Assessing utility of clinical exome sequencing in diagnosis of rare idiopathic neurodevelopmental disorders in Indian population

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Abstract

Background: Neurological diseases are phenotypically and genotypically heterogeneous. Clinical exome sequencing (CES) has been shown to provide a high diagnostic yield for these disorders in the European population but remains to be demonstrated for the Indian population. **Methods:** A cohort of 19 idiopathic patients with neurological phenotypes, primarily intellectual disability and developmental delay, were recruited. CES covering 4620 genes was performed on all patients. Candidate variants were validated by Sanger sequencing. **Results:** CES in 19 patients provided identified 21 variants across 16 genes which have been associated with different neurological disorders. Fifteen variants were reported previously and 6 variants were novel to our study. Eleven patients were diagnosed with autosomal dominant de novo variants, 7 with autosomal recessive and 1 with X-linked recessive variants. CES provided definitive diagnosis to 10 patients, hence the diagnostic yield was 53%. **Conclusion:** Our study suggests that the diagnostic yield of CES in the Indian population is comparable to that reported in the European population. CES together with deep phenotyping could be a cost-effective way of diagnosing rare neurological disorders in the Indian population.

Background

The brain is an incredibly complex organ consisting of a plethora of interconnected cell types. During development and day-to-day functioning, a variety of neurons and numerous proteins are required in the right amount at the right place and at the right time. Hence, any pathogenic mutation affecting genes that are involved in the production of these proteins can have consequences on brain development and functioning. Neurological disorders are conditions in which the motor, sensory, and cognitive functions decline due to variation(s) in the genotype of one or more genes involved in the functions of neurons, spinal cord, and peripheral nerves [1]. They are ranked as the leading disorder to cause 10.2% of global disability-adjusted-life-years compared to 7.3% in 1990, and second-leading disorder responsible for 16.8% of the global deaths [2, 3]. These disorders are clinically heterogeneous and genetically diverse group of disorders affecting all age group with sporadic (autosomal dominant) or acquired (autosomal or X-linked recessive) inheritance. This makes the diagnosis more challenging using the conventional techniques and often deprives the patient of proper treatment. Furthermore, genetic counselling during pregnancy becomes challenging when families approach for prenatal diagnosis.

An extensive genotypic overlap amongst a range of neurodegenerative disease involving neuropathy, myopathy, epileptic encephalopathy, ataxia, paraphasia, intellectual disability, and sensory impairment hampers the genetic diagnosis and makes it difficult to target specific genes for study [4]. For instance, EpilepsyGene, designed in 2015, includes 499 genes and 3931 variants associated with epilepsy [5]. Moreover, with respect to intellectual disability, 528 confirmed genes and 628 candidate genes are reported [6]. Different variations in a single gene can lead to different clinical entities in neurological disorders. An ideal example is of a variation in *LIS1* gene (also called as *PAFAH1B1*: platelet activating factor acetylhydrolase 1b regulatory subunit 1 gene). A small deletion in *LIS1* gene leads to an isolated lissencephaly sequence. However, a large deletion covering *LIS1* gene and neighbouring genes causes Miller-Dieker syndrome [7]. Both the diseases exhibit similar clinical traits except for the facial dysmorphism, as observed only in Miller-Dieker syndrome [8]. Thus, identification of the genetic cause of a neurological disease using conventional techniques like polymerase chain reaction (PCR) and Sanger sequencing (one-loci-at-a-time approach) seems true in the diseases with well-established genotypic-phenotypic correlation. However, many neurological disorders, even after a meticulous evaluation, remain undiagnosed due to the presence of mild or unusual traits, and lack of precise molecular basis. Sanger sequencing approach is laborious, expensive and falls short in detecting nucleotide repeat expansions, large indels, or copy number variations.

