A novel UBE2A splice site mutation with intellectual disability type Nascimento

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Abstract

Recently, only two splice-site mutations of the UBE2A gene have been observed in patients with X-linked ID type Nascimento (XLID). We found a novel splice site mutation in UBE2A (c.241+1 G>A) and novel clinical appearances, including a typical four-finger line and erected head unstable.

Title

A novel UBE2A splice site mutation with intellectual disability type Nascimento

Author names and affiliations

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Abstract

Recently, only two splice-site mutations of the UBE2A gene have been observed in patients with X-linked ID type Nascimento (XLID). The patients with XLID had similar phenotypes, including speech impairment, severe intellectual disability, hearing loss, wide face, synophrys, generalized hirsutism, urogenital abnormalities. Here, we report a Chinese boy with a clinically very similar syndromic form of XLID, such as speech impairment, severe intellectual disability, moderate hearing loss. However, there are also different characteristics, including erected head unstable, typical four-finger line. Subsequent whole-exome sequencing showed a novel splice site mutation in UBE2A (c.241+1 G>A). Together, not only our study expands the mutation spectrum and clinical characteristics of UBE2A deficiency syndrome (also called XLID), but also this study may provide clinical evidence for genetic diagnosis.

Keywords: UBE2A;X-linked ID type Nascimento; Mutation;Splice site mutation; Whole-exome sequencing;Intellectual disability

Introduction

X-linked ID type Nascimento (XLID), characterized by a syndromic intellectual disability due to gene mutation on the X chromosome, has great attention caused by the high incidence rate of males in intellectual disability [1-5]. According to recent reports, almost 15 percent of the X-chromosome genes that is known to be related to intellectual disability, while only accounts for about 5 percent of the human genome[6]. However, the majority of mutations in XLID genes remain unknown.

Ubiquitin-conjugating enzyme E2 (UBE2A), involved in the proteasome pathway of protein degradation and DNA repair [7], is located on Xq24 [8-10]. UBE2A deficiency syndrome, also known as X-linked ID type Nascimento (MIM #300860), was first described by Nascimento in 2006, which was characterized clinically by pronounced retardation of psychomotor development, wide face, synophrys, generalized hirsutism, urogenital abnormalities [11]. Since then, two splice-site mutations in UBE2A, seven missense mutations in UBE2A, and four larger deletions in UBE2A have been found [7, 12]. However, there have been fewer reports of UBE2A splice site mutation in china.

Here, we report a Chinese patient diagnosed with XLID, and a novel UBE2A splice site mutation (c.241+1 G>A). In addition to the clinical features of white matter abnormalities in MRI and a recognizable face like wide faces are the same as the typical features reported in XLID. Moreover, the novel clinical features of erected head unstable, no hirsutism, no synophrys,healthy heart, were found. Taken together, the finding of novel mutations of UBE2A in XLID will be better to prevent disability in humans and more possibility to explore the molecular basis of intellectual disability.

Methods

Ethical compliance

The written informed consent was obtained from his parents, and all procedures were reviewed and approved by the Ethics Committee of Changsha Hospital for Maternal and Child Health Care Attached to Hunan Normal University (Hunan, Changsha, China).

DNA extraction

Genomic DNA was extracted from peripheral blood of the proband using DNA extraction kits and standard protocols (TSP201-50, Tsingke, China).

Sanger sequencing

For analysis of UBE2A splice site mutation, the intron-based exon specific primers were designed with Primer 5 (primer-F: TGGGCCCAGTTTCTTAAGGA; primer-R: AATCAGGAGGCTCCCAGACT). The primers were used for amplify UBE2A exons. PCR was amplified with FastStart Taq DNA Polymerase, dNTPack (Roche) and purified with DNA Gel Extraction Kit (GE0101-50, Tsingke, China) following standard protocols. BigDye Terminator v3.1 Cycle Sequencing Kit was used for sequencing reactions prior to sequencing on a 48-capillary 3730 DNA Analyzer (Applied Biosystems).

