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Improved Locus-Specific Database for *OPA1* Mutations Allows Inclusion of Advanced Clinical Data

Marc Ferré,[1,2]* Angélique Caignard,[1,3] Dan Milea,[1,3,4] Stéphanie Leruez,[1,3] Julien Cassereau,[1,5] Arnaud Chevrollier,[1] Patrizia Amati-Bonneau,[1,2] Christophe Verny,[1,5] Dominique Bonneau,[1,2] Vincent Procaccio,[1,2] and Pascal Reynier[1,2]

[1]*CNRS 6214/INSERM 1083, Angers University, Angers, France;* [2]*Department of Biochemistry and Genetics, University Hospital, Angers, France;* [3]*Department of Ophthalmology, University Hospital, Angers, France;* [4]*Singapore National Eye Centre, Singapore Eye Research Institute, Duke-NUS, Singapore;* [5]*Department of Neurology, University Hospital, Angers, France*

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ABSTRACT: Autosomal-dominant optic atrophy (ADOA) is the most common inherited optic neuropathy, due to mutations in the optic atrophy 1 gene (*OPA1*) in about 60%–80% of cases. At present, the clinical heterogeneity of patients carrying *OPA1* variants renders genotype–phenotype correlations difficulty. Since 2005, when we published the first locus-specific database (LSDB) dedicated to *OPA1*, a large amount of new clinical and genetic knowledge has emerged, prompting us to update this database. We have used the Leiden Open-Source Variation Database to develop a clinico-biological database, aiming to add clinical phenotypes related to *OPA1* variants. As a first step, we validated this new database by registering several patients previously reported in the literature, as well as new patients from our own institution. Contributors may now make online submissions of clinical and molecular descriptions of phenotypes due to *OPA1* variants, including detailed ophthalmological and neurological data, with due respect to patient anonymity. The updated *OPA1* LSDB (http://opa1.mitodyn.org/) should prove useful for molecular diagnoses, large-scale variant statistics, and genotype–phenotype correlations in ADOA studies.

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KEY WORDS: optic atrophy 1; OPA1; locus-specific database; LSDB; *e*OPA1

Introduction

Autosomal-dominant optic atrophy (ADOA; MIM #165500), the most frequent form of hereditary optic atrophy, was first described by Kjer (1959). The frequency of the disease is estimated at 1/30,000 worldwide [Yu-Wai-Man et al., 2010a], whereas the greater proportion of 1/10,000 reported in Denmark has been attributed to a founder effect [Eiberg et al., 1994; Kjer et al., 1996]. The disease, generally diagnosed in early childhood, is characterized by a progressive bilateral loss of visual acuity, blue-yellow dyschromatopsia or generalized color vision deficits, variable centrocecal, central or paracentral visual field defects, and temporal or diffuse optic nerve pallor with optic disc excavation [Lenaers et al., 2012]. ADOA is associated with a marked intra- and interfamilial clinical variability and incomplete penetrance, estimated at about 90% in the familial forms of the disease [Cohn et al., 2007]. Extraocular symptoms, typical of mitochondrial disorders, have been reported in about 20% of the cases [Yu-Wai-Man et al., 2010b].

Mutations in the optic atrophy 1 gene (*OPA1*; MIM #605290), located on chromosome 3q28-q29, are responsible for about 60%–80% of the cases of ADOA [Kjer et al., 1983; Alexander et al., 2000; Delettre et al., 2000; Amati-Bonneau et al., 2005]. *OPA1*, which has 30 coding exons, including three alternative exons [Delettre et al., 2001], encodes a mitochondrial dynamin-related GTPase, an ubiquitously expressed protein anchored to the mitochondrial inner membrane [Delettre et al., 2002; Olichon et al., 2006]. The OPA1 protein, which is involved in multiple functions, plays a key role in the fusion of mitochondria and thus in the organization of the mitochondrial network [Delettre et al., 2002; Olichon et al., 2006]. The other functions of the OPA1 protein are related to oxidative phosphorylation, the maintenance of membrane potential [Olichon et al., 2003; Lodi et al., 2004; Amati-Bonneau et al., 2005], the maintenance of mtDNA [Amati-Bonneau et al., 2008; Hudson et al., 2008], the organization of mitochondrial cristae, and the control of apoptosis through the compartmentalization of cytochrome *c* [Olichon et al., 2003; Frezza et al., 2006]. Phenotype–genotype studies of optic atrophies have led to the identification of severe ADOA phenotypes, the so-called ADOA "plus" phenotypes, which associate *OPA1* variants with syndromic forms of optic atrophy, including sensorineural deafness (ADOAD; MIM #125250) [Amati-Bonneau et al., 2003; Leruez et al., 2013], and ataxia, myopathy, peripheral neuropathy, and progressive external ophthalmoplegia [Hoyt, 1980; Meire et al., 1985; Treft et al., 1984; Payne et al., 2004; Amati-Bonneau et al., 2008; Hudson et al., 2008] in up to 20% of the patients [Yu-Wai-Man et al., 2010b]. *OPA1*-related diseases have become so diverse since the initial description of ADOA by Kjer (1959) that they now cover a broad clinical spectrum in children and adults.