Clinical and whole exome sequencing (CES and WES) has facilitated clinical utility in identifying and characterizing the genes and variants involved in the clinical presentation of the idiopathic neurological disorders because of their ability to sequence multiple genes at a time in a cost-effective manner. With the application of WES, the diagnosis rate in clinical practice has increased which helps in early diagnosis, prognosis, reproductive counselling, medical management and prenatal diagnosis [9]. Furthermore, it is useful in the diagnosis of the etiologically misleading neurological disorders that give false positive result using conventional techniques.

However, most of the studies carried out to date has been in the white European population and western healthcare settings. The diagnostic utility and cost-effectiveness of WES and CES is currently unknown for the Indian population. Since the goal of introducing any technique in clinical practice is to maximize diagnostic yield and minimize cost to the patient, our aim was to assess the utility of CES in diagnosing rare idiopathic neurological disorders in a cohort of 19 patients from the Indian population.

Methods

Patient recruitment

The present study comprised of 19 unrelated idiopathic patients with variable neurodevelopmental phenotypes including intellectual disability and developmental delay that were referred between 2015 and 2017. All patients were evaluated according to the clinically validated developmental scales by their referring clinicians. Each referring physician provided details on their phenotype, particularly: developmental, neurological, behavioral and epilepsy history, accompanied by imaging data if available. At the time of recruitment, a *pro forma* comprising of patient's clinical details including history of clinical test performed previously, family history, parent's consanguinity and ethnicity was recorded. The ethics committee of the Foundation for Research in Genetics and Endocrinology at the Institute of Human Genetics approved the study and it was performed in accordance with the tenets of the Declaration of Helsinki. A

written informed consent for investigation and publication of the data was obtained from the patients or from the guardian of the patients at the time of recruitment, as per the institutional ethics committee guidelines. Peripheral blood was collected from all patients and their parents, if consented, for downstream genomic testing.

DNA extraction

Four milliliters of whole blood drawn from each patient in an EDTA vacutainer was used for the genomic DNA isolation using the salting-out technique [15]. DNA was quantified using QIAxpress (Qiagen, Germany). To ensure the absence of any salts or inhibitors in downstream applications, all DNA samples were purified using Genomic DNA Clean & Concentrator™-25 kit (Zymo Research, U.S.A) as per the manufacturer's instructions. High quality DNA was subsequently used for clinical exome and Sanger sequencing.

Clinical exome sequencing and variant validation

DNA from probands were sequenced for clinical exome by Strand Life Sciences, India. Exon and splice site regions of >4600 genes associated with known inherited diseases were captured using TruSight One kit (Illumina, USA) (Supplementary File 1). Paired-end 150bp sequencing was carried out on Illumina HiSeq 2500 platform (Illumina, USA) in accordance with the manufacturer's protocols, with an average coverage of 100x. Bioinformatic analysis was subsequently carried out using an in-house pipeline developed by Strand Life Sciences. Briefly, unique sequencing reads passing quality filters were aligned against the reference genome (GRCh37/ hg19) using a local alignment tool called STRAND® NGS v2.5 (Strand Life Sciences, India). Single nucleotide variants (SNVs) and small indels were called using STRAND® NGS v2.5 variant caller at loci that were covered by at least 10 reads and had a variant allele in at least 2 reads. Copy number variants (CNVs) were called following sequence coverage normalization and Z-score estimation for a panel of regions against a profile of multiple control samples in the in-house database. All the variants were exported to StrandOmics v5.0 (Strand Life Sciences, India) where variant annotation, filtering and prioritization was carried out. Variants were filtered based on their impact on gene (missense, nonsense, frameshift or canonical splice site variants) and a minor allele frequency of <1% in databases (1000 Genomes Database, HapMap Database, Exome Variant Server, Exome Aggregation Consortium, gnomAD and in-house database consisting data of >1500 people) Lastly, candidate variants were annotated according to the ACMG-AMG classification into 5 classes: benign, likely benign, uncertain significance, likely pathogenic and pathogenic using semi-automated InterVar [10].