Case presentation

A 2-years-old male proband (figure 1a, 1b)was diagnosed with severe intellectual disability. However, we did not find chromosome abnormality or the abnormal number of chromosomes. Notably, only one mutation of the patient was found by whole-exome sequencing,which was a novel UBE2A splice site mutation (c.241+1 G>A) (figure 2a, 2b). This splice site mutation was not previously reported or annotated in any public databases,and it modified one nucleotide near exon 4 (figure 3a), likely influencing its splicing. Similarly, the splice site mutation was assessed with a pathogenic criterion (PVS1). His parents without mental retardation were examined by whole-exome sequencing, and the results indicated that the boy had inherited 241+1 G>A mutation from his mother (Figure 2a).

The proband was born in the 35th week of gestation with a birth weight of 2150 g as the first child of a healthy, non-consanguineous couple of Chinese descent. After born by cesarean section due to fetal hypoxia,

the infant was admitted to the neonatal intensive care unit for 28 days because of hypoxia and premature delivery.according to his parents. Four-dimensional color doppler of gestation age 34+4w showed stricture of the aortic arch, isthmus narrowing, abnormal shape of the umbilical vein, higher the systolic-diastolic ratio (S/D) of the umbilical artery, poor S/D, and pulsatility index (PI) of the middle cerebral artery. Normal fetal karyotype was examined by using umbilical cord blood.

A male proband at the age of 7 months, was consulted in the Changsha Hospital for Maternal&Child Health Care after initial symptoms were detected and which were characterized by still erected head unstable and frequent receded head. Thus, he was examined by Gesell's infant development scale score (Gesell) to 12, whereas Gesell's score < 25 indicates very severe neurological damage [13]. The facial appearance included a wide round face, ocular hypertelorism, short hands and feet, and a typical four-finger line [14] (figure 1a, 1b). Brain magnetic resonance image (MRI) performed abnormal signal changes in the deep white matter area near the lateral ventricle and mild delay of myelination compared to a healthy child at the age of 7 months (Figure 4).

Discussion

In the present study, we used whole-exome sequencing to identify a novel UBE2A splice site mutation (c.241+1 G>A) in a Chinese proband with an X-linked Intellectual Disability. According to recent reports, this is the second case report of this syndrome with a novel splice site mutation in China.

Notably, we report novel molecular and clinical data of this patient with intellectual disability. Thus far, only two splice-site mutations in UBE2A, seven missense mutations in UBE2A, and four larger deletions in UBE2A have been reported [7, 12, 15-23]. Besides, all probands with UBE2A deficiency syndrome have resemblance phenotypes, including characteristic facial appearance, speech anomalies, and intellectual disability [20, 24]. However, our proband found novel clinical appearance, including a typical four-finger line and erected head unstable, which has not been described in previous patients.

In addition, the phenotypes of all reported proband with UBE2A mutational syndrome and a patient described in the present study were analyzed, three groups of UBE2A mutational syndrome could be classified: (1) the group of those with larger deletions (largedel), (2) the group of those with missense mutation (miss) and (3) the group of those with splice site mutation (splice) (Table 1). All patients were male and showed severe intellectual disability and speech impairment.

Interestingly, the boys with splice site mutation had a significantly higher erected head unstable (EHU) (1/1), white matter abnormalities (WMA) (2/2), wide face (WF) (4/4) and small penis (SP) (2/2), compared to boys with a missense mutation (0/0 EHU, 3/6 WMA, 3/7 WF, 8/12 SP) or larger deletions (0/0 EHU, 6/7 WMA, 0/0 WF, 7/9 SP). Furthermore, these results confirmed that splice site mutation of UBE2A significantly decreased the risk of synophrys (2/4), Heart defects (HD) (0/2) , Upslanting palpebral fissures (UPF) (0/4), compared with a missense mutation of UBE2A (12/13 synophrys, 3/4 HD, 3/8 UPF) or larger deletions of UBE2A (6/9 synophrys, 9/9 HD, 7/9 UPF) [7, 11, 18, 19, 22, 25]. According to recent reports, four patients have not been reported with upslanting palpebral fissures. Although these analyses were based on a small statistically significant number of patients that could not get a valid conclusion, it is also worth noting this observation suggested that UBE2A splice site mutation might not be at improved risk for upslanting palpebral fissures and heart defects. Conversely, UBE2A splice site mutation might be at improved risk for wide face, white matter abnormalities and small penis.

