2.272	Neutral
rs1412427073	Gly [G]/Ser [S]	0.28	Tolerant	0.004	Benign	−1.628	Neutral
rs966895511	Ala [A]/Ser [S]	0.83	Tolerant	0.004	Benign	−0.449	Neutral
rs1199349184	Ala [A]/Val [V]	0.24	Tolerant	0.004	Benign	−1.611	Neutral
rs374630641	Arg [R]/Ser [S]	0.94	Tolerant	0.001	Benign	0.45	Neutral
rs771586150	Pro [P]/Gln [Q]	0.47	Tolerant	0.007	Benign	−1.564	Neutral
rs776597156	Lys [K]/Asn[N]	0.04	Intolerant	0.017	Benign	−1.772	Neutral
rs770462591	Ala [A]/Asp [D]	0.41	Tolerant	0.002	Benign	−1.217	Neutral
rs770462591	Ala [A]/Val [V]	0.16	Tolerant	0.007	Benign	−1.309	Neutral
rs141574520	Phe [F]/Tyr [Y]	1	Tolerant	0.003	Benign	0.369	Neutral
rs147959014	Gly [G]/Glu [E]	0.01	Intolerant	0.104	Benign	−2.153	Neutral
rs752687355	Glu [E]/Gly[G]	0.03	Intolerant	0.009	Benign	−2.391	Neutral
rs781215842	Thr [T]/Ser [S]	0.82	Tolerant	0.004	Benign	0.326	Neutral
rs758607933	Val[V]/Met[M]	0	Intolerant	0.004	Benign	−1.155	Neutral

Variants with tolerance index $\leq$ 0.05 score of SIFT was considered as deleterious while others are taken to be tolerant. By PolyPhen, the variations with probabilistic score above 0.85 and 0.15 were considered to be "Probably damaging" and "possibly damaging" respectively while all the resting were categorized to be "Benign". Provean score was equal to or below −2.5 it may be considered as deleterious and if the score was above −2.5, it was considered as neutral.

Henikoff, 2001). It mainly considers homologous sequence alignment and physical amino acid properties to forecast possible influence of nsSNPs on protein. Out of 293 nsSNPs, 167 were forecasted to be damaging (Table 2). PolyPhen-2 (Adzhubei et al., 2010) was used to predict structural and functional influence of the nsSNPs lying in GLUT2. It considers homologous sequences and 3D structures of protein to predict the possible potential effect of SNPs on protein. Out of 293 nsSNPs, 165 were considered to be benign. 65 were predicted to be possibly damaging and 77 were considered to be probably damaging as shown in Table 2.

PROVEAN gave score to forecast neutral and deleterious effect of 293 nsSNPs present in coding region of GLUT2 protein. If the score was equal to or below −2.5 the results were deleterious and if the score was above −2.5, it was neutral. Out of 293 nsSNPs, 162 were considered to be neutral and 138 were predicted to be deleterious. It also gave the results of inframe deletion and insertion. Out of 4 inframe deletion 2 (rs772999215), (rs774721090) were found to be deleterious while others have shown no results. 3 SNPs were inframe insertion (rs1161394690), (rs1463507753), (rs749789723) and no results were found for them (Table 2).

The SNPeffect server was used to predict the effect of molecular phenotype of nsSNPs present in coding region of GLUT2. To find the effect of 293 nsSNPs on aggregation tendency, amyloid propensity and chaperon binding tendency, the dTANGO, dWALTZ and dLIMBO score was obtained. In a protein sequence, aggregation propensity was detected by dTANGO. Out of 293 nsSNPs, 61 were predicted to decrease and 27 to increase the aggregation propensity while 211 had not affect. Amyloid propensity was given by dWALTZ. 23 were expected to increase the amyloid propensity, 16 to decrease the amyloid propensity and 257 had not affect. According to dLIMBO, the chaperon binding tendency was given. None of the nsSNPs had any affecte on chaperon binding tendency (Table 3).

The recessive autosomal disease characterized by acquisition of hepatorenal glycogen, Fanconi nephropathy, galactose and improper carbohydrate utilization is FBS (Fanconi, 1949). Santer *et al* firstly recognized the underlying defect and GLUT2 as a possible site for the central defect, and three mutations in the GLUT2 gene have been investigated in this concern. At neucleotide 1405, the C / T transition was reported to result in production of truncated GLUT-2 protein leading to development to FBS. (Santer et al., 1997). Our rsults are in line with this study because same nsSNP is predicted to be intolerant, probably damaging and deleterious by SIFT, PolyPhen and PROVEAN respectively.

In human SLC2A2 several SNPs have been described: that are situated at the coding region rs7637863 Pro[P]/Leu[L] at position 68 and rs5400 Thr[T]/Ile[I] at 110 position. The connection of these SNPs with type 2 diabetes is contentious (Barroso et al., 2003). Since then, this "historical" GLUT2 SNP has been analyzed in several genetic studies, and incompatible conclusions were reached: the SNP Thr[T]/Ile[I] at 110 position was showed either related (Barroso et al., 2003; Burgdorf et al., 2011) or not related (Miller et al., 2001;) with a risk of type 2 diabetes. Other study finds out that, rs5400 was related with the alteration from impaired glucose tolerance to hypercholesterolemia and type 2 diabetes (Laukkanen et al., 2005). During an OGTT performed on subjects stratified according to rs5400 genotype, no variation was shown in insulin secretion (Burgdorf et al., 2011), indicates that neither insulin content nor β cell mass are affected. (Laukkanen et al., 2005). In our study rs5400 was predicted to be tolerant, benign, neutral and responsible for increased aggregation tendency by SIFT, PolyPhen, PROVEAN and dTANGO respectively. Interestingly, this GLUT2 vari-

Table 3
Analysis of nsSNPs by SNPeffect in coding region of human GLUT2 protein.