Candidate SNVs were validated using bi-directional Sanger sequencing on the SeqStudio Genetic Analyzer platform (Applied Biosystems, USA), according to the manufacturer's protocols. Primer sequences were designed using Primer3 v0.4.0 online tool (<http://bioinfo.ut.ee/primer3-0.4.0/>) and PCR conditions used for validation are listed in Supplementary Table 1.

Results

Clinical presentation

Out of 19 patients in our cohort, 12 were males and 9 were females, with the mean age at the time of study being 10.8 years (range 9 months to 45 years) (Figure 1). Recurrent features included global developmental delay, intellectual disability and muscle abnormalities such as hypotonia, walking difficulty and poor control of neck and body in these patients (Table 1, Supplementary Table 2). Approximately 30% of the patients also suffered from seizures and epilepsy. Genomic DNA from all patients were analysed by clinical exome sequencing.

Genetic analysis of patients

In our cohort of 19 patients with neurodevelopmental disorders, we identified 21 variants across 16 genes which have been associated with different neurological disorders (Table 2, Supplementary File 2). Interestingly, 15 of the 21 variants have been reported previously in the literature and the remaining were novel to our study. Out of 21 variants, 14 were missense, 3 splice site, 2 frameshift and 2 nonsense variants. Out of 19 patients, 7 patients were identified with autosomal recessive, 1 with X-linked recessive and 11 with autosomal dominant disorders. Of 11 patients with autosomal dominant *de novo* variants, 8 (73%) have been described previously in the literature [Table 2]. Three novel *de novo* variants included 2 missense variants in genes *SCN1A* (c.5351T>A/ p.Val1784Asp) and *BSCL2* (c.461C>T/ p.Ser154Leu), and a frameshift mutation that led to a premature stop in gene *SCN2A* (c.1153delT/ p.Phe385SerfsTer8). With the unavailability of parental samples for all 11 patients with presumed *de novo* mutations, Sanger sequencing for *de novo* mutation confirmation was not carried out.

Of interest, out of the 5 novel mutations identified in the current study, 1 was classed as pathogenic (*SCN2A* c.1153delT), 2 as likely pathogenic (*SCN1A* c.5351T>A and *BSCL2* c.461C>T) and 2 as variants of unknown significance (*PGAP1* c.2286+5G>A and *AFG3L2* c.1951A>G). Furthermore, segregation analysis of *PGAP1* c.2286+5G>A variant showed parents to be heterozygous carriers and affected siblings to be homozygous for the variants. However, due to the absence of parental DNA for the patient with *AFG3L2* c.1951A>G mutation, segregation analysis was not carried.

Overall, out of 21 variants, 4 were classed as pathogenic, 9 as likely pathogenic and 8 as variant of unknown significance according to the ACMG-AMG guidelines. With the clinical exome sequencing approach, we were able to provide definitive diagnosis to 10 patients; hence, our diagnostic yield with this

approach was 53%.

Discussion

In the current study, our aim was to assess the utility of clinical exome sequencing in the diagnosis of rare neurological disorders in India. Exome sequencing of 19 patients with intellectual disability and/ or developmental delay provided confirmed diagnosis of 10 patients, whereby, ~50% of the mutations were of *de novo* origin. The study also elucidated 15 rare diseases that were diagnosed in these patients that would have otherwise been difficult to diagnose with cheaper but lower-resolution orthogonal methods such as microarray and karyotyping.

Eleven patients were identified carrying autosomal dominant *de novo* mutations, which is a known disease mechanism in rare neurological disorders [26, 27]. Furthermore, 8 out of 11 variants have previously been reported in other studies, thereby, further strengthening the evidence for the role of these variants in causing respective diseases. It is noteworthy that out of these 8 known *de novo* variants, 50% were missense variants and the remaining were either splice site or nonsense mutations. This finding has direct implication on genetic counselling whereby, *de novo* missense mutations can be associated with incomplete penetrance, whereas, nonsense and splice site mutations are not, as shown for *SCN1A* gene [28].

