A novel UBE2A mutation causes X-linked intellectual disability type Nascimento

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DATA REPORT

X-linked intellectual disability (ID) type Nascimento (MIM #300860), also known as ubiquitin-conjugating enzyme E2 A (UBE2A) deficiency syndrome, is a congenital malformation syndrome characterized by moderate to severe ID, speech impairment, dysmorphic facial features, genital anomalies and skin abnormalities. Here, we report a Japanese patient with severe ID and congenital cataract. We identified a novel hemizygous mutation (c.76G>A, p.Gly26Arg) in UBE2A by whole-exome sequencing.

Human Genome Variation (2017) 4, 17019; doi:10.1038/hgv.2017.19; published online 8 June 2017

Received 19 January 2017; revised 23 March 2017; accepted 24 March 2017

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Intellectual disability (ID) is a neurodevelopmental disorder that is characterized by significant limitations in intellectual functioning and adaptive behavior that are apparent before 18 years of age. An IQ score of < 70 is characteristic. The prevalence of ID has been estimated at 1% of the worldwide population. To date, > 700 causative genes have been reported for all forms of ID. Among these genes, > 100 are implicated in X-linked ID.

X-linked ID type Nascimento (MIM #300860), also known as ubiquitin-conjugating enzyme E2 A (UBE2A) deficiency syndrome, was first shown to be caused by a nonsense mutation in UBE2A in three affected males of a two-generation family. Their mothers were clinically normal. UBE2A, located on Xq24, encodes UBE2A. Ubiquitin-conjugating enzymes catalyze the covalent attachment of ubiquitin to substrate proteins. The protein ubiquitination pathway requires three ubiquitination enzymes, E1, E2 and E3. Ubiquitination of proteins is involved in the ubiquitin proteasome pathway required for the degradation of proteins. In subsequent studies, 19 mutations in UBE2A have been reported (seven missense or nonsense mutations, two small insertions or deletions, and 10 gross deletions). Common clinical findings of this syndrome are moderate to severe ID, speech impairment, dysmorphic facial features, genital anomalies and skin abnormalities. All patients carrying UBE2A mutations are males. Further, when the mothers of these patients were submitted to an X-chromosome inactivation assay, all of them showed skewed X-inactivation.

In this study, we identified a novel UBE2A mutation (c.76G>A, p.Gly26Arg) in a Japanese patient with severe ID and congenital cataract using whole-exome sequencing.

The patient was an 8-year-old Japanese male born at 39 weeks of gestation by normal vaginal delivery to a non-consanguineous 29-year-old gravida 1, para 1 mother and 33-year-old father. The mother was noted to have intrauterine growth restriction and oligohydramnios from the 36th week of gestation. APGAR scores were 8 at 1 min, and 9 at 5 min. His birth weight was 2,355 g (~1.8 s.d.), length 45.6 cm (~1.6 s.d.), and occipitofrontal circumference 32 cm (~0.9 s.d.). At birth, he required supplemental oxygen for tachypnea and retreactive breathing, and was admitted to the neonatal intensive care unit. He had transient hypoglycemia due to a relative decrease in plasma volume due to polycthemia. Magnetic resonance imaging of his brain on the third day of life showed hypoplasia of the corpus callosum and the basilar part of the pons (Figure 1a). Brain magnetic resonance imaging at 1 year and 8 months of age showed some areas of hyperintensity in the deep white matter, mild delay of myelination and reduced white matter volume (Figure 1b). Echocardiography showed tetralogy of Fallot. At the age of 10 months, radical repair for the tetralogy of Fallot was performed. He was noted to have bilateral congenital cataract at 9 months of age, and he underwent cataract surgery at the age of 2 years. Physical therapy for lower limb hypertonicity was started at the age of 5 months. Bilateral lower limb triceps extension surgery for bilateral pes equinus was performed at the age of 3 years and 7 months. He had an episode of febrile convulsion at the age of 2 years and 2 months, but showed normal EEG patterns. His developmental milestones were severely delayed: rolling over at 7 months, sitting at 1 year and 6 months, crawling at 3 years and walking alone at 6 years of age. He could not speak meaningful words, and his developmental quotient score was ~20 at the age of 8 years. He also had obsessive-compulsive behaviors.

Physical examination at 1 year of age revealed mild growth delay with weight 8.36 kg (~1.0 s.d.), height 72.4 cm (~1.0 s.d.) and occipitofrontal circumference 42.5 cm (~2.6 s.d.). Dysmorphic facial appearance included strabismus, high forehead, hypertelorism, large ears, prominent philtrum and thin upper lip (Figure 1c and Supplementary Table S1). At 8 years 1 month, occipitofrontal circumference was 48.3 cm (~1.4 s.d.).

