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UBE2A-Related X-linked Intellectual Disability

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Abstract

UBE2A-related XLID is characterized by a distinctive facial phenotype (dense eyebrows and eyelashes, synophrys, hypertelorism, upslanted palpebral fissures, wide mouth and thin lips), generalized hirsutism, hypoplastic genitalia, short stature, hypotonia, seizures and severe intellectual disability. Five affected males in 2 families are described here and compared with the previously reported 17 males in 8 families. The new cases are notable for the absence of nail dystrophy, previously considered a defining manifestation, and for the presence of hypogammaglobulinemia and adult onset ataxia.

Keywords

intellectual disability; X-chromosome; syndrome; dysmorphology; *UBE2A*; seizures; hirsutism

INTRODUCTION

Distinctive or unique growth, craniofacial features, malformations, neurological manifestations, sexual maturation, cutaneous findings, or other characteristics are usually required for the clinical recognition of a syndrome. Among the 183 X-linked intellectual disability (XLID) syndromes, less than half have such distinctive or unique patterns of clinical findings. Prominent among these are Aarskog, Aicardi, ATR-X, Börjeson-Forssman-Lehmann, Fragile X, Incontinentia Pigmenti, Hunter, Rett, XLID-Cleft lip/palate and Hydrocephaly-MASA syndromes. Most XLID syndromes require imaging, biochemical or molecular studies before diagnosis.

UBE2A-related XLID (AKA XLID-nail dystrophy-seizures, *UBE2A* deficiency syndrome, XLID syndrome type Nascimento: OMIM #300860) has facial, cutaneous, genital and neurological manifestations that should allow recognition in the clinic. The face is characterized by thickened eyebrows and eyelashes, synophrys, hypertelorism, upslanted palpebral fissures, depressed nasal root, wide mouth, thin lips, short broad neck and low nuchal hairline. In addition to generalized hirsutism, the cutaneous findings include dry thin

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CONFLICTS OF INTEREST

All authors declare that there are no conflicts of interest.

and nail dystrophy. The penis is small. Developmental delay, intellectual disability, abnormal behaviors, seizures, hypotonia and short stature add to the clinical presentation but are not specific to *UBE2A*-related XLID.

Since the report by Nascimento et al. 2006, seven additional families with *UBE2A* sequence variants have been identified (Nascimento et al., 2006, Budny et al., 2010, Czeschik et al., 2013, Tzschach et al., 2015, Tsurusaki et al., 2017, Giugliano et al., 2018). Other males with deletions of *UBE2A* as a part of contiguous gene deletions and more complex phenotypes have been reported (de Leeuw et al., 2010, Honda et al., 2010, Czeschik et al., 2013, Utine et al., 2014, Thunstrom et al., 2015). Two additional kindreds with *UBE2A* mutations including one reported before the 2006 report of Nascimento et al. as XLID-Seizures-Hypogammaglobulinemia-Gait Disturbance and assigned OMIM #300861 (X-linked Mental Retardation, Chudley-Schwartz type) are added with this report.

CLINICAL REPORTS

A summary of the clinical findings in the 5 cases described here and the 17 previously reported cases is given in Table 1. Additional details on kindreds 8905 and 8435 are provided below.

K8905. Two affected brothers, a nonaffected carrier mother, and a noncarrier sister comprise the first kindred (Figure 1A). The mother experienced 2 pregnancy losses, the first of the fetuses having anencephaly.

III.2 was born at 41 weeks with normal growth parameters (weight 3544 g, length 50.8 cm, head circumference 33.5 cm). He developed hypoglycemia and myoclonic seizures on the first day of life. Growth slowed in childhood with ultimate height of 147 cm, weight 43 kg and head circumference 53.7 cm all below the 3rd centile. Development was globally delayed. He has never walked alone nor spoken meaningful words. He is considered to have severe intellectual disability with a mental age of less than 1 year. Facial manifestations include dense eyebrows, long eyelashes, synophrys, upslanted palpebral fissures, left ptosis, strabismus, overhanging columella, short philtrum, wide mouth, high palate, thin lips and prognathism (Figure 2A, 2B). The neck is broad with a low posterior hairline. He had a small ventricular septal defect and patent ductus arteriosus which did not require surgery. The genitalia are hypoplastic. He has short toes, generalized hirsutism, hypotonia, hyperreflexia, seizures and hearing loss. He has low IgA and has experienced unexplained anemia and chronic thrombocytopenia.

During childhood, microcephaly, hypertelorism and the large open mouth with tented upper lip dominated the craniofacial phenotype of III.2 (Figure 2A). This combined with severe developmental delay, hypotonia and hypoplastic genitalia evoked consideration of alpha thalassemia intellectual disability syndrome as the diagnosis which was excluded by molecular testing.