To date, more than three hundred *OPA1* variants, often family specific, have been reported (see http://opa1.mitodyn.org/). In cases of ADOA, most of these variants result in the loss of function of the mutated allele, supporting the notion that haploinsufficiency may be the most likely pathological mechanism of the disease [Pesch et al., 2001]. In 2009, we reported the results of molecular screening for hereditary optic neuropathies in 980 patients referred to our

*Correspondence to: Marc Ferré, Institut de Biologie en Santé, 4 rue Larrey, 49933 Angers Cedex 9, France. E-mail: marc.ferre@univ-angers.fr

laboratory over a 4-year period [Ferre et al., 2009]. The original *e*OPA1 database, published in 2005 [Ferre et al.], contained only the published variants together with references to the corresponding publications. At the time, the standardized nomenclature for sequence variants was not in general use. In addition, reference sequences were often omitted, the description of variants was sometimes unclear, and the publications lacked information concerning genomic positions. Since the creation of the original database, several new causative variants of ADOA have either been published or directly submitted without publication. In the absence of available clinical data, the database focused initially on a list of pathogenic variants. But today, the results of tests on more than a thousand patients in our laboratory [Ferre et al., 2009] have revealed the large gap between the genotypic and the phenotypic expressions of ADOA.

We have therefore transformed our purely molecular database into a clinico-biological database for ADOA. Our locus-specific database (LSDB) aims at collecting the data of all patients harboring variants incriminated in disorders involving mitochondrial dynamics and bioenergetics, with a full record of clinical, electrophysiological, and biochemical data. We here describe the construction of the new database, the procedure for data submission, and the presentation of the data.

Materials and Methods

The original *e*OPA1 database, published in 2005 [Ferre, et al.], was used as the starting point.

Nomenclature of *OPA1* Variants

All names, symbols, and OMIM numbers were checked for correspondence to the current official names indicated by the HUGO Gene Nomenclature Committee [Gray et al., 2013] and the Online Mendelian Inheritance in Man database — OMIM® [Hamosh et al., 2000; Hamosh et al., 2005]. In addition, updated information about the genomic variants was collected from the literature, using the NCBI PubMed search tool [Sayers et al., 2010], and incorporated into the database.

The *OPA1* variants are described according to the *OPA1* transcript variant 8 (RefSeq: NM_130837.2), representing the longest transcript. Compared with transcript variant 1, the original transcript identified, transcript variant 8, based on an alternate splice pattern characterized by Delettre et al. [2001], contains two additional exons, 4b and 5b. However, it maintains the same reading-frame encoding an isoform (8) of 1,015 amino acids. For standardization, the exons are numbered 1–30, instead of 1–4, 4b, 5, 5b, 6–28, as originally proposed by Delettre et al. [2001]. Furthermore, to maintain historical compatibility, we have added three columns to describe variants with nomenclature according to variant 1 (*DNA change/variant 1*, *Exon/variant 1*, and *Protein/isoform 1*). The numbering of the nucleotides reflects that of cDNA, with "+1" corresponding to the "A" of the ATG translation initiation codon in the reference sequence as recommended by the Human Genome Variation Society (HGVS): http://www.hgvs.org/mutnomen [den Dunnen and Antonarakis, 2001; den Dunnen and Paalman, 2003], according to which the initiation codon is codon 1.