dbSNP rs#cluster id	Proteinresidue	dTANGO	Aggregationtendency	dWALTZ	Amyloidpropensity	dLIMBO	Chaperone bindingtendency
rs759495940	Met [M]/Ile [I]	0	No effect	0	No effect	0	No effect
rs773205789	Thr [T]/Pro [P]	0	No effect	0	No effect	0	No effect
rs200073044	Asp [D]/His [H]	−101	Decrease	0.76	No effect	0	No effect
rs1372689853	Lys [K]/Glu [E]	−110.2	Decreases	−0.49	No effect	0	No effect
rs767313610	Val [V]/Ile [I]	−5.8	No effect	0	No effect	0	No effect
rs369700669	Thr [T]/Asn [N]	−109.6	Decreases	0.01	No effect	0	No effect
rs1481905618	Phe [F]/Leu [L]	−1.1	No effect	0.12	No effect	0	No effect
rs1247912820	Thr [T]/Asn [N]	−9.9	No effect	0.97	No effect	0	No effect
rs1247912820	Thr [T]/Ser [S]	−2.7	No effect	0.34	No effect	0	No effect
rs372441014	Val [V]/Leu [L]	−0.5	No effect	0.12	No effect	0	No effect
rs766364438	Ile [I]/Thr [T]	−19.8	No effect	0.96	No effect	0	No effect
rs867315854	Ala [A]/Thr [T]	−5.6	No effect	0.04	No effect	0	No effect
rs761992056	Gly [G]/Asp [D]	−66	Decreases	2.67	No effect	0	No effect
rs369781481	Phe [F]/Leu [L]	−22.4	No effect	0.12	No effect	0	No effect
rs1409436045	Phe [F]/Tyr [Y]	−8.7	No effect	0.21	No effect	0	No effect
rs1049223265	Ile [I]/Thr [T]	0	No effect	−0.09	No effect	0	No effect
rs1437312005	Gly [G]/Ser [S]	0	No effect	0.76	No effect	0	No effect
rs1437312005	Gly [G]/Arg [R]	0	No effect	−0.09	No effect	0	No effect
rs775531825	Asn [N]/Ser [S]	0.1	No effect	−0.08	No effect	0	No effect
rs143528640	Ala [A]/Thr [T]	0	No effect	0	No effect	0	No effect
rs746158263	Pro [P]/Thr [T]	4	No effect	−0.02	No effect	0	No effect
rs1158195535	Gln [Q]/Lys [K]	−4.3	No effect	−559.66	Decreases	0	No effect
rs1158195535	Gln [Q]/Glu [E]	11	No effect	−62.94	Decreases	0	No effect
rs1451394300	Val [V]/Ile [I]	−0.9	No effect	−116.97	Decreases	0	No effect
rs1477523180	Ile [I]/Leu [L]	−2.5	No effect	−3.89	No effect	0	No effect
rs1360464436	Ile [I]/Lys [K]	−4.3	No effect	−417.77	Decreases	0	No effect
rs1176350402	Ile [I]/Thr [T]	−4.3	No effect	−571.42	Decreases	0	No effect
rs758670698	Arg [R]/Ile [I]	110.7	Increases	−0.73	No effect	0	No effect
rs760618624	His [H]/Tyr [Y]	1.1	No effect	0	No effect	0	No effect
rs775791143	Val [V]/Ile [I]	0	No effect	0.01	No effect	0	No effect
rs149108283	Val [V]/Asp [D]	1.7	No effect	−0.72	No effect	0	No effect
rs149108283	Val [V]/Ala [A]	0	No effect	0.01	No effect	0	No effect
rs1159338702	Gly [G]/Ser [S]	0	No effect	0.02	No effect	0	No effect
rs561765982	Val [V]/Ile [I]	0	No effect	0	No effect	0	No effect
rs983907950	Pro [P]/Ser [S]	24.1	No effect	−0.27	No effect	0	No effect
rs1211075508	Leu [L]/Pro [P]	0	No effect	0.23	No effect	0	No effect
rs1311902495	Asp [D]/Asn [N]	−1.9	No effect	1.14	No effect	0	No effect
rs1311902495	Asp [D]/Tyr [Y]	−1.9	No effect	1.01	No effect	0	No effect
rs771477447	Arg [R]/Gly [G]	0.7	No effect	0.07	No effect	0	No effect
rs145210664	Arg [R]/Gln [Q]	0.6	No effect	−0.52	No effect	0	No effect
rs546539032	Lys [K]/Asn [N]	2.3	No effect	0.11	No effect	0	No effect
rs747555903	Val [V]/Ile [I]	−0.1	No effect	−58.27	Decreases	0	No effect
rs977284195	Ile [I]/Thr [T]	−1	No effect	0.02	No effect	0	No effect
rs780903829	Ile [I]/Met [M]	−1	No effect	0.01	No effect	0	No effect
rs1373290524	Ser [S]/Thr [T]	1	No effect	0	No effect	0	No effect
rs1310901426	Thr [T]/Ala [A]	−0.1	No effect	0.02	No effect	0	No effect
rs1354126805	Thr [T]/Arg [R]	1.6	No effect	−0.03	No effect	0	No effect
rs754585542	Asp [D]/Asn [N]	−1.9	No effect	0.76	No effect	0	No effect
rs1217666649	Asp [D]/Glu [E]	0	No effect	0.01	No effect	0	No effect
rs1391257598	Pro [P]/Thr [T]	0	No effect	0.33	No effect	0	No effect
rs7637863	Pro [P]/Leu [L]	6.5	No effect	7.11	No effect	0	No effect
rs779977931	Thr [T]/Lys [K]	0	No effect	−0.35	No effect	0	No effect
rs1182852354	Ile [I]/Val [V]	0	No effect	−0.44	No effect	0	No effect
rs750405382	Met [M]/Val [V]	3.5	No effect	0.26	No effect	0	No effect
rs1207297111	Asn [N]/Asp [D]	1.7	No effect	−0.72	No effect	0	No effect
rs1342979475	Asn [N]/Thr [T]	0	No effect	0	No effect	0	No effect
rs1274084408	Pro [P]/Ala [A]	0	No effect	0	No effect	0	No effect
rs778655073	Pro [P]/Leu [L]	0	No effect	0	No effect	0	No effect
rs549263048	Trp [W]/Arg [R]	0	No effect	0	No effect	0	No effect
rs531049536	Trp [W]/Cys [C]	0.1	No effect	−0.05	No effect	0	No effect
rs150851401	Glu [E]/Lys [K]	−1.3	No effect	0.86	No effect	0	No effect
rs766762468	Thr [T]/Ser [S]	−3.4	No effect	0.72	No effect	0	No effect
rs766762468	T (Thr) > I (Ile)	56.4	Increases	−14.66	No effect	0	No effect
rs763255363	Ala [A]/Ser [S]	−17.7	No effect	6.87	No effect	0	No effect
rs144715667	Ile [I]/Val [V]	12	No effect	−212.15	Decreases	0	No effect
rs1415169647	Met [M]/Arg [R]	−820.3	Decreases	227.06	Increases	0	No effect
rs1407375423	Trp [W]/Cys [C]	−662.7	Decreases	200.31	Increases	0	No effect
rs1800572	Val [V]/Ile [I]	−16	No effect	5.29	No effect	0	No effect
rs1800572	V (Val) > L (Leu)	−161.8	Decreases	45.81	No effect	0	No effect
rs770135219	Val [V]/Ala [A]	−382.9	Decreases	93.15	Increases	0	No effect
rs1399091893	Ala [A]/Val [V]	456.9	Increases	−154.77	Decreases	0	No effect
rs1332764085	Val [V]/Ile [I]	−12.4	No effect	3.22	No effect	0	No effect
rs5400	Thr [T]/Ile [I]	142.4	Increases	−3.5	No effect	0	No effect
rs377238940	Ala [A]/Pro [P]	−7.5	No effect	−7.19	No effect	0	No effect