III.4 had normal prenatal growth (birth weight 2784 g, length 47 cm and head circumference 33 cm at 38 weeks). The newborn course was uneventful. Development was globally delayed but less severe than his older brother. His facial characteristics, genital hypoplasia,

and hypotonia were the same as III.2 (Figures 2C, 2D). He had one febrile seizure. His adult height (152.4 cm) was below the 3rd centile but his head circumference (57.2 cm) and weight were at the 50th centile. He has severe intellectual disability with an IQ of 42. He has hearing loss, a ventricular septal defect and low IgM.

K8435. Abbreviated details are available in the report by Chudley et al. (1999) and updated clinical findings in the three affected males are given in Table 1 and Figure 3. Two major findings in K8435 which had not been reported in the other published families are hypogammaglobulinemia and progressive ataxia after age 40 years.

RESULTS

K8905. Genomic DNA from one affected brother was screened for mutations in a panel of 91 XLID genes at the Greenwood Genetic Center. A change, c.208C>G, was identified in *UBE2A*. The alteration resulted in a missense mutation, p.P68R and segregated in the family (Figure 1). The alteration was not present in either ExAC or gnomAD databases.

K8435. Exon capture and Sanger sequencing of 718 genes on the X chromosome was done as previously described (Tarpey et al., 2009). A c.238C>G change was found in the *UBE2A* gene which segregated in the family (Figure 1). The change results in a missense mutation, p.Q110E. The alteration was not present in ExAC or gnomAD databases.

DISCUSSION

UBE2A plays an important role in the cell's ubiquitination process. This is evident by its high level of conservation during eukaryotic evolution. It interacts with the ligating enzyme, E3 ligase. In general, the process of ubiquitination marks proteins for degradation, a proteasome-mediated process. However, the *UBE2A* protein does contribute to the health of a cell in other ways (Haddad et al., 2013). It has been shown that it controls the clearance of dysfunctional mitochondria and is thus quite instrumental in maintaining the health of a cell's mitochondria. Additionally, *UBE2A* is involved in the posttranslational modification process as it assists in the ubiquitination of the histone H2B at lysine 120. H2B K120 marks the portion of the genome which is actively transcribed and then triggers other histone modification pathways which results in altering chromatin structure.

Only a minority of the 141 genes that cause XLID are associated with syndromes that are readily recognizable on clinical examination (Table 2). Most XLID syndromes are rare, and because of the low prevalence and the lack of distinctive somatic or neurologic manifestations, elude ready recognition. *UBE2A*-related XLID although rare with only 10 families reported, should be an exception. The craniofacial features alone should be sufficient in most cases for the clinician to suspect the diagnosis and to confirm the same using molecular technologies.

With few exceptions among the 23 affected males reviewed here, prenatal growth was normal (Table 1). Postnatally statural growth slowed with adult height below the third centile in 11/20 (55%). All experienced global developmental delay with speech acquisition most severely impaired. All except 1 affected male walked alone with the age of walking between

age 18 months and 6 years. Seizures of variable types and time of onset occurred in most affected males (15/21–71%). In addition to the major manifestations summarized in Table 1, 2 affected males had sparse hair, 2 had epicanthus, 2 had cataracts, 3 had short philtrum, 2 had high or cleft palate, 2 had preauricular pits or tags, 3 had short thumbs, 1 had horseshoe kidney, 2 had hernias, 2 had gallstones, 2 had neonatal hypoglycemia, 2 had hyperreflexia, and 2 had recurrent infections.

Very few other syndromes will be confused with *UBE2A*-related XLID. Waardenburg, Sanfilippo, de Lange, Hajdu-Cheney and ATR-X syndromes are the most problematic of the single gene disorders and deletion 9q34.3 (Kleefstra syndrome) among the contiguous gene syndromes. In each case there are distinguishing characteristics and laboratory testing to assist the clinician (Table 3). It should be noted that in early childhood, the facial phenotype in some patients appears strikingly similar to Alpha Thalassemia Intellectual Disability (ATR-X), another XLID syndrome. Other manifestations, particularly the severe developmental impairment, hypoplastic genitalia, and hypotonia further added to the phenotypic similarity of the two syndromes during childhood.

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A. K8905 **B. K8435** **Figure 1.**

A. Partial pedigree for K8435 showing segregation of the missense variant (c.328C>G) and marked skewing of X-inactivation in all carrier females except one (III-1). B. Partial pedigree of K8905 showing segregation of the missense variant (c.203C>G) and marked skewing of X-inactivation in the carrier mother.

Figure 2.

K8905. A. III-2 in infancy. B. III-2 at age 26 years. C. III-4 in infancy. D. III-4 at 22 years.

Note: microcephaly, hypertelorism, small nose, and wide mouth with tented upper lip in infancy, and dense eyebrows, synophrys, wide face and mouth with thin lips in adulthood.