Information concerning changes in RNA levels has been added from original papers, or deduced from DNA if not experimentally studied. Following the HGVS guidelines, deduced changes are indicated between brackets.

Data Collection of *OPA1* Variants

The nomenclature of all causative variants in the original *e*OPA1 database, published in 2005 [Ferre, et al.], was reexamined. New causative variants were also searched and collected from the literature, using the NCBI PubMed search tool [Sayers et al., 2010].

The position and adjacent sequences of each poorly localizable variant was checked against the original article. The positions of variants in the reference transcripts were determined and updated according to the current nomenclature of the HGVS [den Dunnen and Antonarakis, 2001; den Dunnen and Paalman, 2003] (http://www.hgvs.org/mutnomen). Correct naming at the nucleotide and protein levels was verified, and reestablished when necessary, using the batch interface for the Mutalyzer 2.0.beta-21 *Name Checker* [Wildeman et al., 2008] (https://mutalyzer.nl/batchNameChecker). Genomic positions were determined using the batch interface for the Mutalyzer 2.0.beta-21 *Position Converter* (https://mutalyzer.nl/batchPositionConverter). Exon numbering was updated to correspond to the longest reference sequence (transcript variant 8) rather than the originally identified reference sequence (transcript variant 1).

Information on the number of patients carrying each causative variant, as well as the geographical origin of the patients, and the homo- or heterozygosity of the sequence variant, was determined from original or review papers as well as from data collected during our ophthalmology consultations. Further information on the genetic origin of the allele, segregation with the disease phenotype, and frequency data in the control population was recorded. Results of functional studies were also incorporated. The NCBI *Variation Reporter* tool (http://www.ncbi.nlm.nih.gov/variation/tools/reporter) was used to identify known variants, and to obtain reference SNP (*rs*) numbers for our database. Single-nucleotide changes, not present in the NCBI dbSNP database, were submitted to that database as clinical variants (http://www.ncbi.nlm.nih.gov/projects/SNP/tranSNP/VarBatchSub.cgi), to retrieve their *rs* numbers.

The criteria of pathogenicity, which depend upon the clinical context and molecular findings, are stated in the "*Variant data*" fields under the headings: "*Reported pathogenicity*" and "*Concluded pathogenicity*" (Fig. 1b). Putative novel variants detected in affected patients should segregate according to disease status and not be present in control individuals. Putative variants are graded according to type of mutation: frameshift and nonsense variants are considered to be pathogenic; missense variants are described as being of unknown pathogenicity when detected in single families, or as probably pathogenic when detected in a group of families; the variants are considered to be pathogenic when so proven by experimental evidence or detected in multiple families.

As new patients with existing variants are added to the database, the status of variants is reviewed by a Variant Curation Committee composed of all the authors of this article. This committee, which includes molecular biologists, geneticists, neurologists, and ophthalmologists, meets twice a year to reassess the variants on the basis of the new patient data submitted.

Implementation of the Database for *OPA1* Mutations

One of our main objectives is to provide a user-friendly way to submit, curate, and share variants. We have therefore transferred our database to the *Leiden Open Variation Database* (LOVD) platform

[Fokkema et al., 2005; Fokkema et al., 2011], following the guidelines for LSDBs [Vihinen et al., 2012]. The implementation of the database is based on the LOVD v.2.0 Build 35 [Fokkema et al., 2005; Fokkema et al., 2011]; the hosting is done on our servers together with the *GDAP1* gene database for which we ensure the curation [Cassereau et al., 2011].

This database for *OPA1* mutations includes a total of 30 clinical items and 21 variant items. Figure 1 shows a typical entry. A standardized description of the clinical and molecular items is set up using drop-down lists or list boxes with predefined variables. The clinical features are based on a large panel of symptoms encountered in mitochondrial diseases.

The data are openly accessible and should prove a valuable tool for clinicians and researchers alike since it will contain published as well as unpublished sequence variants. Contributors may submit their variants online to the database after registering for a login and password. This contact information is collected for reference purposes and clarification of the data submitted. Variations submitted directly to the LSDB are rechecked as described above.