Table 3 (*continued*)

dbSNP rs#cluster id	Proteinresidue	dTANGO	Aggregationtendency	dWALTZ	Amyloidpropensity	dLIMBO	Chaperone bindingtendency
rs768407637	Gly [G]/Val [V]	395.8	Increases	−4.57	No effect	0	No effect
rs753980727	Trp [W]/Cys [C]	−4.8	No effect	0	No effect	0	No effect
rs746632604	Gly [G]/Ala [A]	3.2	No effect	−0.03	No effect	0	No effect
rs772002572	Thr [T]/Ile [I]	3.6	No effect	−0.02	No effect	0	No effect
rs1476520648	Ile [I]/Asn [N]	6.4	No effect	0.04	No effect	0	No effect
rs760201098	Ala [A]/Asp [D]	179.3	Increases	−3.71	No effect	0	No effect
rs1267904495	Met [M]/Thr [T]	−39.4	No effect	0.97	No effect	0	No effect
rs1212980167	Met [M]/Ile [I]	212.1	Increases	−4.25	No effect	0	No effect
rs367856967	Val [V]/Ala [A]	−393	Decreases	11.97	No effect	0	No effect
rs970550665	Ala [A]/Gly [G]	−345	Decreases	−1.75	No effect	0	No effect
rs775283150	Ile [I]/Phe [F]	13.1	No effect	−3.23	No effect	0	No effect
rs913419413	Leu [L]/Arg [R]	−1039.9	Decreases	−4.86	No effect	0	No effect
rs771843187	Ser [S]/Pro [P]	−962.7	Decreases	49.25	No effect	0	No effect
rs144125084	Val [V]/Leu [L]	−119	Decreases	5.37	No effect	0	No effect
rs993833041	Val [V]/Ala [A]	−567.9	Decreases	28.42	No effect	0	No effect
rs1300072764	Gly [G]/Glu [E]	−327.2	Decreases	5.99	No effect	0	No effect
rs778548964	Leu [L]/Phe [F]	87.5	Increases	−2.88	No effect	0	No effect
rs1016384738	Met [M]/Lys [K]	−378.4	Decreases	11.06	No effect	0	No effect
rs770941010	Gly [G]/Arg [R]	−228.7	Decreases	6.26	No effect	0	No effect
rs777718289	Gly [G]/Glu [E]	3.5	No effect	−0.81	No effect	0	No effect
rs777718289	Gly [G]/Val [V]	0.6	No effect	0.19	No effect	0	No effect
rs372621339	Pro [P]/Arg [R]	−2.6	No effect	1.25	No effect	0	No effect
rs747025551	Ile [I]/Thr [T]	−254.4	Decreases	−380.89	Decreases	0	No effect
rs376064965	Leu [L]/Phe [F]	90.6	Increases	99.92	Increases	0	No effect
rs1188886679	Ile [I]/Leu [L]	−87.4	Decreases	−29.47	No effect	0	No effect
rs1188886679	Ile [I]/Val [V]	9.3	No effect	−467.67	Decreases	0	No effect
rs192720796	Ile [I]/Lys [K]	−292.7	Decreases	−470.84	Decreases	0	No effect
rs910976682	Ala [A]/Val [V]	190.3	Increases	−165.8	Decreases	0	No effect
rs750836049	Gly [G]/Arg [R]	−136.3	Decreases	37.18	No effect	0	No effect
rs1278964539	Arg [R]/Lys [K]	−0.1	No effect	−0.07	No effect	0	No effect
rs1231468128	Leu [L]/Gln [Q]	−8	No effect	−0.23	No effect	0	No effect
rs1445887606	Tyr [Y]/His [H]	−9.1	No effect	−6.28	No effect	0	No effect
rs1271546287	Ile [I]/Thr [T]	−10.1	No effect	−12.03	No effect	0	No effect
rs760095835	Gly [G]/Asp [D]	−2.3	No effect	−0.62	No effect	0	No effect
rs1335888503	Val [V]/Leu [L]	0	No effect	−0.02	No effect	0	No effect
rs1293130515	Met [M]/Thr [T]	0	No effect	−0.02	No effect	0	No effect
rs1019696977	Ile [I]/Val [V]	0	No effect	−5.05	No effect	0	No effect
rs144822218	Gly [G]/Ser [S]	0	No effect	43.87	No effect	0	No effect
rs759047405	Gly [G]/Asp [D]	1.7	No effect	−6.74	No effect	0	No effect
rs1441606652	Ala [A]/Val [V]	0	No effect	7.16	No effect	0	No effect
rs368626129	Ala [A]/Thr [T]	0	No effect	0.02	No effect	0	No effect
rs368626129	Ala [A]/Ser [S]	0	No effect	0.01	No effect	0	No effect
rs200213178	Ala [A]/Thr [T]	−0.1	No effect	0.01	No effect	0	No effect
rs200213178	Ala [A]/Pro [P]	−0.1	No effect	0	No effect	0	No effect
rs748052042	Leu [L]/Phe [F]	0.7	No effect	0	No effect	0	No effect
rs1412289847	Gly [G]/Ser [S]	0.1	No effect	0.02	No effect	0	No effect
rs776498787	Gly [G]/Asp [D]	0.4	No effect	−0.61	No effect	0	No effect
rs779065938	Leu [L]/Val [V]	36.5	No effect	146.08	Increases	0	No effect
rs1469335096	Ala [A]/Thr [T]	−20.5	No effect	4.53	No effect	0	No effect
rs771182536	Ile [I]/Asn [N]	−603.7	Decreases	96.63	Increases	0	No effect
rs771182536	Ile [I]/Thr [T]	−306.2	Decreases	63.05	Increases	0	No effect
rs121909741	Val [V]/Ile [I]	−2.4	No effect	−10.45	No effect	0	No effect
rs149460434	Thr [T]/Lys [K]	502	Increases	54.29	Increases	0	No effect
rs149460434	Thr [T]/Met [M]	14.7	No effect	−16.93	No effect	0	No effect
rs1276756236	Leu [L]/Ile [I]	16.9	No effect	−17.56	No effect	0	No effect
rs779591826	Ile [I]/Met [M]	−147	Decreases	82.45	Increases	0	No effect
rs1262860274	Ile [I]/Thr [T]	−148.5	Decreases	77.8	Increases	0	No effect
rs1186359171	Gly [G]/Ser [S]	12.2	No effect	−13.3	No effect	0	No effect
rs1215469128	Leu [L]/Ser [S]	0.7	No effect	−9.46	No effect	0	No effect
rs1347267249	Asn [N]/His [H]	1	No effect	−3.73	No effect	0	No effect
rs573292685	Asn [N]/Ser [S]	0.9	No effect	−5.01	No effect	0	No effect
rs764799427	Asp [D]/Val [V]	905.2	Increases	−37.64	No effect	0	No effect
rs1380319602	Ile [I]/Asn [N]	−54	Decreases	−78.29	Decreases	0	No effect
rs760641937	Gly [G]/Ala [A]	209.4	Increases	−34.8	No effect	0	No effect
rs1413841367	Leu [L]/Pro [P]	−45.1	No effect	8.09	No effect	0	No effect
rs771075989	Val [V]/Met [M]	−2.4	No effect	0.47	No effect	0	No effect
rs773581866	Arg [R]/Gly [G]	174.1	Increases	−49	No effect	0	No effect
rs770126214	Leu [L]/Ile [I]	60.4	Increases	−3.97	No effect	0	No effect
rs1374154306	Leu [L]/Gln [Q]	−491.6	Decreases	317.25	Increases	0	No effect
rs748588515	Leu [L]/Phe [F]	15.7	No effect	32.66	No effect	0	No effect
rs757087261	Phe [F]/Ile [I]	−4.5	No effect	−9.69	No effect	0	No effect
rs777020657	Phe [F]/Cys [C]	−264.3	Decreases	1.76	No effect	0	No effect
rs777020657	F (Phe) > S (Ser)	−295.4	Decreases	40.37	No effect	0	No effect
rs769089021	Ser [S]/Asn [N]	−0.1	No effect	0	No effect	0	No effect
rs780381836	Arg [R]/Gly [G]	4.2	No effect	147.36	Increases	0	No effect