Despite finding known disease associated variants in majority of the patients, our study identified 5 novel variants in 5 genes- *SCN1A*, *SCN2A*, *PGAP1*, *AFG3L2* and *BSCL2*. Diseases associated with these genes include Dravet syndrome (OMIM#607208), early infantile epileptic encephalopathy type 11 (OMIM#613721), mental retardation type 42 (OMIM#615802), spastic ataxia type 5 (OMIM#614487) and hereditary spastic paraplegia (OMIM#270685), respectively. Whilst 3 of the 5 variants are classed as pathogenic or likely pathogenic according to the ACMG-AMG classification [29], they are to be interpreted with caution as these variants would require replication in other patient and control cohorts as well as functional follow-up to implicate them as disease causing [30]. None of the novel variants identified in the current study had an autosomal recessive or X-linked recessive inheritance pattern. This suggests an intriguing hypothesis of a reduced probability of finding novel recessive genes compared to dominant genes in neurological diseases in the Indian population; one that is supported by the data available from studies in the European population [27].

Interestingly, the diagnostic yield of clinical exome in our cohort was 53%, which is in concordance with the published literature [27]. However, this needs to be placed in contrast with the role of *de novo* copy number variants (CNVs) that also play role in neurological disorder pathogenesis [27]. Genomic microarray-based studies have shown a strong correlation between the number of genes affected by a CNV and phenotypic severity [27, 31]. Indeed, microarray-based studies have shown presence of rare, autosomal dominant form of *de novo* CNVs in approximately 10% of patients [27]. Whilst microarray has been the mainstay for detection of CNVs, exome sequencing based large CNV detection (>400 kb) are increasingly becoming prominent in diagnosing neurological disorders [32]. Furthermore, it is estimated that 45-60 *de novo* single nucleotide variants occur per genome per generation whereas the frequency of *de novo* >500kb CNVs is approximately 0.01 per genome per generation [33, 34]. This difference in mutation rates together with difference in mutation detection abilities could explain an enhancement in the diagnostic yield of exome sequencing by 24-33% over microarray [27]. Therefore, utilization of an exome sequencing technique in identifying *de novo* variants (both SNV and CNV) compared to microarray-based approach in identifying only *de novo* CNVs in neurological diseases is likely to be an attractive approach.

Whilst the current study highlights several benefits of using an exome sequencing based approach in diagnosing neurological diseases, there are some caveats which needs to be highlighted. First, the diagnostic yield of 53% in our study could be misleading if taken at face value. Indeed, overall diagnostic yield has been reported between 50-70% in diagnosing moderate to severe intellectual disability diseases [27], depth and quality of patient phenotyping can impact diagnostic yield [35]. The current study carried out an in-depth patient phenotype which may have aided in interpreting genotype data and disease diagnosis. Second, 11 patients in whom *de novo* SNVs were identified, Sanger validation for the mode of inheritance confirmation wasn't carried out due to the unavailability of parental samples. Without Sanger sequencing confirmation in parental samples, it is conceivable that these variants may have been inherited from one of the parents. However, since these disorders have a significant impact on patient's fitness [27], it is unlikely for either of the parents to be a carrier of these mutations. Hence, despite the absence of parental samples, replication of variants from the literature together with heterozygous status in the patient's sample suggests these variants to be likely of *de novo* origin. Third, the current study had a small sample size compared to the large multicenter project like Deciphering Developmental Disorders (<https://www.ddduk.org>). However, the study was aimed to assess the utility of clinical exome sequencing in the Indian population rather than identification of novel genes and pathways involved in neurological disorders, hence had a requirement for a small sample size.

Conclusions

Genetic studies have significantly improved in the past decade and consequently, there has been a substantial improvement in the diagnosis of neurological disorders. Due to the phenotypic and genetic heterogeneity of neurological disorders, it is required to carry out hypothesis-free exome-wide approaches as a first-tier diagnostic test. Even with the current lack of knowledge around all neurological disease causing genes and pathogenic variants, it seems that *de novo* mutations are the main cause of neurological diseases. Results from our study suggests carrying out deep phenotyping along with clinical exome sequencing as a first-line diagnostic test in neurological disorders in the Indian population.