The *OPA1* database reviews clinical and molecular data of patients carrying *OPA1* variants published in peer-reviewed literature, as well as unpublished contributions that may be directly submitted. While most variants can be described in terms of the latest update of the standard nomenclature [den Dunnen and Antonarakis, 2000; den Dunnen and Paalman, 2003], some inaccuracies may persist because gene anomalies discovered earlier might have been named according to a convention now out of use. Eventually, the "*DNA published*" field of the page dedicated to each variant (Fig. 1b) indicates whether the published name of the mutation has been modified by the curator. The *OPA1* LSDB Website requires full compliance with the rules set out above for the description of sequence variants in order to provide uniform and comparable data.

Results and Discussion

The database for OPA1 mutations contains two independent tables, visible on the display of a typical Web page entry: one for molecular data (Fig. 1a) and the other for clinical data (Fig. 1b).

Molecular Data of *OPA1* Mutations

To date, the *OPA1* database contains 302 unique variants of which 241 are considered pathogenic sequence variants, 48 as nonpathogenic sequence variants, and the remainder as having an unknown effect. Pathogenic variants, which affect the coding sequence of the gene, are more frequently found in exon 11 (17 variants) and exons 16, 19, and 22 (15 variants each) (Fig. 2a). The most frequent variants are missense variants, observed in 26% of the cases, followed by frameshift variants in 16%, nonsense variants in 14%, silent variants (so-called "p.(=)" variants, i.e., genomic variants with no change expected at the protein level) in 12%, and deletion variants in 7% of the cases (Fig. 2b).

Whereas only a few variants are recurrent, some have been frequently reported; for instance, the c.2873_2876del variant with consequence p.(Val958Glyfs*3) has been reported five times.

Among the pathogenic variants mentioned in the database, more than two-thirds are located in the dynamin-GTPase domains of the protein (Fig. 2c), highlighting the important role of these domains in protein function.

Clinico-Ophthalmological Data of OPA1 Variants

To date, the database includes 328 patients (15 females, 19 males, and 294 unspecified): 270 with isolated ADOA, six with ADOA "plus," three with ADOAD, and 49 asymptomatic. The database shows the first set of clinical data collected in our institution from 21 patients as well as data from 293 patients, retrieved by the curator from previous publications.

The clinical information recorded includes the date of the first visual symptoms, the best corrected visual acuity, visual field parameters, and the presence of thinning of the mean thickness of the retinal nerve fiber layer (RNFL) and the ganglion cell layer (GCL) as measured by optical coherence tomography (OCT). Visual acuity is expressed using the logarithm of the minimum angle of resolution (LogMAR) chart, the de facto standard in vision research: excellent vision is defined as LogMAR < 0.1; moderately impaired vision as LogMAR 0.1–0.2; severely impaired vision as LogMAR 0.3–0.9; and profound visual loss as LogMAR > 0.9. OCT data, namely, the mean thickness of the RNFL and the GCL, are recorded together with the name of the manufacturer of the OCT apparatus because of possible differences in the technique of measurement. The visual handicap item refers to the consequences of visual loss, that is, the diminished ability to work and lead a normal social life.

The evolution of vision since the time of diagnosis (qualified as "worsening" if two or more decimal lines are lost, "improving" if two or more decimal lines are gained, and "stable" in between these two situations) may be recorded. The features of hearing loss may be detailed with the inclusion of results of quantitative analyses based on pure tone audiometry, auditory brainstem responses, and otoacoustic emission testing.

A standardized description of the clinical and molecular items uses drop-down lists with predefined variables. We specifically propose list widgets that address neuro-ophthalmic features, without a "free text" option. However, the submitter may interact with the expert curator for appropriate submissions. A dedicated field, "*Non-public remarks,*" has been designed for this purpose. All submissions are required to be signed.

To test the modified database for *OPA1* mutations, we have successfully registered 21 patients with clinical data from our institution. Obviously, we had to limit the amount of detail in the clinical fields to simplify data entry and make it readable, but we made sure that the data were sufficient for statistical evaluation. Although our interim analysis of the limited data entered with full clinical description does not yet allow us to identify new genotype–phenotype correlations, we hope that an increasing number of submissions will allow a comprehensive analysis of such complex relationships.