(*continued on next page*)

Table 3 (*continued*)

dbSNP rs#cluster id	Proteinresidue	dTANGO	Aggregationtendency	dWALTZ	Amyloidpropensity	dLIMBO	Chaperone bindingtendency
rs1480881050	Tyr [Y]/His [H]	−1.6	No effect	−8.07	No effect	0	No effect
rs1250722271	Tyr [Y]/His [H]	−2.3	No effect	−8.13	No effect	0	No effect
rs1158317020	Tyr [Y]/Phe [F]	7.6	No effect	−6.38	No effect	0	No effect
rs867996396	Ile [I]/Asn [N]	−2.3	No effect	−8.12	No effect	0	No effect
rs867996396	I (Ile) > T (Thr)	−2.3	No effect	−8.19	No effect	0	No effect
rs536261161	Lys [K]/Asn [N]	62.3	Increases	385.31	Increases	0	No effect
rs745373269	Asp [D]/Asn [N]	−4.2	No effect	0.87	No effect	0	No effect
rs745373269	Asp [D]/His [H]	−4.2	No effect	1.41	No effect	0	No effect
rs1367431424	Glu [E]/Ala [A]	11.5	No effect	0.95	No effect	0	No effect
rs865881030	Glu [E]/Lys [K]	−1.8	No effect	1.2	No effect	0	No effect
rs778607566	Glu [E]/Gly [G]	4	No effect	1.31	No effect	0	No effect
rs1309254226	Glu [E]/Asp [D]	−0.1	No effect	0.45	No effect	0	No effect
rs777225980	Ser [S]/Arg [R]	−0.2	No effect	−0.6	No effect	0	No effect
rs76026576	Leu [L]/Phe [F]	0	No effect	0.07	No effect	0	No effect
rs1490504926	Asp [D]/Asn [N]	−1.9	No effect	0.74	No effect	0	No effect
rs935009475	Asp [D]/Glu [E]	0	No effect	0.01	No effect	0	No effect
rs140285191	Asp [D]/Asn [N]	−1.9	No effect	1.25	No effect	0	No effect
rs140285191	Asp [D]/Tyr [Y]	−1.9	No effect	2.54	No effect	0	No effect
rs754932741	Met [M]/Ile [I]	0	No effect	0.08	No effect	0	No effect
rs750579210	Arg [R]/Gly [G]	−0.2	No effect	0.03	No effect	0	No effect
rs1304842107	Lys [K]/Gln [Q]	−0.2	No effect	0.03	No effect	0	No effect
rs765426962	Lys [K]/Thr [T]	−0.2	No effect	0.03	No effect	0	No effect
rs761756532	Lys [K]/Asn [N]	−0.2	No effect	0.03	No effect	0	No effect
rs1329237779	Glu [E]/Lys [K]	−1.9	No effect	0.76	No effect	0	No effect
rs1384542256	Glu [E]/Ala [A]	−1.9	No effect	0.76	No effect	0	No effect
rs776912318	Ser [S]/Arg [R]	−1.3	No effect	−0.29	No effect	0	No effect
rs776912318	Ser [S]/Cys [C]	0.1	No effect	−0.04	No effect	0	No effect
rs764161243	Lys [K]/Thr [T]	123	Increases	−19.4	No effect	0	No effect
rs780873643	Val [V]/Gly [G]	−69.1	Decreases	4.31	No effect	0	No effect
rs775691314	Ser [S]/Cys [C]	30.7	No effect	−9.87	No effect	0	No effect
rs772619265	Ile [I]/Val [V]	10.1	No effect	97.69	Increases	0	No effect
rs760061096	Ile [I]/Lys [K]	−201.9	Decreases	−43.38	No effect	0	No effect
rs1205719797	Leu [L]/His [H]	−203	Decreases	−200.41	Decreases	0	No effect
rs1364855365	Thr [T]/Ser [S]	−54.4	Decreases	69.79	Increases	0	No effect
rs368432491	Asn [N]/Ser [S]	5.5	No effect	−2.26	No effect	0	No effect
rs182778895	Ser [S]/Pro [P]	−4.4	No effect	−0.59	No effect	0	No effect
rs777540740	Ser [S]/Cys [C]	0.9	No effect	0.46	No effect	0	No effect
rs769325995	Tyr [Y]/His [H]	−0.9	No effect	−0.61	No effect	0	No effect
rs374492763	Arg [R]/Gln [Q]	0.6	No effect	0.05	No effect	0	No effect
rs374492763	Arg [R]/Leu [L]	0.5	No effect	0.06	No effect	0	No effect
rs938526894	Leu [L]/Pro [P]	−548.4	Decreases	0.15	No effect	0	No effect
rs1312418962	Met [M]/Thr [T]	−36.1	No effect	0.01	No effect	0	No effect
rs1421580115	Val [V]/Met [M]	−30.3	No effect	0.05	No effect	0	No effect
rs1324205444	Ala [A]/Thr [T]	−4.9	No effect	−0.03	No effect	0	No effect
rs1324205444	Ala [A]/Ser [S]	−15	No effect	−0.04	No effect	0	No effect
rs780067980	Gly [G]/Arg [R]	−12.6	No effect	0.05	No effect	0	No effect
rs369101584	Asn [N]/Ser [S]	42.5	No effect	−0.2	No effect	0	No effect
rs757366672	Gly [G]/Cys [C]	33.1	No effect	−190.41	Decreases	0	No effect
rs767670296	Ile [I]/Asn [N]	−470.3	Decreases	−49.94	No effect	0	No effect
rs1272816101	Ile [I]/Met [M]	−365.7	Decreases	−30.37	No effect	0	No effect
rs759952425	Tyr [Y]/His [H]	−553.7	Decreases	−590.8	Decreases	0	No effect
rs751917665	Thr [T]/Met [M]	14.8	No effect	−0.05	No effect	0	No effect
rs1441375275	Ala [A]/Thr [T]	−2.3	No effect	0.02	No effect	0	No effect
rs763345848	Gly [G]/Asp [D]	−8.9	No effect	−0.68	No effect	0	No effect
rs1461795294	Ser [S]/Gly [G]	−0.1	No effect	0	No effect	0	No effect
rs773717998	Thr [T]/Asn [N]	−0.9	No effect	0.03	No effect	0	No effect
rs1162318193	Ile [I]/Thr [T]	−61.4	Decreases	0	No effect	0	No effect
rs1050103029	Val [V]/Ala [A]	−116.3	Decreases	0.03	No effect	0	No effect
rs764683908	Gly [G]/Asp [D]	−148.2	Decreases	2.22	No effect	0	No effect
rs776435170	Ala [A]/Thr [T]	−37.9	No effect	0.01	No effect	0	No effect
rs1236921754	Ala [A]/Val [V]	274.6	Increases	0	No effect	0	No effect
rs746863503	Met [M]/Arg [R]	−234.8	Decreases	3.51	No effect	0	No effect
rs775407568	Met [M]/Ile [I]	86.5	Increases	0.83	No effect	0	No effect
rs771855037	Ala [A]/Thr [T]	−1.1	No effect	0.01	No effect	0	No effect
rs140815551	Val [V]/Ile [I]	−0.1	No effect	0.01	No effect	0	No effect
rs1348497054	Ser [S]/Cys [C]	0.2	No effect	−0.05	No effect	0	No effect
rs1469035471	Val [V]/Leu [L]	−0.2	No effect	0.16	No effect	0	No effect
rs372845210	Leu [L]/Ile [I]	0.5	No effect	0.06	No effect	0	No effect
rs372845210	Leu [L]/Phe [F]	0.5	No effect	0.03	No effect	0	No effect
rs1380054283	Glu [E]/Gln [Q]	−16.6	No effect	0.77	No effect	0	No effect
rs999185720	Glu [E]/Asp [D]	−0.1	No effect	0	No effect	0	No effect
rs745619267	Lys [K]/Asn [N]	−10.2	No effect	0.03	No effect	0	No effect
rs76362149	Ala [A]/Ser [S]	−0.1	No effect	0	No effect	0	No effect
rs781225543	Arg [R]/Gln [Q]	1.3	No effect	−0.54	No effect	0	No effect
rs1321655963	Arg [R]/Cys [C]	10	No effect	−10.88	No effect	0	No effect