Abbreviations

ABCD1: ATP binding cassette subfamily D member 1, **ACMG**: American College of Medical Genetics and Genomics, **AFG3L2**: AFG3 like matrix AAA peptidase subunit 2, **ALD**: adrenoleukodystrophy, **ASSP**: Alternative Splice Site Predictor, **BSCL2**: Berardinelli-Seip Congenital Lipodystrophy 2, **CDCBM7**: complex cortical dysplasia with other brain malformations-7, **CES**: clinical exome sequencing **CSMD1**: cub and sushi multiple domains 1, **dbSNP**: Single Nucleotide Polymorphism Database, **EDTA**: Ethylenediaminetetraacetic acid, **EIEE**: Early Infantile Epileptic Encephalopathy, **ExAC**: The Exome Aggregation Consortium, **FATHMM**: Functional Analysis Through Hidden Markov Models, **GPI**: glycosylphosphatidylinositol, **GWAS**: Genome-wide association study, **HGMD**: Human Gene Mutation Database, **HPO**: Human Phenotype Ontology, **LINS1**: lines homolog 1, **LIS1**: Lissencephaly 1, **LIS2**: Lissencephaly-2, **LTR**: Long terminal repeats **LZTR1**: leucine zipper like transcription regulator 1, **MRD5**: mental retardation 5, **MRT27**: mental retardation 27, **MRT42**: mental retardation 42, **NCBI**: The National Center for Biotechnology Information, **NGS**: Next generation sequencing, **NNSPLICE**: Splice Site Prediction by Neural Network, **NS10**: Noonan syndrome-10, **OMIM**: Online Mendelian Inheritance in Man, **PAFAH1B1**: platelet activating factor acetylhydrolase 1b regulatory subunit 1 gene, **PARK**: Parkinson disease, **PCR**: polymerase chain reaction, **PGAP1**: post-GPI attachment to proteins 1, **RefSeq**: Reference Sequence database, **RELN**: reelin, **RFLP**: Restriction Fragment Length Polymorphism, **SCN1A**: sodium voltage-gated channel alpha subunit 1, **SCN2A**: sodium voltage-gated channel alpha subunit 1, **SD**: Salla disease, **SIFT**: Scale-invariant feature transform, **SLC17A5**: solute carrier family 17 member 5, **SPAX5**: spastic ataxia-5, **SPG17**: spastic paraplegia, **SYNGAP1**: synaptic Ras GTPase activating protein 1, **TCOF1**: treacle ribosome biogenesis factor 1, **TCS1**: Treacher Collins syndrome 1, **TUBB2B**: tubulin beta 2B class IIb.

Declarations

Ethics approval and consent to participate

The present study has been approved by the institutional ethics committee [FRIGE's Institute of Human Genetics] with approval number FRIGE/IEC/14/2016 dated 19th November 2016. This process is in accordance with the declaration of Helsinki. An informed consent for investigation was obtained from the family of the proband at the time of enrollment for the study [This was in accordance with the requirement of the institutional ethics committee]. An informed consent for publication was also obtained from the individuals included in the submission [This was in accordance with the requirement of the institutional ethics committee].

Consent for publication

Informed written consent was obtained from parents for publication of the proband's clinical details and/or clinical images. A copy of the written consent is available for review to the editor of this journal.

Availability of data and material

Fastq files are available upon request from the corresponding authors JS and HS.

Competing Interests

The authors declare that they have no competing interests (financial or non-financial) in the present study.

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Authors' contributions

Conceived and designed the experiments: JS, FS and HS; Clinical analysis: JS, FS, MC, SS, and DS; Manuscript writing, tables and figure preparation: DP and HS; Laboratory workup: RB, DP, AM, and AG; Data analysis: AUM, AG and HS; Critical revisions and approval of final manuscript: JS, HS, and FS. All authors reviewed and approved the final manuscript.