Figure 3.

K8435 A. III-4 at age 43 years. Note prominent supraorbital ridge, dense eyebrows, synophrys, and thin lips. B-1 and B-2. III-11 at ages 2 and 42 years. Note the open mouth and tented upper lip at age 2 years; prominent supraorbital ridge, dense eyebrows, synophrys, hypertelorism, thin lips and prognathism at age 42 years. C-1, C-2, and C-3. IV-2 at ages 5, 22, and 42 years. Note hypertelorism, thin lips and open mouth at age 5 years; hypertelorism, synophrys and tented upper lip at age 22 years; and hypertelorism, synophrys, wide face and hirsutism at age 42 year.

Table 1.

History and clinical manifestations of males with UBE2A mutations.

		Nascimento et al. 2006	Budny et al. 2010	Czeschik et al. 2013	Tzschach et al. 2015*	Tsurusaki et al. 2017	Giugliano et al. 2017	GGC - K8905		K8435			All Cases
								III-2	III-4	III-4	III-11	IV-2	
Prenatal Growth													
Birth weight		0/3	0/3	0/3	0/1	1/1	0/2	-	-	-	-	-	1/18
	< 3rd centile												
	> 97th centile	1/3	1/3	0/3	0/1	0/1	0/2	-	-	-	-	-	2/18
Birth length		NA	NA	0/2	0/1	1/1	0/2	-	-	NA	NA	NA	1/8
	< 3rd centile												
	> 97th centile	NA	NA	0/2	1/1	0/1	0/2	-	-	NA	NA	NA	1/8
Birth head size		NA	NA	0/1	0/1	0/1	0/2	-	-	NA	NA	NA	0/7
	< 3rd centile												
	> 97th centile	NA	NA	0/1	0/1	0/1	0/2	-	-	NA	NA	NA	0/7
Postnatal Growth													
Height		1/3	3/5	1/5	0/1	NA	2/2	+	+	+	+	-	11/21
	< 3rd centile												
	> 97th centile	0/3	0/5	4/5	0/1	NA	0/2	-	-	-	-	-	4/21
Weight		0/3	0/5	0/5	0/1	NA	0/2	+	+	+	+	-	3/21
	< 3rd centile												
	> 97th centile	2/3	1/5	0/5	0/1	NA	0/2	-	-	-	-	-	3/21
Head size		0/3	0/5	1/5	0/1	1/1	0/2	+	+	-	-	-	3/22
	< 3rd centile												
	> 97th centile	2/3	1/5	0/5	0/1	0/1	0/2	-	-	-	-	+	4/22
Development		3/3	3/3	5/5	1/1	1/1	2/2	-	+	+	+	+	19/20
	Walk alone												
	Nonverbal/limited words	3/3	5/5	4/5	1/1	1/1	2/2	+	+	NA	+	-	19/21
	Intellectual disability Moderate/Severe	3/3	3/4	5/5	1/1	1/1	2/2	+	+	+	+	+	20/21
Behavioral issues						Obsessive-compulsive	Aggressive, Hypertonia, Hyperphagia, Sleep disorder, Self harming		Tantrums				
Facial features		2/3	4/5	NA	NA	+	2/2	-	+	NA	+	+	12/15
	Wide face												
	Heavy eyebrows	NA	5/5	NA	NA	-	2/2	+	+	+	+	+	12/13
	Long dense eyelashes	NA	NA	NA	NA	-	NA	+	+	NA	+	+	4/5
	Synophrys	3/3	5/5	5/5	+	-	2/2	+	+	+	+	+	21/22
	Hypertelorism	1/3	0/5	3/5	+	+	0/2	NA	+	NA	+	+	9/20
	Upslanted palpebral fissures	3/3	0/5	4/5	-	+	2/2	+	+	-	-	-	12/22