Table 3 (*continued*)

dbSNP rs#cluster id	Proteinresidue	dTANGO	Aggregationtendency	dWALTZ	Amyloidpropensity	dLIMBO	Chaperone bindingtendency
rs755000812	Arg [R]/His [H]	8.8	No effect	−10.45	No effect	0	No effect
rs1223071449	Phe [F]/Leu [L]	−5	No effect	−25.18	No effect	0	No effect
rs1430684701	Leu [L]/Pro [P]	−10.5	No effect	−27.2	No effect	0	No effect
rs747262541	Ser [S]/Asn [N]	−3.6	No effect	46.65	No effect	0	No effect
rs868182136	Gly [G]/Glu [E]	286.1	Increases	249.54	Increases	0	No effect
rs780255530	Met [M]/Val [V]	63.2	Increases	−24.52	No effect	0	No effect
rs758699271	Met [M]/Ile [I]	62.1	Increases	−24.31	No effect	0	No effect
rs946622803	Phe [F]/Leu [L]	−20.9	No effect	28.63	No effect	0	No effect
rs1381085405	Phe [F]/Tyr [Y]	−39.4	No effect	54.3	Increases	0	No effect
rs1381085405	Phe [F]/Ser [S]	−178.9	Decreases	280.03	Increases	0	No effect
rs750782646	Ile [I]/Asn [N]	−318.3	Decreases	268.28	Increases	0	No effect
rs765728439	Met [M]/Thr [T]	−3.8	No effect	14.75	No effect	0	No effect
rs757805176	Gly [G]/Arg [R]	−191	Decreases	26.9	No effect	0	No effect
rs757805176	Gly [G]/Arg [R]	−191	Decreases	26.9	No effect	0	No effect
rs1199637811	Val [V]/Gly [G]	−117.4	Decreases	11.9	No effect	0	No effect
rs121909747	Leu [L]/Arg [R]	−125.4	Decreases	11.4	No effect	0	No effect
rs 121,909,747	L (Leu) > P (Pro)	−133.3	Decreases	12.33	No effect	0	No effect
rs760200790	Leu [L]/Arg [R]	−62.3	Decreases	8.37	No effect	0	No effect
rs766191732	Phe [F]/Leu [L]	−25.2	No effect	0.37	No effect	0	No effect
rs1464417991	Ser [S]/Pro [P]	−94.9	Decreases	1.83	No effect	0	No effect
rs762668792	Val [V]/Glu [E]	−565.8	Decreases	46.57	No effect	0	No effect
rs1457657980	Met [M]/Val [V]	23.2	No effect	−2.74	No effect	0	No effect
rs374702599	Ile [I]/Thr [T]	−72.2	Decreases	43.39	No effect	0	No effect
rs1419532672	Ile [I]/Val [V]	−0.1	No effect	−2.52	No effect	0	No effect
rs2229608	Ile [I]/Thr [T]	5.3	No effect	−1.6	No effect	0	No effect
rs760729620	Phe [F]/Ser [S]	−14.9	No effect	−2.61	No effect	0	No effect
rs140791627	Ser [S]/Cys [C]	85.1	Increases	−1.9	No effect	0	No effect
rs746136121	Phe [F]/Leu [L]	−35.7	No effect	2.96	No effect	0	No effect
rs1353890919	Phe [F]/Cys [C]	4.5	No effect	5.85	No effect	0	No effect
rs966424064	Ile [I]/Thr [T]	0	No effect	0	No effect	0	No effect
rs779212294	Ile [I]/Met [M]	0	No effect	0	No effect	0	No effect
rs121909744	Pro [P]/Arg [R]	9.1	No effect	−0.44	No effect	0	No effect
rs121909744	Pro [P]/Leu [L]	−0.1	No effect	4.65	No effect	0	No effect
rs1309197020	Ile [I]/Met [M]	−0.2	No effect	−0.05	No effect	0	No effect
rs1309197020	I (Ile) > I (Ile)	0	No effect	0	No effect	0	No effect
rs749661374	Met [M]/Val [V]	230.5	Increases	−18.16	No effect	0	No effect
rs778490867	Met [M]/Thr [T]	−27.3	No effect	2.19	No effect	0	No effect
rs28928874	Val [V]/Glu [E]	−56.9	Decreases	–33.24	No effect	0	No effect
rs367980651	Arg [R]/Cys [C]	17.1	No effect	−2.91	No effect	0	No effect
rs75144723	Arg [R]/His [H]	16.7	No effect	−2.79	No effect	0	No effect
rs754405476	Ala [A]/Thr [T]	−15.2	No effect	−42.65	No effect	0	No effect
rs1379813904	Ala [A]/Glu [E]	−158.8	Decreases	−15.31	No effect	0	No effect
rs751226875	Ile [I]/Thr [T]	−147.2	Decreases	−53.16	Decreases	0	No effect
rs762675284	Ala [A]/Ser [S]	−118.2	Decreases	48.11	No effect	0	No effect
rs1262058831	Ala [A]/Val [V]	346.5	Increases	54.41	Increases	0	No effect
rs758246412	Ala [A]/Glu [E]	−113.4	Decreases	126.69	Increases	0	No effect
rs1203908311	Asn [N]/Ser [S]	90	Increases	−44.34	No effect	0	No effect
rs765196886	Ile [I]/Leu [L]	18.3	No effect	38.73	No effect	0	No effect
rs761784655	Ile [I]/Thr [T]	−138.3	Decreases	205.72	Increases	0	No effect
rs776395971	Val [V]/Ala [A]	−96.7	Decreases	204.13	Increases	0	No effect
rs1238600269	Ala [A]/Thr [T]	10.6	No effect	20.07	No effect	0	No effect
rs1418589512	Cys [C]/Arg [R]	−104.2	Decreases	339.43	Increases	0	No effect
rs759480075	Tyr [Y]/His [H]	−83.6	Decreases	−6.52	No effect	0	No effect
rs771274850	Ile [I]/Thr [T]	−80	Decreases	−6.87	No effect	0	No effect
rs749710583	Ala [A]/Glu [E]	−69.6	Decreases	−5.77	No effect	0	No effect
rs749710583	Ala [A]/Val [V]	142	Increases	−15.87	No effect	0	No effect
rs774542648	Gly [G]/Arg [R]	6	No effect	0	No effect	0	No effect
rs1272353608	Pro [P]/His [H]	−169.7	Decreases	−11.73	No effect	0	No effect
rs1381049817	Tyr [Y]/Cys [C]	12.4	No effect	−0.04	No effect	0	No effect
rs1336322605	Phe [F]/Leu [L]	−0.3	No effect	0	No effect	0	No effect
rs140138702	Leu [L]/Val [V]	0	No effect	0	No effect	0	No effect
rs770197371	Leu [L]/Arg [R]	−614.7	Decreases	0.4	No effect	0	No effect
rs748401954	Phe [F]/Ser [S]	−6.2	No effect	0.01	No effect	0	No effect
rs374342938	Gly [G]/Ala [A]	0	No effect	0	No effect	0	No effect
rs769037887	Val [V]/Met [M]	−0.3	No effect	0.04	No effect	0	No effect
rs556023421	Phe [F]/Leu [L]	−0.4	No effect	0.01	No effect	0	No effect
rs5397	Leu [L]/Val [V]	0.9	No effect	0	No effect	0	No effect
rs5398	Phe [F]/Leu [L]	−4.5	No effect	0.01	No effect	0	No effect
rs757137603	Thr [T]/Ile [I]	19.1	No effect	0	No effect	0	No effect
rs1441249949	Phe [F]/ Ile [I]	−2.8	No effect	0.01	No effect	0	No effect
rs1195253424	Val [V]/Ile [I]	0	No effect	0	No effect	0	No effect
rs753575081	Pro [P]/Thr [T]	0	No effect	0	No effect	0	No effect
rs777806589	Lys [K]/Arg [R]	0	No effect	0.07	No effect	0	No effect
rs766600474	Ser [S]/Thr [T]	0	No effect	27.03	No effect	0	No effect
rs766600474	Ser [S]/Ala [A]	0	No effect	151.16	Increases	0	No effect