In conclusion, this report has demonstrated a novel splice site mutation (c.241+1 G>A) in UBE2A gene resulting in an aberrant appearance and severe intellectual disability in a Chinese proband. The patient was found novel clinical appearances, including a typical four-finger line and erected head unstable. Together, our report expands the mutation spectrum and clinical characteristics of UBE2A deficiency syndrome (also called XLID) and may provide clinical evidence into genetic diagnosis.

Conflict of Interests

The authors declare that they have no conflict of interest.

Acknowledgments

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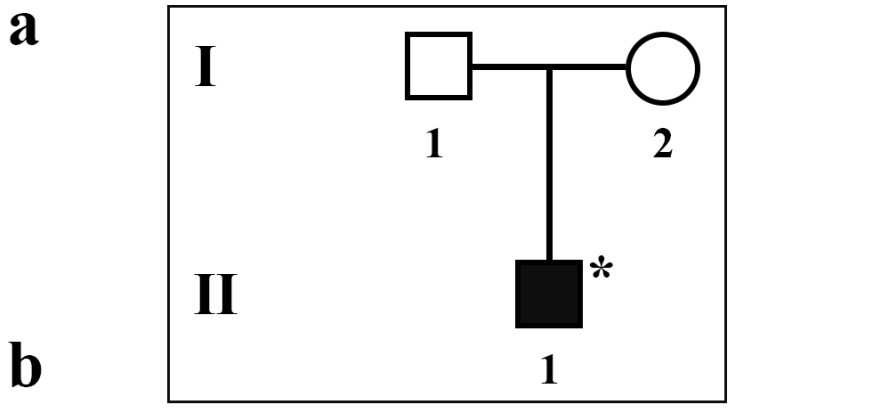
Table 1. Clinical and Molecular Data of Patients with UBE2A Deficiency Syndrome Due to Missense mutation of UBE2A (Each in a Separate Column), as Well as of Patients with Splice site mutation (splice) , Each Type of Mutation are Summarized in a Separate Column—Larger Deletions (largedel), Missense mutation (miss) and Splice site mutation (splice) in UBE2A.

References		Dingyun Ma et al.(2019)	Giuliano et al. (2018)		Nascimento et al. (2008)		Budny et al. (2010)				Haddad et al. (2013)			Czeschik et al. (2013)	Tezuruaki et al. (2017)	Weimin Jia et al. (2019)	de Leeuw et al,Honda et al; Thunstrom et al,Czeschik et		
Patient	1	1	III.3	III.8	1	2	IV:4	V:2	IV:13	III:12	IV:3	III-5	III-6	III-7	5	1	II:3			
General																				
Type of mutation	splice	splice	splice		miss				miss				miss		miss	miss	miss	largedel	miss	splice
Number of different mutation																		4	7	3
Number of patients																		9	13	4
Gender	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Ethnicity	Chinese	Chinese	Caucasian		Brazilian		Caucasian					Caucasian				Japanese	Chinese			
Mutation	c.241+1G>A	c.331-2A>G (p.L112Sfs X17)	c.3300>A (p.Y828dsX4)		c.382C>T		c.67G>A (p.G23R)				c.32G>A (p.R11Q)	c.19C>T (p.R7W)			c.256C>G (p.P73R)	c.76G>A (p.G26R)	c.245A>G (p.Y82C)			
Gestational weeks	35+4W	NA	39	40	35	35	NA	39	40	NA	39	NA	NA	NA	40	39	NA			
Birth weight(g)	2150	NA	3970	3150	2405	3200	NA	3500	5500	NA	3600	NA	NA	NA	2800	2355	NA			
Birth height(cm)	NA	NA	36	35	48	50	NA	NA	NA	NA	NA	NA	NA	NA	NA	46	NA			
Development																				
Erected head unstable	+	NA	NA	NA	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/0	0/0	1/1
Speech impairment	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	9/9	13/13	4/4
Intellectual disability	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	9/9	13/13	4/4
Heart defects	-	NA		NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	-	+	NA	9/9	3/4	0/2
White-matter abnormalities	+	+	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	-	+	-	+	-	6/7	3/6	2/2
Dysmorphic features																				
Synophrys	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	6/9	12/13	2/4
Ocular hypertelorism	+	-	+	+	+	+	-	-	-	-	-	NA	NA	NA	-	-	+	8/9	3/10	3/4
Wide face	+	+	+	+	NA	NA	-	-	+	+	-	NA	NA	NA	-	+	NA	0/0	3/7	4/4
Upslanting palpebral fissures	-	-	-	-	+	+	NA	NA	NA	NA	NA	-	-	-	-	-	+	7/9	3/8	0/4
Small feet	+	NA	-	-	+	+	-	-	+	+	-	-	-	-	-	NA	-	5/8	4/12	1/3
Generalized hirsutism	-	NA	+	+	+	-	NA	NA	+	+	+	+	+	+	+	+	+	4/9	10/11	2/3
Hearing loss impairment	+	NA	-	-	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	2/8	2/2	1/3
Genital anomalities																				
Small penis	+	NA	+	NA	+	+	-	+	+	+	+	-	+	+	-	NA	-	7/9	8/12	2/2

