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Expanding the phenotypic spectrum associated with *OPHN1* variants

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ABSTRACT

Genomic sequencing has allowed for the characterization of new gene-to-disease relationships, as well as the identification of variants in established disease genes in patients who do not fit the classically-described phenotype. This is especially true in rare syndromes where the clinical spectrum is not fully known. After a lengthy and costly diagnostic odyssey, patients with atypical presentations may be left with many questions even after a genetic diagnosis is identified. We present a 22-year old male with hypotonia, developmental delay, seizure disorder, and dysmorphic facial features who enrolled in our rare disease research center at 18 years of age, where exome sequencing revealed a novel, likely pathogenic variant in the *OPHN1* gene. Through efforts by the study team and collaborations with the larger genetics community, contacts with other families with *OPHN1* variants were eventually made, and outreach by these families expanded the patient network. This partnership between families and researchers facilitated the gathering of phenotypic information, allowing for comparison of clinical presentations among three new patients and those previously reported in the literature. These comparisons found previously unreported commonalities between the newly identified patients, such as the presence of otitis media and the lack of genitourinary abnormalities (i.e. hypoplastic scrotum, microphallus, cryptorchidism), which had been noted to be classic features of patients with *OPHN1* variants. As genomic sequencing becomes more common, connecting patients with novel variants in the same gene will facilitate phenotypic analysis and continue to refine the clinical spectrum associated with that gene.

1. Introduction

Orphan diseases, while individually rare, collectively affect approximately 25–30 million Americans, or about 10% of the United States population (Field and Boat, 2010). Despite millions of people affected with rare diseases, connecting families with the same diagnosis can be a challenge as affected individuals can span national and international borders. The continued integration of genomic sequencing into clinical practice is inevitably leading to the identification of cases that expand previously described "classic" phenotypes (Chung et al., 2015; Moortgat et al., 2018; Toledo and Dahia, 2015). Connecting families with shared genetic etiologies can create valuable scientific resources to understand the natural history of diseases, and centralized registries can aid in recruitment for studies of rare disorders. One such program, the Gene Discovery Core (GDC) of The Manton Center for Orphan Disease Research at Boston Children's Hospital (BCH), was founded in 2008 to increase scientific knowledge about rare diseases by building collaborations in the rare disease community and creating an infrastructure for patient-focused research. The GDC has created an IRB-approved sample and data repository to facilitate the discovery of novel disease genes and of potential therapies for rare or unknown conditions using genomic technologies. Although many patients enrolling in the GDC are from BCH, patients from around the world can enroll by providing their consent and DNA for genomic analysis, with the hope of identifying the etiology of the rare disease in their family. Many families who enroll in the GDC have already undergone numerous tests and have been evaluated by a number of subspecialists on their "diagnostic odyssey" (Brownstein et al., 2013; Cao et al., 2017; Lo et al., 2018; Mehta et al., 2017).

We present one individual enrolled in this study who was found to have an extremely rare condition, *OPHN1*-associated X-linked intellectual disability. Nonsense, frameshift, and missense variants in

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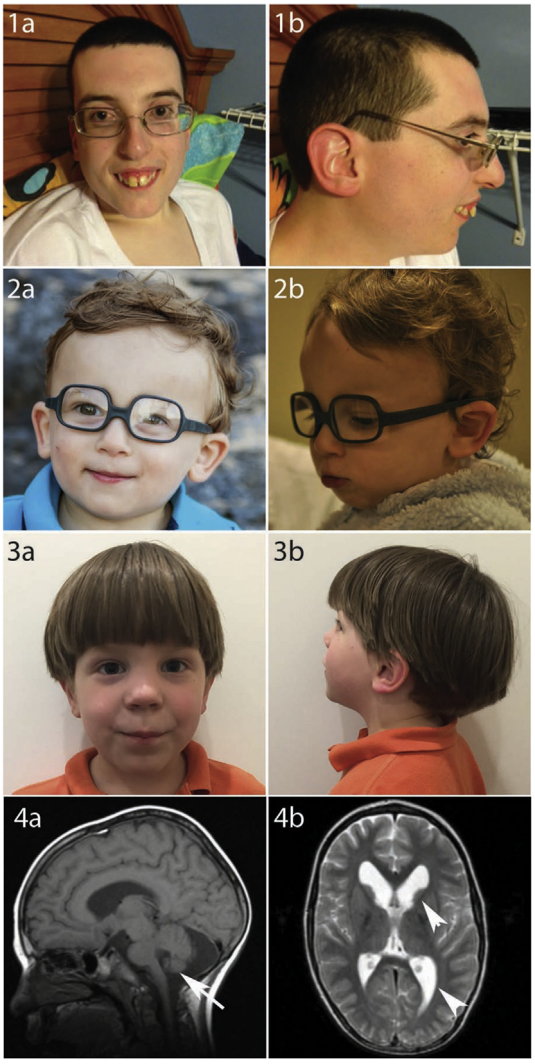