(*continued on next page*)

Table 3 (*continued*)

dbSNP rs#cluster id	Proteinresidue	dTANGO	Aggregationtendency	dWALTZ	Amyloidpropensity	dLIMBO	Chaperone bindingtendency
rs1379944645	Glu [E]/Lys [K]	−1.9	No effect	−13.73	No effect	0	No effect
rs1353603250	Glu [E]/Gln [Q]	−1.9	No effect	−13.48	No effect	0	No effect
rs1446857276	Glu [E]/Asp [D]	0	No effect	−14.56	No effect	0	No effect
rs1283734332	Ile [I]/Thr [T]	0	No effect	−14.46	No effect	0	No effect
rs1445660295	Ala [A]/Val [V]	0	No effect	16.65	No effect	0	No effect
rs201797691	Ala [A]/Thr [T]	0	No effect	0.17	No effect	0	No effect
rs201797691	Ala [A]/Pro [P]	0	No effect	0.21	No effect	0	No effect
rs200160167	Ala [A]/Glu [E]	1.7	No effect	−0.33	No effect	0	No effect
rs200160167	Ala [A]/Val [V]	0	No effect	31.4	No effect	0	No effect
rs762305192	Phe [F]/Leu [L]	0	No effect	−2.56	No effect	0	No effect
rs776826621	Lys [K]/Asn [N]	−0.2	No effect	0.23	No effect	0	No effect
rs5399	Lys [K]/Asn [N]	−0.2	No effect	0.05	No effect	0	No effect
rs1412427073	Gly [G]/Ser [S]	0	No effect	0.01	No effect	0	No effect
rs966895511	Ala [A]/Ser [S]	0	No effect	0	No effect	0	No effect
rs1199349184	Ala [A]/Val [V]	0	No effect	0	No effect	0	No effect
rs374630641	Arg [R]/Ser [S]	−0.2	No effect	0.03	No effect	0	No effect
rs771586150	Pro [P]/Gln [Q]	0	No effect	0	No effect	0	No effect
rs776597156	Lys[K]/Asn[N]	−0.2	No effect	0.03	No effect	0	No effect
rs770462591	Ala [A]/Asp [D]	3	No effect	−0.72	No effect	0	No effect
rs770462591	Ala [A]/Val [V]	8.5	No effect	0	No effect	0	No effect
rs141574520	Phe [F]/Tyr [Y]	−2.7	No effect	0.06	No effect	0	No effect
rs147959014	Gly [G]/Glu [E]	2.8	No effect	−0.72	No effect	0	No effect
rs752687355	Glu[E]/Gly[G]	−4.4	No effect	0.76	No effect	0	No effect
rs781215842	Thr [T]/Ser [S]	0	No effect	0	No effect	0	No effect
rs758607933	Val[V]/Met[M]	0	No effect	0	No effect	0	No effect

Variations with dTANGO, dWALTZ and dLIMBO between −50 and 50 were supposed to have no effect on aggregation tendency, amyloid propensity and chaperone binding tendency, respectively.

ant was related with high sugar consumption (Eny et al., 2008), indicating a GLUT2 arbitrate mechanism of glucose sensing that could modulate intake of food and sugar preference and consequently be associated with type 2 diabetes mellitus (Mueckler, 1994).

The rs7637863 Pro[P]/Leu[L] at position 68 GLUT2 SNP transported less sugar per unit of transporter, but this characteristic did not support any homeostatic disturbance, at any rate in the physiological situation. The outcome of this study showed that no affect occurs but only SIFT predicted it to be intolerant. Mostly the SLC2A2 gene mutations associated with FBS have been examined by DNA screening. The resulting GLUT2 mutants show transport function loss although biosynthesis of protein and targeting plasma membrane that is similar to wild-type protein for both of them. The syndrome of the patients having these mutations can consequently be recognized as lack of GLUT2 transport activity. Recently, compound heterozygous SLC2A2 mutations characterized by a deletion p.153–4delLI related with a missense mutation rs121909744 Pro[P]/Arg[R] at position 417 has been associated with mild FBS (mild glucosuria) (Grünert et al., 2012). Here, they showed that substitution of leucine Pro[P]/Leu[L] at position 417 diminished transport activity (Yang and Li, 2011). SIFT, PolyPhen and PROVEAN predicted (rs121909744) to have an influence on protein structure and function but SNPeffect showed no affect. Three algorithm (SIFT, PolyPhen and PROVEAN) predicted 101 SNPs to be damaging. Our results seem helpful to those epidemiologists who are involved in large-scale population-based studies. Moreover, on basis of our *in silico* predictions, actual role of nsSNPs can be assured by conducting demarcated *in vitro* and *in vivo* studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2021.101529.