Some patients with *OPA1* variants referred to our database also carried a variant in another gene. Our database will allow such cases of multiple gene variants to be reported. The *OPA1* database is part of the MITOchondrial DYNamics variation portal (http://mitodyn.org), dedicated to disorders of mitochondrial dynamics, such as the *GDAP1* gene [Cassereau et al., 2011]. This portal will therefore incorporate other genes involved in neurological diseases affecting mitochondrial dynamics and bioenergetics. Thus, it will integrate *MFN2*, responsible for CMT2A2 (MIM #609260) [Zuchner et al., 2004], and *DNM1L* associated with encephalopathy with lactic acidosis (MIM #603850) [Waterham et al., 2007]. The presence of both ophthalmological and neurological evaluations is of particular interest in these diseases since peripheral neuropathies have been linked to *OPA1* variants and optic neuropathies to *MFN2* variants, thus revealing the close proximity of the diseases [Rouzier et al., 2012]. Finally, since the same patients may be affected by different diseases involving mitochondrial dysfunction, the data

A

Patient data (#0000522)	
Gender	Male
Disease	ADOA
Age of onset	11-20 years
Age at last examination	23 years
Duration of disease	< 11 years
Affected relatives	Yes
Additional features	-
Visual acuity	OD: moderately impaired vision (Log MAR: 0.2-0.1), OS: severely impaired vision (Log MAR: 0.9-0.3)
Evolution of vision loss	unknown
Optic disc	OD: Temporal pallor, OS: Temporal pallor
Cupping	OD: [0-0.4], OS: [0-0.4]
Color vision	OD: Normal, OS: Normal
Visual field	OD: Type: humphrey/octopus automated perimetry, OD: MD: [0 to −4], OD: Result: Central scotoma, OS: Type: Humphrey/Octopus automated perimetry, OS: MD: [0 to −4], OS: Result: Central scotoma
OCT	OD: Mean RNFL: Thinning in two or more quadrants, OD: Mean GCL: Mean average GCL thickness thinner, OS: Mean RNFL: Thinning in two or more quadrants, OS: Mean GCL: Mean average GCL thickness thinner, Device: Cirrus
Visual handicap	D: Able to drive, F: Able to eat, cook and buy food without help, SL: No difficulty at all
Hearing loss	No
Pure tone audiometry	-
Auditory brainstem responses	-
Otoacoustic emission	-
Functional disability	-
Clinical score	-
Electroneuromyography	-
Histology	Muscle biopsy: not performed, nerve biopsy: Not performed
Brain imaging	-
Habits	Tobacco: occasionally, alcohol: occasionally
Geographic origin	France
Reference	France:Angers
Remarks	-
# Reported	1
Submitter	Angelique Caignard

B

Variant data	
Allele	Unknown
Reported pathogenicity	Pathogenic
Concluded pathogenicity	Unknown
DB-ID	OPA1_00207
DNA change (cDNA)	c.2635C>T (View in UCSC Genome Browser, Ensembl)
Type	Substitution
Location	Exon
Exon	26
Affected domain	Dynamin Central (exons 18-26)
RNA change	-
Protein	p.(Arg879*)
Reference	Ferre et al. (2009)
Technique	SEQ
Template	DNA
Tissue	Blood
Re-site	-
DNA change/variant 1	NM_015560.1:c.2470C>T
Exon/variant 1	24
Protein/isoform 1	NP_056375.1:p.(Arg824*)
DNA published	-
Variant remarks	eOPA1 identifier (obsolete):OA_00216; nucleotide change: C to T at 2470 (reference: OPA1 transcript variant 1, NM_015560.1)
Frequency	-

Figure 1. Sample record in the *OPA1* database. **A**: Clinical items. **B**: Molecular items.