Fig. 1. Photographs of study participants (1a-3b) and MRI findings (4a,b) in Patient 1.
Front (1a, 2a, 3a) and side (1b, 2b, 3b) profiles of Patients 1 (1a, 1b), 2 (2a, 2b), and 3 (3a,3b) are included. Features typical for patients with *OPHN1* variants that are seen in the three study participants include the following: 1a-b) long face, short philtrum, large ears, and strabismus 2a) strabismus and 3a-b) deep-set eyes and long tubular nose. 4a,4b) Brain MRI findings in Patient 1 at 4 years of age illustrating the common neurological findings associated with *OPHN1* mutations: Sagittal T1, cerebellar hypoplasia marked by arrow (4a) and Coronal T2, ventriculomegaly marked by arrowheads (4b).

OPHN1, in addition to chromosomal deletions encompassing this gene, have been reported to cause a syndromic form of intellectual disability associated with cerebellar hypoplasia and distinctive facial features (Fig. 1(1a–1b, 4a-4b)) (Fig. 2A) (Al-Owain et al., 2011; Bergmann et al., 2003; Billuart et al., 1998; Billuart et al., 2000; Busa et al., 2017; Chabrol et al., 2005; Classen et al., 2013; des Portes et al., 2004; Madrigal et al., 2008; Philip et al., 2003; Santos-Reboucas et al., 2014; Zanni et al., 2005) (OMIM300486). After almost two decades of inconclusive testing and misdiagnoses, this individual had been referred to the GDC with a leading clinical diagnosis of Cohen syndrome (OMIM216550), although he lacked central obesity. Whole exome sequencing (WES) identified a variant in *OPHN1* as the likely underlying cause of his presentation, although he exhibited additional features not previously associated with *OPHN1* variants. The family expressed a strong desire to be connected with other families with this diagnosis in order to increase understanding of this rare condition.

2. Clinical report

2.1. Index patient

The subject was a former term gestation, 3.51 kg (48th %ile) product born to a 37-year old G3P2 female. Birth length was 50.5 cm (58th %ile) and head circumference was 34.5 cm (35th %ile). Amniocentesis was performed at 16 weeks gestation which revealed a normal male karyotype (46,XY), AFP, and negative Tay-Sachs screening. He was delivered by normal vaginal delivery and had an uneventful neonatal course. During infancy, his mother describes a lack of eye contact and visual tracking as well as a poor feeding. Brain MRI was performed at 5 months which revealed abnormal ventricular dilatation and expansion of the extra-axial spaces, enlarged cisterna magna and underdevelopment of the vermis (Fig. 1 (4a–4b)). He experienced the onset of seizures at 6 months of age, with EEG monitoring showing continual multifocal seizures, and he was placed on phenobarbital. During childhood, he had repeated sinus and ear infections, despite being status post myringotomy tubes, tonsillectomy, and adenoidectomy, and had numerous episodes of diarrhea lasting months at a time. Additionally, he developed problems with temperature regulation such that his extremities become cold quickly and, in the warm conditions, he did not sweat but became floppy, overheated and needed help to cool down. His facial features included a long face, short philtrum, large ears, and strabismus as shown in Fig. 1 (1a–1b). He was also diagnosed with scoliosis during late adolescence. Extensive molecular genetic testing was negative, including sequencing of *COH1*, *BBS1*, *BBS2*, *TMEM67/MKS3*, *CEP290*, *AH11*, *NPHP1*, *AIPL1, CEP290, CRB1, CRX, GUCY2D, RDH12, RPE65,* and *RPGRIP1*. Chromosomal microarray, mitochondrial genome sequencing, FISH 22q11.2, and postnatal karyotype were also negative. At 17 years of age, his measurements were weight 52.6 kg (5th %ile, z-score: −1.66), length 166.8 cm (10th %ile, z-score: −1.27) and head circumference 56 cm (50^{th} %ile). The subject and the family subsequently enrolled in the Manton Center GDC study.