References

Adzhubei, I.A., Schmidt, S., Peshkin, L., Ramensky, V.E., Gerasimova, A., Bork, P., Sunyaev, S.R., 2010. A method and server for predicting damaging missense mutations. Nat. Methods 7 (4), 248.

Alcolado, J.C., Alcolado, R., 1991. Importance of maternal history of non-insulin dependent diabetic patients. Br. Med. J. 302 (6786), 1178–1180.

Bady, I., Marty, N., Dallaporta, M., Emery, M., Gyger, J., Tarussio, D., Foretz, M., Thorens, B., 2006. Evidence from glut2-null mice that glucose is a critical physiological regulator of feeding. Diabetes 55 (4), 988–995.

Bamshad, M.J., Ng, S.B., Bigham, A.W., Tabor, H.K., Emond, M.J., Nickerson, D.A., Shendure, J., 2011. Exome sequencing as a tool for Mendelian disease gene discovery. Nat. Rev. Genet. 12 (11), 745–755.

Barroso, I., Middelberg, R.P., Harding, A.H., Franks, P.W., Jakes, R.W., Clayton, D., Wareham, N.J., 2003. Candidate gene association study in type 2 diabetes indicates a role for genes involved in β-cell function as well as insulin action. PLoS Biol. 1, (1) e20.

Burcelin, R., Da Costa, A., Drucker, D., Thorens, B., 2001. Glucose competence of the hepatoportal vein sensor requires the presence of an activated glucagon-like peptide-1 receptor. Diabetes 50 (8), 1720–1728.

Burgdorf, J., Kroes, R.A., Weiss, C., Oh, M.M., Disterhoft, J.F., Brudzynski, S.M., Panksepp, J., Moskal, J.R., 2011. Positive emotional learning is regulated in the medial prefrontal cortex by GluN2B-containing NMDA receptors. Neuroscience 192, 515–523.

Cant, J.P., Trout, D.R., Qiao, F., Purdie, N.G., 2002. Milk synthetic response of the bovine mammary gland to an increase in the local concentration of arterial glucose. J. Dairy Sci. 85 (3), 494–503.

Choi, Y., Sims, G.E., Murphy, S., Miller, J.R., Chan, A.P., 2012. Predicting the functional effect of amino acid substitutions and indels. PLoS ONE 7, (10) e46688.

De Baets, G., Van Durme, J., Reumers, J., Maurer-Stroh, S., Vanhee, P., Dopazo, J., Schymkowitz, J., Rousseau, F., 2012. SNPeffect 4.0: on-line prediction of molecular and structural effects of protein-coding variants. Nucl. Acids Res. 40 (D1), D935–D939.

Deshpande, N., Addess, K.J., Bluhm, W.F., Merinoott, J.C., Townsend-Merino, W., ZHANG, Q., Knezevich, C., Xie, L., Chen, L., Feng, Z., Green, R.K., Flippen-

Anderson, J.L., Westbrook, J., Berman, H.M. and Bourne, P.E., 2005. The RCSB Protein Data Bank: a redesigned query system and relational database based on the mmCIF schema. Nucl. Acids Res., 33: D233-237.

Eny, K. M., Wolever, T. M., Fontaine-Bisson, B., & El-Sohemy, A. (2008). Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. Physiological genomics, 33(3), 355-360.

Fanconi, G., 1949. Chronic amino aciduria (amino acid diabetes or nephrotic-glucosuric dwarfism) in glycogenosis and cystine disease. Helv Pediat Acta. 4, 359–396.

Fernandez-Escamilla, Ana-Maria, Rousseau, Frederic, Schymkowitz, Joost, Serrano, Luis, 2004. Prediction of sequence-dependent and mutational effects on the aggregation of peptides and proteins. Nat. Biotechnol. 22 (10), 1302–1306.

Godoy, A., Ulloa, V., Rodríguez, F., Reinicke, K., Yañez, A.J., García, M.D.L.A., Martínez, F., 2006. Differential subcellular distribution of glucose transporters GLUT1–6 and GLUT9 in human cancer: ultrastructural localization of GLUT1 and GLUT5 in breast tumor tissues. J. Cell. Physiol. 207 (3), 614–627.

Grünert, Sarah Catharina, Schwab, Karl Otfried, Pohl, Martin, Sass, Jörn Oliver, Santer, René, 2012. Fanconi-Bickel syndrome: GLUT2 mutations associated with a mild phenotype. Mol. Genet. Metab. 105 (3), 433–437.

Guillam, Marie-Thérèse, Hümmler, Edith, Schaerer, Elisabeth, Wu, J.-Y, Birnbaum, Morris J., Beermann, Friedrich, Schmidt, Andrea, Dériaz, Nathalie, Thorens, Bernard, 1997. Early diabetes and abnormal postnatal pancreatic islet development in mice lacking Glut-2. Nat. Genet. 17 (3), 327–330.

Ilahi, Naureen Ehsan, Anwar, Sobia, Noreen, Mamoona, Hashmi, Shoaib Naiyar, Murad, Sheeba, 2016. Detection of human papillomavirus-16 DNA in archived clinical samples of breast and lung cancer patients from North Pakistan. J. Cancer Res. Clin. Oncol. 142 (12), 2497–2502.

Joost, Hans-Georg, Thorens, Bernard, 2001. The extended GLUT-family of sugar/polyol transport facilitators: nomenclature, sequence characteristics, and potential function of its novel members. Mol. Membr. Biol. 18 (4), 247–256.

Joost, H.G., Bell, G.I., Best, J.D., Birnbaum, M.J., Charron, M.J., Chen, Y.T., Moley, J.F., 2002. Nomenclature of the GLUT/SLC2A family of sugar/polyol transport facilitators. Am. J. Physiol.-Endocrinol. Metabol. 282 (4), E974–E976.

Kellett, G. L., & Brot-Laroche, E. (2005). Apical GLUT2: a major pathway of intestinal sugar absorption. Diabetes, 54(10), 3056-3062.

Krogh, A., Larsson, B., Von Heijne, G., Sonnhammer, E.L., 2001. Predicting transmembrane protein topology with a hidden Markov model: application to complete genomes. J. Mol. Biol. 305 (3), 567–580.

Laukkanen, O., Lindström, J., Eriksson, J., Valle, T. T., Hämäläinen, H., Ilanne-Parikka, P., and Laakso, M. (2005). Polymorphisms in the SLC2A2 (GLUT2) gene are associated with the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes, 54(7), 2256-2260.

Liu, Y., Liu, F., Iqbal, K., Grundke-Iqbal, I., Gong, C.X., 2008. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. FEBS Lett. 582 (2), 359–364.

Manolescu, Andrei R., Witkowska, Kate, Kinnaird, Adam, Cessford, Tara, Cheeseman, Chris, 2007. Facilitated hexose transporters: new perspectives on form and function. Physiology 22 (4), 234–240.