Patients with missense mutation (miss) and splice site mutation (splice) include patient 1(described here. The patients with Larger Deletions (largedel) reported by de Leeuw et al.(2010), Hoddad et al. (2010), Czeschik et al. (2013), Thunstrom et al.(2015). Each Type of Mutation are Summarized in a Separate Column—Larger Deletions (largedel), missense mutation (miss) and splice site mutation (splice), number of affected individuals with available clinical data; NA, not available.



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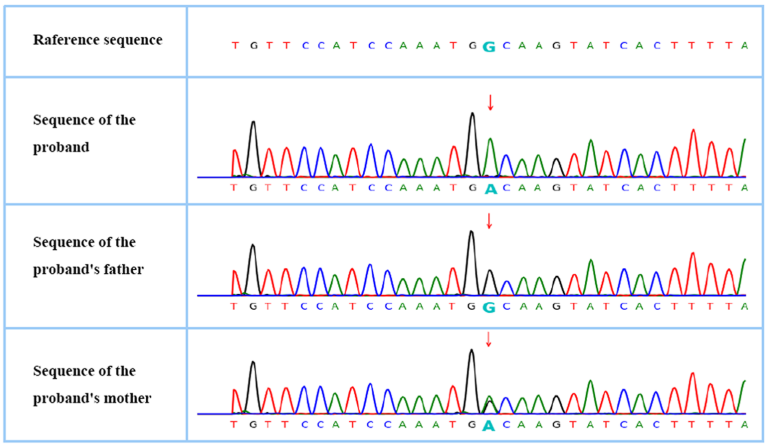

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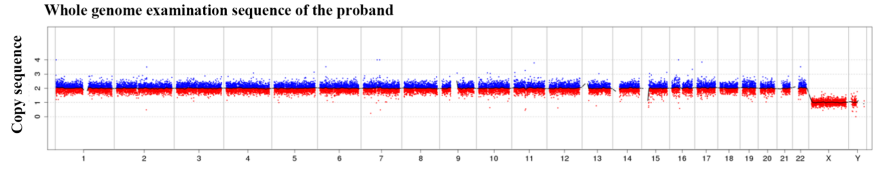

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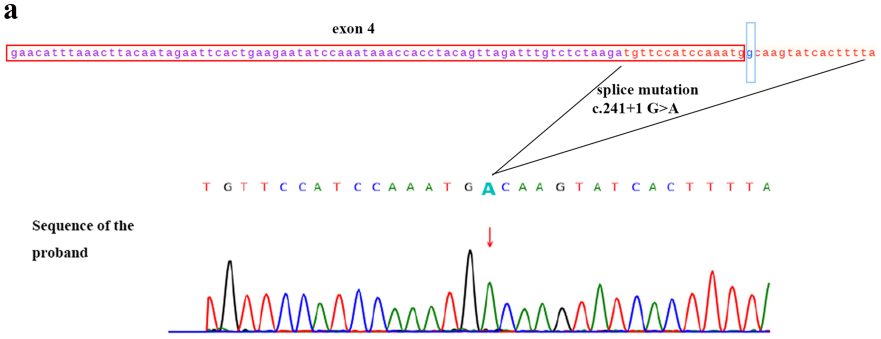

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