2.2. Genomic analyses on the index patient

Blood samples were collected for the proband (Patient 1) and his parents, and WES was performed on the trio by Axeq Technologies (Seoul, South Korea) using Illumina TruSeq Exome Enrichment kits (62 Mb) on the Illumina HiSeq 2000 platform. The methodology performed for gene filtration and analysis has been previously described (Joshi et al., 2014). A *de novo* variant in *OPHN1* was identified and confirmed by Sanger sequencing (Fig. 2C). The sequencing was repeated in a CLIA-approved laboratory to be returned to the family for clinical purposes. The identified variant is a novel X-linked hemizygous missense mutation (hg19; chrX:67433711, RefSeq NM_002547.2, c.590 T > A, p. Val197Glu) in *OPHN1*. This variant is absent from the Exome Aggregation Consortium (ExAC) (Lek et al., 2016) and gnomAD databases and is classified as damaging by multiple *in silico* models including MutationTaster, SIFT and Polyphen-2. The valine 197 residue is highly conserved and is present in vertebrate species (Fig. 2b). The description of “mental retardation, X-linked, with cerebellar hypoplasia and distinctive facial appearance” seen with *OPHN1* mutations according to OMIM (300486) was consistent with the clinical features and brain MRI findings of Patient 1 (Fig. 1(1a–1b, 4a-4b)). His other findings, including hypotonia, seizures, moderate intellectual disability, strabismus, hypoplasia of the cerebellar vermis, dilated cisterna magna and ventriculomegaly, have all been previously described with *OPHN1* mutations (Table 1). No additional *de novo* or biallelic variants associated with his phenotype were identified. The family history was negative for any features suggesting a dominantly-inherited disorder.