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Tables

Table 1: Clinical details and demographic profile of the patients with neurological disorder.

Patient ID	P ₁	P ₂	P ₃	P ₄	P ₅	P ₆	P ₇	P ₈	P ₉	P ₁₀	P ₁₁	P ₁₂	P ₁₃	P ₁₄	P ₁₅	P ₁₆	P ₁₇	P ₁₈	P ₁₉
Age at the time of investigation (in years)	3.5	19	12	3.6	5	21	7	2	5.9	9 months	28	45	2	17	5	10	7	2	10
Sex	M	F	M	M	F	M	F	M	F	M	F	M	M	M	M	M	F	F	M
Symptoms																			
Seizures	+	+	+						+						+				
Motor seizures	+																		
Epilepsy	+	+	+	+				+	+										
Up rolling eyes	+																		
Vision regression																+			
Hearing regression																+			
Drop attacks					+														
Day time sleepiness					+														
Increased dullness					+														
Failure to thrive							+						+						
Tongue bite	+																		
Obesity																	+		
Global developmental delay																			
Autism				+		+													
Developmental delay	+	+		+		+	+	+	+	+			+		+				
Cognitive impairment	+		+				+		+	+									
Motor delay							+			+			+		+				
Intellectual disability		+				+	+		+										
Speech delay		+		+	+	+		+	+	+			+		+				
Hyperactive behavior		+		+	+												+		
Poor eye contact				+											+				
Poor psychosocial development							+												
Blank facial expressions											+								
Cortical sensory deficit									+										
Brain abnormalities																			
Microcephaly							+			+			+		+				
Chorea											+								
Lissencephaly								+	+										
Leukodystrophy																			+
Muscle abnormalities																			
Walking difficulty					+			+			+			+	+				
Hypotonia				+	+				+	+									
Foot drop														+					
Poor neck control									+			+							
Poor body control									+					+					
Brisk reflexes																+			
Myoclonus													+						
Drooling of saliva											+								
Bladder and bowel dysfunction							+												
Facial dysmorphism																			
Low hairline		+																+	
Elongated face		+				+													
Large ears					+														
Strabismus																+		+	
Thick lower lip					+														
Coarse features							+										+		
Kinky hair								+											
Neck webbing																		+	
Skeletal abnormalities																			
Arachnodactyly					+														
Limb-Trunk dyskinesia											+	+	+						
Painful/restricted hand movements (can't eat/write)												+		+					

Abbreviations: Female (F), Male (M)

+ sign indicates the presence of symptom

Table 2: Candidate variants identified by clinical exome sequencing in patients with idiopathic neurological disorders.