		Nascimento et al. 2006	Budny et al. 2010	Czeschik et al. 2013	Tzschach et al. 2015*	Tsurusaki et al. 2017	Giugliano et al. 2017	GGC - K8905		K8435			All
								III-2	III-4	III-4	III-11	IV-2	Cases
	Depressed nasal root	2/3	1/5	4/5	+	+	0/2	+	+	-	-	-	11/22
	Midface hypoplasia	2/3	NA	NA	NA	+	1/2	-	-	-	+	-	5/11
	Wide mouth	3/3	4/5	5/5	+	-	2/2	+	+	+	+	+	20/22
	Thin lips	3/3	NA	NA	NA	+	NA	+	-	+	+	+	8/9
	Short broad neck	3/3	3/5	4/5	+	-	2/2	+	+	NA	-	+	16/21
	Low posterior hairline	3/3	3/5	4/5	NA	+	2/2	+	+	NA	+	-	16/20
Skin	Hirsutism	3/3	4/5	5/5	-	-	1/2	+	+	+	+	+	18/22
	Dry skin	3/3	0/5	5/5	NA	+	2/2	-	-	NA	NA	NA	11/18
	Nail dystrophy	2/3	2/5	2/5	-	-	2/2	-	-	NA	NA	Fungus toes	8/20
	Thick/redundant/ myxedematous	3/3	4/5	3/5	+	-	1/2	+	-	NA	NA	NA	13/19
Genitalia	Small penis	3/3	4/5	1/5	+	-	1/2	+	+	+	+	+	15/22
	Undescended testes	0/3	NA	0/5	-	-	0/2	-	+	-	-	+	2/17
Neurological	Hypotonia	0/3	NA	NA	+	+	1/2	+	+	NA	+	+	7/11
	Spasticity/Cerebral Palsy	0/2	1/5	NA	+	+	1/2	-	-	NA	-	-	4/15
	Seizures (onset)	3/3	3/5	3/5	+	-	0/2	+	+	+	+	+	15/22
	Other								Ataxia	Adult ataxia	Adult ataxia	Ataxia	
Musculoskeletal	Wide nipples	3/3	4/5	2/3	+	-	2/2	-	-	NA	NA	NA	12/17
	Small feet +/- dorsal swelling	3/3	NA	4/5	NA	+	NA	+	+	NA	NA	-	10/12
Other findings	Hearing loss	0/3	0/5	1/5	-	-	0/2	+	+	NA	+	+	5/21
	Heart defect	0/3	0/5	1/5 (VSD)	+	T/F	0/2	VSD, PDA	VSD	NA	-	-	5/21
	Hypogammaglobu-linemia	NA	NA	NA	NA	-	NA	+	+	+	+	+	5/6
	White matter abnormality (MRI)	2/2	0/3	1/3	-	+	NA		NA	NA	-	-	5/13
	Cerebellar hypoplasia	0/2	1/2	0/3	-	-	NA	NA	NA	+	-	-	2/12
Mutation		p.Q128X	4:p.G23R 1:p.R11Q	3:del exon 1-3 2:p.P79R	p.Y130Vfs*9	p.C26R	p.Y82Sfs*4	p.P68R	p.P68R	p.Q110E	p.Q110E	p.Q110E	

* Same patient as patient 6 in Czeschik et al. 2013

T/F - Tetralogy of Fallot, VSD-ventricular septal defect, PDA; patent ductus arteriosus, NA-observation not available

Table 2.

XLID syndromes with distinctive somatic and/or neurologic manifestations.

Aarskog (<i>FGDY</i>)	Lenz Microphthalmia
Aicardi	Lowe (<i>OCRL1</i>)
Alpha Thalassemia XLID (<i>ATRX</i>)	Menkes (<i>ATP7A</i>)
ARX-related * (<i>ARX</i>)	Mucopolysaccharidosis II (<i>IDS</i>)
Borjeson-Forssman-Lehmann (<i>PHF6</i>)	Nance-Horan (<i>NHS</i>)
Coffin-Lowry (<i>RPS6KA3</i>)	Norrie (<i>NDP</i>)
Duchenne Muscle Dystrophy (<i>DMD</i>)	Opitz FG (<i>MED12</i>)
Dyskeratosis Congenita (<i>DKC1</i>)	Oral-Facial-Digital I (<i>OFD1</i>)
Fragile X (<i>FMR1</i>)	FLNA-related * (<i>FLNA</i>)
Goltz (<i>PORCN</i>)	Rett (<i>MECP2</i>)
Graham Anophthalmia	Simpson-Golabi-Behmel (<i>GPC3</i>)
Hydrocephaly-MASA (<i>LICAM</i>)	Telecanthus-Hypospadias (<i>MID1</i>)
Incontinentia Pigmenti (<i>IKBKG</i>)	XLID-Cleft Lip/Palate (<i>PHF8</i>)

* some types only are clinically recognizable

Table 3.

Differential diagnosis for *UBE2A*-related XLID and distinguishing features to assist the clinician

Disorder	Inheritance Pattern	Helpful distinguishing characteristics
ATR-X	XLR	Microcephaly, HgH inclusions in erythrocytes
de Lange	AD, XLD	Intrauterine growth impairment, low pitched cry, anteverted nares, long philtrum, downturned corners of mouth, limb reduction defects, GI reflux
Hajdu-Cheney	AD	Broad nose, long philtrum, osteolysis
Sanfilippo	AR	Macrocephaly, corneal clouding, progressive course, behavioral challenges, dysostosis multiplex
Waardenburg	AD	White forelock, anisocoria, dystopia canthorum, narrow alae nasi, deafness
Del 9q34.3 (Kleefstra)	AD	Prenatal overgrowth, microcephaly, protruding tongue, stereotypies, prominent behavioral abnormalities