2.3. Finding additional patients with OPHN1 variants

In order to identify other patients with *OPHN1* alterations,

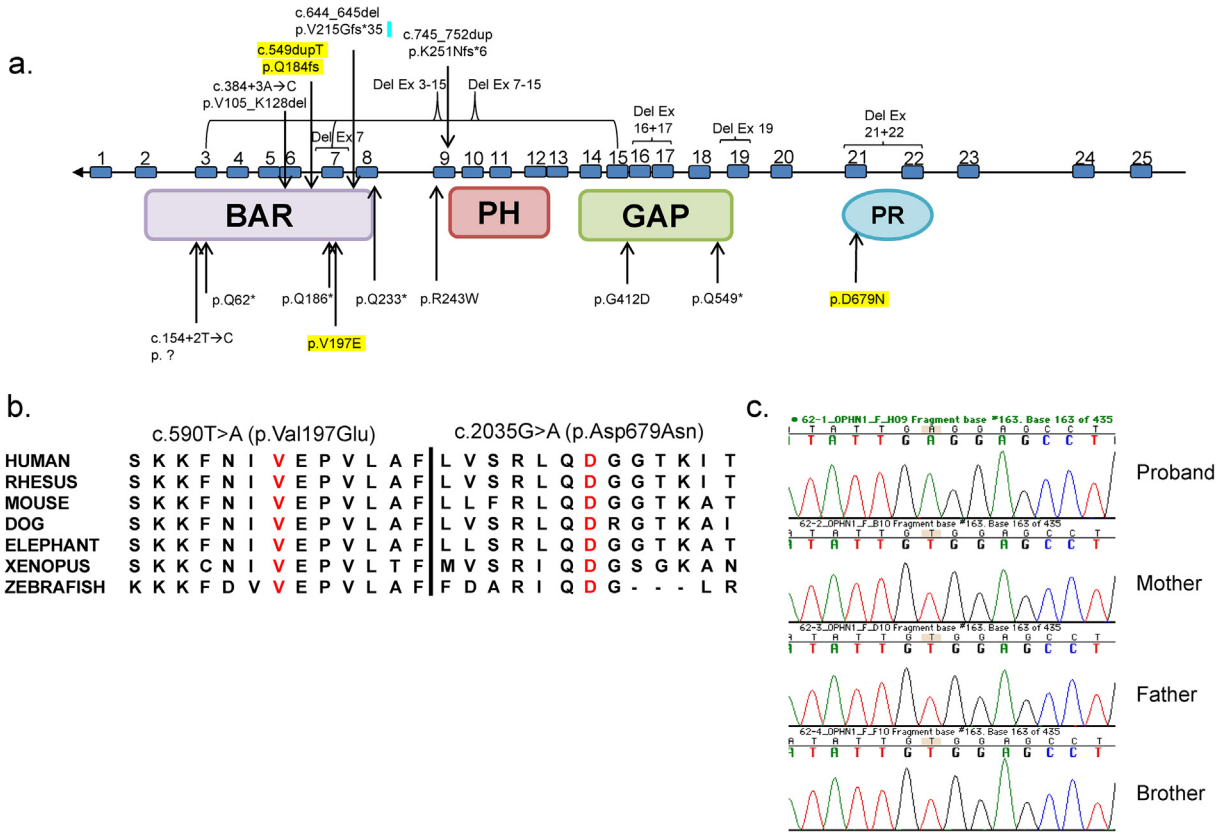

Fig. 2. (a) Schematic of *OPHN1*, demonstrating functional domains and locations of all previously reported males' variants and chromosomal deletions and duplications, highlighting the three variants found in our study (b) Evolutionary conservation of both missense mutations seen in Patients 1 and 3 (c) Chromatogram from Sanger sequencing of the *OPHN1* mutation in Family 1.

commercial and academic laboratories in the United States that offer clinical testing for *OPHN1* and the authors of previous case reports were contacted. Two additional previously-unpublished patients were identified from clinical sequencing laboratories (Patients 2, Baylor Genomics, Houston, TX, and 3, HudsonAlpha Institute for Biotechnology, Huntsville, AL) and were permitted to be contacted by the index patient's family and subsequently enrolled in the GDC. The *OPHN1* variants in all three patients were identified through WES.

Patient 2 is a former 3.7 kg (43%ile) male product (length: 48.5 cm [5%ile] and head circumference: not available) of in vitro fertilization, delivered at 41 weeks gestation to a 35-year old G1P1 female. 3D ultrasound at 32 weeks gestation revealed hypoplastic cerebellum and cerebellar vermis of the fetus. After birth, a head ultrasound was performed which revealed a posterior fossa abnormality, which subsequently lead to a brain MRI that showed hypoplasia of the cerebellar vermis. A genetics workup was initiated, beginning with high-resolution chromosomal analysis and comparative genomic hybridization. Karyotype was negative (46, XY) and a maternally inherited 389 kb 1q21.1 duplication was detected by oligonucleotide-SNP array, though is not thought to be clinically significant. He presented with hypotonia in infancy, and esotropia requiring glasses. Due to previous negative or inconclusive testing, the patient was recommended to have clinical whole exome sequencing performed. At one year of age he was identified to have a truncating alteration c.549dupT (p.Gln184fs*23) in *OPHN1* and was enrolled in the GDC at approximately 2.5 years of age. His growth measurements at approximately 3 years of age were weight 12.9 kg (24 %ile, z-score: −0.69) and length 86.4 cm (3rd %ile, z-score: −1.81). At 4.5 years, he developed seizures recognized on EEG monitoring.

Patient 3 is a former 2.64 kg (73rd %ile) male product born to a 30-year old G3P3 delivered at 34 weeks and 3 days via cesarean section (length: 46.4 cm [53rd %ile] and head circumference: 31.1 cm [30th %ile]). Immediately after birth, he required respiratory support and remained inpatient for two weeks on continuous positive airway pressure (CPAP). As an infant, he presented with tracheobronchomalacia, supraventricular tachycardia, partial innominate artery compression, and Sandifer-like syndrome. In early childhood he was evaluated by a myriad of specialists and diagnosed with developmental delay, pervasive developmental disorder, pseudostrabismus, chronic otitis media and frequent strep throat infections, generalized seizures, and joint pain. Brain MRI was performed at 1 year of age with no anomalies observed. His genetics evaluation included negative chromosomal microarray and Prader-Willi testing. Clinical whole exome sequencing identified a maternally-inherited missense alteration c.2035G > A (p.Asp679Asn) in *OPHN1*. Patient 3's mother is unaffected, though there have been descriptions of a mild to moderate phenotype presentation in carrier females depending on X-inactivation (Al-Owain et al., 2011; Bergmann et al., 2003; Moortgat et al., 2018). At his last visit at our institution at three years of age, the patient's measurements were weight 18 kg (95 %ile, z-score: 1.63), height 103 cm (93 %ile, z-score: 1.51) and head circumference 52 cm (> 97 %ile). The variants found in Patient 2 and Patient 3 are also absent from the ExAC database and gnomAD.