ID	Gene	gDNA	cDNA	Protein	Zygosity	Disease [†] (Inheritance pattern)	NGS coverage depth	Allele Frequency		dbSNP reference sequence	Tran (Reference)
								1000 Genomes	ExAC		
P ₁	SCN1A	Chr2:166848434	c.5351T>A	p.Val1784Asp	Het	EIEE6 (AD)	>10x	NR	NR	rs1057518671	ENST00000263660 (NM_001163271.2)
P ₂	SCN1A	Chr2:166911147	c.602+1G>A		Het	EIEE6 (AD)	121x	NR	NR	rs794726827	ENST00000263660 (NM_001163271.2)
P ₃	SCN1A	Chr2:166911245	c.505T>C	p.Ser169Pro	Het	EIEE6 (AD)	>10x	NR	NR	rs796052957	ENST00000263660 (NM_001163271.2)
P ₄	SCN2A	Chr2:166170248	c.1153delT	p.Phe385SerfsTer8	Het	EIEE11 (AD)	320x	NR	NR	rs879253767	ENST00000263660 (NM_001163271.2)
P ₅	SYNGAP1	Chr6:33400447	c.403C>T	p.Arg135Ter	Het	MRD5 (AD)	128x	NR	NR	rs1131692154	ENST00000263660 (NM_001163271.2)
P ₆	LINS1	Chr15:101114141	c.937G>A	p.Glu313Lys	Hom	MRT27 (AR)	>10x	NR	NR	rs1057519019	ENST00000263660 (NM_001163271.2)
P ₇	PGAP1	Chr2:197710601	c.2286+5G>A		Hom	MRT42 (AR)	127x	NR	NR	rs937847069	ENST00000263660 (NM_001163271.2)
P ₈	PAFAH1B1	Chr17:2541604	c.22C>T	p.Arg8Ter	Het	LIS1 (AD)	73x	NR	NR	rs121434489	ENST00000263660 (NM_001163271.2)
P ₉	PAFAH1B1	Chr17:2569296	c.118-14_118-10delTTTAT		Het	LIS1 (AD)	48x	NR	NR		ENST00000263660 (NM_001163271.2)
P ₁₀	RELN	Chr7:103126831	c.9796C>T	p.Pro3266Ser	Het	LIS2 (AR)	130x	0.0008	0.0001486	rs544906913	ENST00000263660 (NM_001163271.2)
	RELN	Chr7:103236965	c.3477C>A	p.Asn1159Lys	Het		189x	0.0010	0.001723	rs114684479	
P ₁₁	PLA2G6	Chr22:38511674	c.1894C>T	p.Arg632Trp	Hom	PARK14 (AR)	71x	NR	0.00003239	rs121908683	ENST00000263660 (NM_001163271.2)
P ₁₂	FBXO7	Chr22:32875119	c.274G>C	p.Asp92His	Het	PARK15 (AR)	263x	NR	0.0003048	rs139135860	ENST00000263660 (NM_001163271.2)
	FBXO7	Chr22:32879986	c.520T>A	p.Ser174Thr	Het		293x	NR	NR		
P ₁₃	AFG3L2	Chr18:12340229	c.1951A>G	p.Arg651Gly	Hom	SPAX5 (AR)	456x	NR	NR	rs764254189	ENST00000263660 (NM_001163271.2)
P ₁₄	BSCL2	Chr11:62469965	c.461C>T	p.Ser154Leu	Het	SPG17 (AD)	222x	NR	NR	rs137852973	ENST00000263660 (NM_001163271.2)
P ₁₅	TUBB2B	Chr6:3227745	c.33G>C	p.Gln11His	Het	CDCBM7 (AD)	42x	NR	NR	rs1135401758	ENST00000263660 (NM_001163271.2)
P ₁₆	ABCD1	chrX:152990970	c.253_254insC	p.Arg85ProfsTer110	Hemi	ALD (XLR)	NA	NR	NR	rs713993050	ENST00000263660 (NM_001163271.2)
P ₁₇	TCOF1	Chr5:149755284	c.1705G>A	p.Glu569Lys	Het	TCS1 (AD)	>10x	NR	0.00006056	rs764314276	ENST00000263660 (NM_001163271.2)
P ₁₈	LZTR1	Chr22:21349277	c.1904C>T	p.Pro635Leu	Het	NS10 (AD)	55x	0.0004	0.0002191	rs148677674	ENST00000263660 (NM_001163271.2)
P ₁₉	SLC17A5	Chr6:74354305	c.116G>A	p.Arg39His	Hom	SD (AR)	166x	NR	0.000008246	rs769235753	ENST00000263660 (NM_001163271.2)

Abbreviations: Autosomal dominant (AD), Autosomal recessive (AR), Heterozygous (Het), Homozygous (Hom), Hemizygous (Hemi), Not Applicable (NA), Next Generation Sequencing (NGS), X-Linked recessive (XLR).

† Disease names are abbreviated as per Online Mendelian Inheritance in Men (OMIM)

Figures

Figure 1

Family pedigree of probands. The square box represents male and the circle represents female. The patient under investigation is marked with an arrow. The numeric value under each pedigree depicts the age of the patient. Filled black squares and circles correspond to the affected status of the person and half black squares and circles correspond to carrier status of the person.

Supplementary Files

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