Standard karyotyping was normal, and cytogenetic microarray analysis using SurePrint G3 8 × 60 k (Agilent Technologies, Santa Clara, CA, USA) showed no pathogenic copy-number variations.

Genomic DNA was extracted from peripheral blood using a QIACube (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. Clinical information was obtained from the family members after written informed consent was secured, in accordance with the institutional review board of Kanagawa Children’s Medical Center. Genomic DNA from the patient was
processed using a SureSelect Human All Exon V5+UTRs Kit (Agilent Technologies). Captured genomic DNA was sequenced on a HiSeq2500 (Illumina, San Diego, CA, USA) with 101 bp paired-end reads. Quality-controlled reads were aligned to the human reference genome (UCSC hg19, NCBI build 37.1) using the Burrows-Wheeler Aligner (BWA, version 0.7.10) (http://bio-bwa.sourceforge.net/index.shtml). PCR duplications were removed using Picard (version 1.118) (http://broadinstitute.github.io/picard/). Variants, including single-nucleotide variants and small insertions and deletions, were called using Genome Analysis Toolkit (GATK, version 3.2-2) (The UnifiedGenotyper and the HaplotypeCaller algorithms) (https://software.broadinstitute.org/gatk/) and were annotated using ANNOVAR (22 March 2015) (http://annovar.openbioinformatics.org/en/latest/). Out of all called variants within exons or ±10 bp from exon–intron boundaries, those registered in the NHLBI GO Exome Sequencing Project 6500, the 1000 Genomes Project, dbSNP138, the Human Genetic Variation Database and our in-house Japanese exome data (57 individuals) were removed. Variants were confirmed as true positives by Sanger sequencing on an Applied Biosystems 3730 × l DNA Analyzer (Life Technologies, Carlsbad, CA, USA). Sequence data were analyzed using Applied Biosystems Variant Reporter software (Gene Codes Corporation, Ann Arbor, MI, USA). The mean coverage of RefSeq protein-coding regions was 82.54 reads, with 94.6% being covered by 20 or more reads. Among the filtered variants, we focused on known ID-causing genes and found a novel hemizygous mutation in UBE2A (c.76G>A, p.Gly26Arg). The UBE2A protein contains a ubiquitin-conjugating enzyme catalytic (UBCc) domain.

Figure 1. Brain magnetic resonance imaging (MRI) and photograph of the patient with a UBE2A mutation. (a) Brain MRI of the patient at birth. T2-weighted sagittal image shows hypoplasia of the corpus callosum (white arrowhead) and the basilar part of the pons (white arrow). (b) Brain MRI of the patient at 1 year and 8 months of age. T2-weighted axial image shows white matter abnormalities. (c) Patient at 1 year and 1 month of age. Photograph of the patient’s face showing strabismus, high forehead, hypertelorism, large ears, prominent philtrum and thin upper lip.

Figure 2. UBE2A mutation. (a) Novel hemizygous mutation (c.76G>A, p.Gly26Arg) identified in the patient. UBE2A comprises six exons, and the UBE2A protein contains an ubiquitin-conjugating enzyme catalytic (UBCc) domain predicted by SMART (http://smart.embl-heidelberg.de/). (b) The mutation occurred at an amino acid that is evolutionarily conserved in nine different species. The changed nucleotide is highlighted in the gray box. (c) Electropherogram of the patient and his mother.
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In this study, we used whole-exome sequencing to identify a novel mutation in UBE2A in a Japanese patient with severe ID and congenital cataract. Our findings strongly suggest that UBE2A mutations are causative for X-linked ID type Nascimento.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.1361.

ACKNOWLEDGEMENTS

We thank the patient and his family for participating in this work. We also thank S. Tsuji (Department of Neurology, Graduate School of Medicine, The University of Tokyo), S. Morishita, and J. Yoshimura (Department of Computational Biology, Graduate School of Frontier Sciences, The University of Tokyo) for their advice, and K. Ida and M. Umegae for technical assistance. This work was supported by MEXT KAKENHI (no 22150002) (KK), CREST, JST (KK), Grant-in-Aid for Young Scientists (B) (no 15K19660) (YT) and the Yokohama Foundation for Advancement of Medical Science (VT).

COMPETING INTERESTS

The authors declare no conflict of interest.

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