3. Discussion

We describe three new patients with *OPHN1*-associated syndromic intellectual disability, highlighting the novel features in these patients as compared to prior characterizations (Table 2). Oligophrenin, encoded by *OPHN1*, is a Rho GTPase-activating protein expressed throughout the body but present in higher levels in the brain (Billuart et al., 1998). It is thought that decreased oligophrenin leads to

Table 1
Variable presence of phenotypic features in patients with *OPHN1* variants in three newly diagnosed individuals compared to previously reported cases.

Study Cohort	Patient 1	Patient 2	Patient 3	Moortgat et al., 2018				Busa et al., 2017	Santos-Reboucas et al., 2014	Al-Owain et al., 2011
Patient Profile				A	B	C	D			
Age (years)	22	5	6	13,9,62,66	15,10	50,49,48,45,42, 27	7	7	8,4,33,18	19,17,15,2
Variant	c.T590A p.V197E[a]	c.549dupT p.Q184fs[a]	c.G2035A p.D679N[a]	c.384+3A→C p.V105_K128del	c.697 C→T p.Q233*	c.727 C→T p.R243W	c.1235 G→A p.G412D	Del Ex 3-15	Del Ex7	Del Ex7-15
de novo	Yes	Yes	No	No	No	No	Yes	NA	No	No
Common Clinical Presentations										
Head and Neck										
Macrocephaly	-	-	-	-,NA	-,-	-,-,-,-,-,-	-	-	-,-,-,-	NA
Prominent forehead	-	-	-	NA	NA	-,-,-,-,-,-	-	NA	+,+,-,-	+,+,+,+
Long face	+	-	-	NA	+,-	-,-,-,-,-,-	-	NA	NA	+,+,+,+
Short philtrum	+	-	-	NA	NA	-,-,-,-,-,-	-	NA	NA	NA
Marked infraorbital creases	+	-	-	NA	NA	-,-,-,-,-,-	-	+	NA	NA
Prominent chin	-	-	-	NA,NA,+,+	+,-	-,-,-,-,-,-	+	NA	Mi., +,+,Mi.	+,+,+,+
Large ears	+	-	-	NA	NA	-,-,-,-,-,-	-	NA	+,+,+,-	+,+,+,+
Hypotelorism	-	-	-	NA	NA	-,-,-,-,-,-	-	NA	-,-,-,-	NA
Deep-set eyes	-	-	+	+,+,-,-	-,-	-,-,-,-,-,-	-	NA	+,+,+,Mi.	+, NA,NA,NA
Long, tubular nose/ Prominent nasal root	-	-	+	NA	+,-	-,-,-,-,-,-	-	NA	+,+,+,+	+,+,+,+
Thin upper lip	-	-	-	NA	NA	-,-,-,-,-,-	-	NA	NA	NA
Strabismus	+	+	- (pseudo)	+,+,+,+	-,-	-,-,-,-,-,-	+	+	+,+,+,-	+,+,+,+
Nystagmus	+	-	-	+,+,NA	NA	-,-,-,-,-,-	-	-	NA	NA
Genitourinary										
Genitourinary abnormalities	-	-	-	NA,+,NA	NA	NA	NA	NA	-,-.+,-	NA
Neurologic										
Developmental delay	+	+	+	+,+,+,+	+,-	NA	+	+	+,+,+,-	+,NA,NA,+
Intellectual disability	+	n.e.	n.e.	+,+,+,+	+,-	+,+,+,+,+,+	+	-	S.,Mi.,S., Borderline	Mo.,Mo.,Mo.,S.
Speech delay	+	+	+	+,+,+,+	+,-	NA	+	+	+, +,Speechless,-	+, NA,NA,+
Behavioral Disorder	+	+	-	+,+,+,+	+,+	NA	+	+	+,+,+,-	+,NA,NA,NA
Hypotonia	+	+	+	+,+,NA	-,-	-,-,-,-,-,-	-	-	+,Mi.,+,-	+,NA,NA,NA
Seizures	+	+	+	-,-,-,-	+,-	-,-,-,-,-,-	+	-	+,+,-,-	+,+,+,+
Seizure Onset	Infancy	4.5 years	2 years	NA	21 months	NA	6 years	NA	Infancy	8 years, NA,NA, Infancy
Ataxic gait	+	+	+	+,+	+,+	NA	+	-	+,+,+,-	Mi.,Mi.,-,NA
Spasticity	-	-	+	+,-,-,-	NA	NA	-	-	NA	NA
Cerebellar hypoplasia	+	+	-	-,-,NA	-,-	NA,NA,NA,-,NA	-	-	+,+,+,+	+,+,Mi.,+
Ventriculomegaly	+	+	-	-,-,NA	+,+	NA,NA,NA,+,NA	-	+	+,+,-,+	+,+,-,+