Matsutani, A., Koranyi, L., Cox, N., Permutt, M.A., 1990. Polymorphisms of GLUT2 and GLUT4 genes: use in evaluation of genetic susceptibility to NIDDM in blacks. Diabetes 39 (12), 1534–1542.

Maurer-Stroh, Sebastian, Debulpaep, Maja, Kuemmerer, Nico, de la Paz, Manuela Lopez, Martins, Ivo Cristiano, Reumers, Joke, Morris, Kyle L, Copland, Alastair, Serpell, Louise, Serrano, Luis, Schymkowitz, Joost W H, Rousseau, Frederic, 2010. Exploring the sequence determinants of amyloid structure using position-specific scoring matrices. Nat. Methods 7 (3), 237–242.

Meglasson, M.D., Burch, P.T., Berner, D.K., Najafi, H., Matschinsky, F.M., 1986. Identification of glucokinase as an alloxan-sensitive glucose sensor of the pancreatic β-cell. Diabetes 35 (10), 1163–1173.

Miller, C.D., Phillips, L.S., Ziemer, D.C., Gallina, D.L., Cook, C.B., El-Kebbi, I.M., 2001. Hypoglycemia in patients with type 2 diabetes mellitus. Arch. Intern. Med. 161 (13), 1653–1659.

Mueckler, M., 1994. Facilitative glucose transporters. Eur. J. Biochem. 219 (3), 713–725.

Navale, Archana M., Paranjape, Archana N., 2016. Glucose transporters: physiological and pathological roles. Biophys. Rev. 8 (1), 5–9.

Ng, P. C., and Henikoff, S. (2001). Predicting deleterious amino acid substitutions. Genome Res., 11(5): 863-874.

Noreen, M., Murad, S., Khan, H., 2015a. In Silico Analysis of SNPs in Coding Region of Human c-Myc Gene. Pakistan J. Zool. 47 (5).

Noreen, Mamoona, Arshad, Muhammad, 2015. Association of TLR1, TLR2, TLR4, TLR6, and TIRAP polymorphisms with disease susceptibility. Immunol. Res. 62 (2), 234–252.

Noreen, Mamoona, Murad, Sheeba, Furqan, Muhammad, Sultan, Aneesa, Bloodsworth, Peter, 2015b. Knowledge and awareness about breast cancer and its early symptoms among medical and non-medical students of Southern Punjab, Pakistan. Asian Pacific J. Cancer Prevent. APJCP 16 (3), 979–984.

Noreen, M., M. A. Shah, S. M. Mall, S. Choudhary, T. Hussain, I. Ahmed, S. F. Jalil & M. I. Raza (2012) TLR4 polymorphisms and disease susceptibility. Inflammation research : official journal of the European Histamine Research Society ... [et al.], 61, 177-88.

Noreen, M., Muhammad Imran, Sher Zaman Safi, Muhammad Amjad Bashir, Sana Gul, Afrah Fahad Alkhuriji, Suliman Yousef Aloma, Hanan Mualla Alharbi, Muhammad Arshad, Protective role of TIRAP functional variant against development of coronary artery disease, Saudi Journal of Biological Sciences, 2021.

Persson, B., and Argos, P. (1994). Prediction of transmembrane segments in proteins utilising multiple sequence alignments.

Powers, Evan T., Morimoto, Richard I., Dillin, Andrew, Kelly, Jeffery W., Balch, William E., 2009. Biological and chemical approaches to diseases of proteostasis deficiency. Annu. Rev. Biochem. 78 (1), 959–991.

Rost, Burkhard, Fariselli, Piero, Casadio, Rita, 1996. Topology prediction for helical transmembrane proteins at 86% accuracy–Topology prediction at 86% accuracy. Protein Sci. 5 (8), 1704–1718.

Santer, R., Schneppenheim, R., Dombrowski, A., Götze, H., Steinmann, B., Schaub, J., 1997. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. Nat. Genet. 17 (3), 324.

Santer, R., Schneppenheim, R., Suter, D., Schaub, J., Steinmann, B., 1998. Fanconi-Bickel syndrome–the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature. Eur. J. Pediatr. 157 (10), 783–797.

Savas, S., Kim, D.Y., Ahmad, M.F., Shariff, M., Ozcelik, H., 2004. Identifying functional genetic variants in DNA repair pathway using protein conservation analysis. Cancer Epidemiol. Biomark. Prev. 13, 801–807.

Schuit, F.C., Huypens, P., Heimberg, H., Pipeleers, D.G., 2001. Glucose sensing in pancreatic β-cells: a model for the study of other glucose-regulated cells in gut, pancreas, and hypothalamus. Diabetes 50 (1), 1–11.

Schymkowitz, J., Borg, J., Stricher, F., Nys, R., Rousseau, F. and Serrano, L., 2005. The FoldX web server: an online force field. Nucl. Acids Res., 33: W382-388.

Sonnhammer, E.L., Von Heijne, G., Krogh, A., 1998. June). A hidden Markov model for predicting transmembrane helices in protein sequences. Ismb 6, 175–182.

Tennessen, J. A., Bigham, A. W., O'Connor, T. D., Fu, W., Kenny, E. E., Gravel, S., and NHLBI Exome Sequencing Project. (2012). Evolution and functional impact of rare coding variation from deep sequencing of human exomes. science, 337 (6090), 64-69.

Thorens, Bernard, Mueckler, Mike, 2010. Glucose transporters in the 21st Century. Am. J. Physiol.-Endocrinol. Metabol. 298 (2), E141–E145.

Thorens, Bernard, Sarkar, Hemanta K., Kaback, H.Ronald, Lodish, Harvey F., 1988. Cloning and functional expression in bacteria of a novel glucose transporter present in liver, intestine, kidney, and β-pancreatic islet cells. Cell 55 (2), 281–290.

Tusnady, G.E., Simon, I., 1998. Principles governing amino acid composition of integral membrane proteins: application to topology prediction. J. Mol. Biol. 283 (2), 489–506.

Tusnady, G. E., and Simon, I. (2001). The HMMTOP transmembrane topology prediction server. Bioinformatics, 17(9), 849-850..

Van Durme, J., Maurer-Stroh, S., Gallardo, R., Wilkinson, H., Rousseau, F., Schymkowitz, J., 2009. Accurate prediction of DnaK-peptide binding via homology modelling and experimental data. PLoS Comput. Biol. 5, (8) e1000475.

Wright, Ernest M., Martín, Martín G., Turk, Eric, 2003. Intestinal absorption in health and disease—sugars. Best Pract. Res. Clin. Gastroenterol. 17 (6), 943–956.

Wright, Ernest M., 2001. Renal Na(+)–glucose cotransporters. Am. J. Physiol. Renal Physiol. 280 (1), F10–F18.

Yang, X., Li, L., 2011. miRDeep-P: a computational tool for analyzing the microRNA transcriptome in plants. Bioinformatics 27 (18), 2614–2615.

Zhu, Y., Spitz, M.R., Amos, C.I., Lin, J., Schabath, M.B. and WU, X., 2004. An evolutionary perspective on single-nucleotide polymorphism screening in molecular cancer epidemiology. Cancer Res., 64: 2251- 2257.