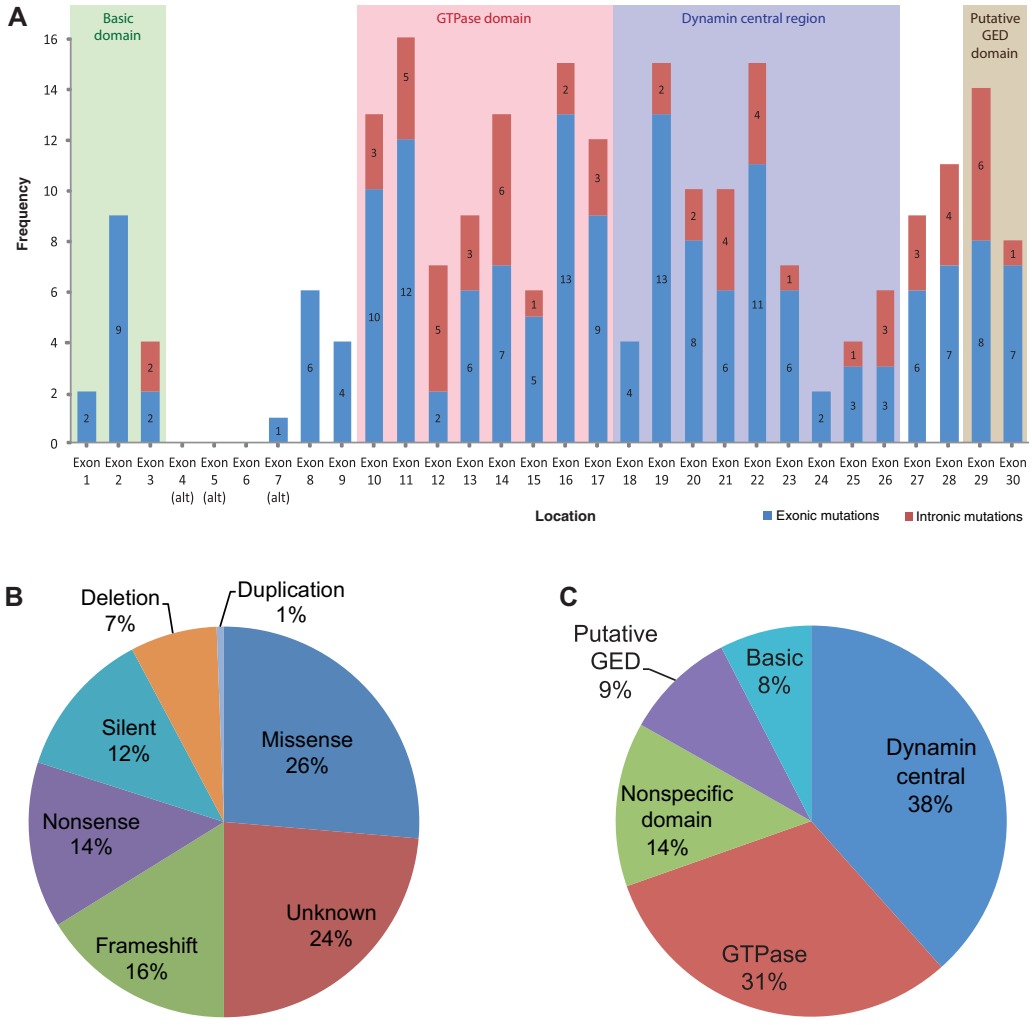

Figure 2. Distribution of the 233 pathogenic variants in the *OPA1* gene. Six large deletions: c.1-?_3048+?del (whole gene), c.1-?_2983+?del (almost the whole gene), c.1-?_678+?del (exons 1–6), c.1036-?_1149+?del (exon 11), c.2013-?_2178+?del (exon 22), and c.2521-?_2661+?del (exon 26) are excluded; and two large duplications: c.33-?_2983+?dup (almost the whole gene), and c.844-?_1149+?dup (exons 9–11) are excluded. Data from mitodyn.org updated on June 7, 2014. **A**: Exons involved in the variants are shown as blue bars; the variants in the intronic neighborhood of the exons are shown as red bars. **B**: Protein consequence type. **C**: Affected domain. alt, alternative exon; bp, base pairs; GED, GTPase effector domain.

collected should interest physicians and researchers alike. We hope to be able to refine genotype–phenotype correlations in diseases involving mitochondrial dynamics by comparing and cross-checking the clinical, ophthalmological, electrophysiological, and biochemical data recorded in the mitodyn.org databases.

Conclusion

Our new *OPA1* LSDB, which is to our knowledge the only *OPA1* gene-related clinico-biological database, is now ready to receive submissions from other centers. We are currently preparing for next-generation screening and plan to move to LOVD 3 as soon as an upgrade script is available.

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