Study Cohort	Madrigal et al., 2008	Zanni et al., 2005				Chabrol et al., 2005	des Portes et al., 2004	Philip et al., 2003		Bergmann et al., 2003
Patient Profile		A	B	C	D			A	B	
Age (years)	NA	6	9, NA	NA,NA,4,27	8, NA	22,16 mo.	59,25,14,5	18,14,NA	13	21,20,13,5,2
Variant	Del 21+22	c.154+2T→C p.?	Del Ex 16+17	c.556 C → T, p.Q186*	c.1645 C →T, p.Q549*	c.644_645del p.V215Gfs*35	Del Ex 19	c.745_752dup p.K251Nfs*6	c.184C→T p.Q62*	Del Ex19
de novo	No	No	No	No	No	No	No	No	Yes	No

(*continued on next page*)

Table 1 (*continued*)

Study Cohort	Madrigal et al., 2008	Zanni et al., 2005				Chabrol et al., 2005	des Portes et al., 2004	Philip et al., 2003		Bergmann et al., 2003
Patient Profile		A	B	C	D			A	B	
Common Clinical Presentations										
Head and Neck										
Macrocephaly	NA	NA	NA	+,+,NA,NA	-,-,-	NA	-,-,-,-	+,+,NA,+	+	-,-,-,-,-
Prominent forehead	NA	NA	NA	NA	NA	NA,+	NA	NA	NA	NA
Long face	+,+,+,+	NA	NA	+,+,NA,NA	+,+,+	+,NA	NA	+,+,+,+	NA	NA
Short philtrum	NA	NA	Mi., +,+,+,+,+	+,+,NA,NA	+,+,+	NA	NA		+	NA
Marked infraorbital creases	NA	NA	NA	NA	NA	+,+	NA	+,+,+,+	+	NA
Prominent chin	+,+,+,+	NA	Mi., +,+,+,+,+	+,+,NA,NA	+,+,+	NA	NA	+,+,+,+	+	NA
Large ears	NA	NA	NA	NA	NA	+,+	NA	NA	NA	NA
Hypotelorism	NA	NA	Mi., +,+,+,+,+	+,+,NA,NA	+,+,+		NA	NA	NA	NA
Deep-set eyes	NA	NA	Mi., +,+,+,+,+	+,+,NA,NA	+,+,+	+,NA	NA	+,+,NA,NA	+	NA
Long, tubular nose/ Prominent nasal root	+,+,+,+	NA	Mi., +,+,+,+,+	+,+,NA,NA	+,+,+	NA	NA	NA	+	NA
Thin upper lip	NA	NA	Mi., +,+,+,+,+	+,+,NA,NA	+,+,+	NA	NA	NA	NA	NA
Strabismus	+,+,+,+	+	NA	NA	NA	+,+	+,+,+,+	NA	NA	+,+,+,+,+
Nystagmus	NA	+	-,+,+,+, +,+	NA	+,+,+	NA	NA	-,-,-,-	-	NA
Genitourinary										
Genitourinary abnormalities	+,+,+,+	NA	NA	+,+,NA,NA	-,-,-	NA	-,-,+,-	NA	NA	+,+,+,+,+
Neurologic										
Developmental delay	NA	+	+, NA,NA,NA,NA,+	+,+,+,+	+,+,+	+,+	+,+,+,+	+,+,+,+	+	+,+,+,+,+
Intellectual disability	+,+,+,+	+	+,Mo.,Mo.,Mo., Mo.,S.	+,+,+,+	+,+,+	+,+	Mo.,Mo., S.,S.	+,+,+,NA	+	+,+,+,+,+
Speech delay	NA	+	+,NA,NA,NA,NA,+	+,+,+,NA	+,+,NA	+,+	+,+,+,+	+,+,+,NA	+	+,+,+,+,+
Behavioral Disorder	NA	NA	NA	NA	+,NA,NA	NA	-,-,+,+	NA,NA,+,NA	+	NA
Hypotonia	NA	+	-,NA,NA,NA,NA,NA	NA	NA	NA,+	NA,+,+,+	+,+,+,-	NA	+,+,+,+,+
Seizures	-,+,+,-	-	-,-,-,-,-,+	+,-,+,+	-,NA,NA	NA,+	+,-,+,+	-,-,-,-	-	+,+,+,+,+
Seizure Onset	'Early'	NA	NA	NA	NA	Infancy	NA, Infancy	NA	NA	Infancy
Ataxic gait	-,-,-,-	+	-,-,-,-,-,-	NA	-,NA,NA	NA,-	-,-,-,-	-,-,-,-	-	+,+,+,+,+
Spasticity	NA	NA	-,-,-,-,-,+	+,-,NA,NA	NA	NA	-,-,-,+	NA,NA,NA,+	-	NA
Cerebellar hypoplasia	-,+,+,-	+	+,+,+,+,+,+,+	NA	+,+,+	+,+,+	NA,+,NA,+	+,+,+,+	+	+,+,+,+,+
Ventriculomegaly	-,+,+,-	+	+,+,+,+,+,+,+	NA,NA, NA,-	+,+,+	+,+,+	NA,-,NA,+	+,+,+,+	+	+,+,+,+,+

'+' indicates presence, whereas '-' symbolizes lack of the feature. 'n.e.' represents a feature that has not been evaluated and 'NA' signifies data that is not available. Abbreviations: Mi. for Mild, Mo. for Moderate, and S. for Severe.

[a] RefSeq NM_002547.2 (hg19).

increased Rho protein activities, resulting in a negative impact on neuronal development (Santos-Reboucas et al., 2014) and thus could explain the phenotype of intellectual disability as well as structural brain abnormalities.

Review of the three patients' medical records revealed variability in their phenotypes in comparison to the common features reported in the literature (Table 1) (Al-Owain et al., 2011; Bergmann et al., 2003; Busa et al., 2017; Chabrol et al., 2005; des Portes et al., 2004; Madrigal et al., 2008; Moortgat et al., 2018; Philip et al., 2003; Santos-Reboucas et al., 2014; Zanni et al., 2005). This was particularly true for the dysmorphisms previously associated with *OPHN1* variants, with Patients 2 and 3 lacking most of the previously reported common facial features (Fig. 1 (1a–3b). In terms of other neurological findings, imaging for Patient 3 was negative for cerebellar hypoplasia and ventriculomegaly. None of the three patients had genitourinary features, such as hypoplastic scrotum, microphallus, cryptorchidism, which had previously been associated with the *OPHN1* variants (Al-Owain et al., 2011; Bergmann et al., 2003; Busa et al., 2017; Chabrol et al., 2005; des Portes et al., 2004; Madrigal et al., 2008; Moortgat et al., 2018; Philip et al., 2003; Santos-Reboucas et al., 2014; Zanni et al., 2005) (Table 1).

All three patients present with psychomotor delay, hypotonia, seizures, speech delay, and ataxic gait, which is consistent with previously reported cases (Al-Owain et al., 2011; Bergmann et al., 2003; Billuart et al., 2000; Busa et al., 2017; Chabrol et al., 2005; des Portes et al., 2004; Madrigal et al., 2008; Moortgat et al., 2018; Philip et al., 2003; Santos-Reboucas et al., 2014; Zanni et al., 2005). Additionally, two of the three probands were diagnosed with strabismus, while the third was reported to have pseudostrabismus (Table 1).

Review of the patient's medical records revealed other clinical findings of note that were not previously reported to be associated with *OPHN1* variants. For example, Patient 1 has retinal dystrophy, micrognathia, scoliosis, eczema, and persistent diarrhea. Additionally, Patient 3 has been diagnosed with reactive airway disease, tracheobronchomalacia, gastroesophageal reflux disease, joint pain, pervasive developmental disorder, and obsessive-compulsive disorder.

Overall, our comparisons found unreported commonalities between the new patients such as chronic otitis media as well as unique presentations of tracheobronchomalacia and eczema, while none had genitourinary abnormalities, which has been noted to be a classic feature of patients with *OPHN1* mutations. As illustrated by the present cases, aspects of the clinical manifestations of the three probands varied from the classic features known to be associated with *OPHN1* variants. However, the previous description of the disorder was based on only a small number of known cases with *OPHN1* variants. As WES becomes more widely used as a diagnostic tool, we can expect to detect more outliers, possibly leading to a redefined phenotypic spectrum for many other conditions.

WES is a powerful tool for diagnosing rare genetic conditions; however, it may place a larger burden on health care providers to educate families on conditions that are poorly understood. Families may also expect their providers to connect them with resources and other similarly affected individuals as a part of the diagnostic and counseling process (Hill et al., 2018). In the case of Patient 1, the primary connection was made because the GDC research protocol allows for the return of clinically relevant results and permits re-contacting participants to connect families, if all parties agree. We found from contacting authors of other case reports that this is not always the case and that according to the consent of some research protocols, re-contacting of families is prohibited. As more studies return results to participants, there will be more opportunities for the families and research coordinators alike to seek out and create patient networks tailored to their specific diagnoses (McLaughlin et al., 2014). The partnership of researchers, clinicians, commercial laboratories, and patients and their families is crucial to create robust family networks and patient cohorts. Such cohorts and inter-family networks fulfill two purposes: first, they create an accessible recruitment pool for researchers to access families, enabling more thorough phenotyping, ability to determine natural history, and enrollment in future studies including potential treatment trials; secondly, it empowers patients and makes them more accessible to experts in the field and could expedite the discovery process.

Table 2
Comparison of previously reported cases in the literature to our study of the most common features of *OPHN1* mutations.

Common Features of *OPHN1*	Reported in the Literature % (n)	Our Study % (n)
Distinctive facies	84 (37/44)	100 (3/3)
Cerebellar hypoplasia	80 (35/44)	67 (2/3)
Ventriculomegaly	80 (36/45)	67 (2/3)
Strabismus	76 (29/38)	67 (2/3)
Genitourinary abnormalities	54 (14/26)	0 (0/3)
Behavioral Disorder	52 (17/33)	67 (2/3)
Seizures	43 (23/53)	100 (3/3)
Ataxia	40 (16/40)	100 (3/3)

In addition to expanding phenotypes, new connections with families and researchers can not only improve diagnostics, but also lead to potential future treatments. A follow-up conference call, organized by the family of Patient 2, connected experts in the fields of clinical genetics, molecular genetics, and patient advocacy. This call addressed pending patents and brainstormed options for drug trials in the United States and Europe. The action of the families to unite such a diverse group of people towards a common goal demonstrates the empowerment of patients and families to work together and it occurred on a timeline much faster than most industry or academia-driven initiatives.

We are currently aware of 50 domestic and international families with *OPHN1* variants, but there are likely other families with the diagnosis who are not yet connected. With this need in mind, it is the responsibility of clinicians and researchers to provide not only medical treatments and further testing options, but also additional resources and support for the families who are living with the disease. Programs such as the Matchmaker Exchange (Sobreira et al., 2017) and Patients Like Me® have started to build the necessary infrastructure for connecting families with the same condition. Whether it is patient-to-patient interactions or collaborations between researchers that indirectly connect families, the ultimate goal of creating rare disease networks is continuing to prove valuable. The benefits of these networks are twofold; the families no longer feel isolated, and by unifying the patient population, families become more accessible to research studies and clinical trials.

Disclosure statement

MCT is currently employed by Ambry Genetics; however no laboratory funding or services were used for this work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2018.06.015.

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Web Resources

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URL: http://omim.org/entry/300127.

URL: http://databases.lovd.nl/shared/variants/0000081497.

URL: http://exac.broadinstitute.org.

URL: http://gnomad.broadinstitute.org/.

URL: http://databases.lovd.nl/shared/variants/0000081500.

URL: http://databases.lovd.nl/shared/variants/0000081502#00696.

URL: https://www.cdc.gov/growthcharts/percentile_data_files.htm.