The first patient with sporadic X-linked intellectual disability with \textit{de novo} ZDHHC9 mutation identified by targeted next-generation sequencing

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\textbf{Abstract}

X-linked intellectual disability (XLID) is a genetically heterogeneous disorder involving more than 100 genes known to date. Here, we describe a Korean male infant with global developmental delay. He had neither facial dysmorphism nor skeletal abnormalities. Bayley scale of infant and toddler development third edition (Bayley-III) measured at age of 2 years revealed marked global developmental delays without Marfanoid habitus, structural brain abnormalities, or epilepsy. The patient’s cognitive, motor, and language developmental ages were 8–9 months, 12 months, and 9 months, respectively. Targeted next-generation sequencing revealed a \textit{de novo} mutation [NM_001008222.2(\text{ZDHHC9}): c.286C>T (p.(Arg96Trp))] in the affected patient. This mutation has been reported previously in a family XLID with Marfanoid features. Sanger sequencing analysis of the proband and his parents revealed that the missense mutation was present in the proband only (absent in his parents). This indicates that the mutation is \textit{de novo} in origin. To the best of our knowledge, this is the first report describing sporadic XLID with \textit{de novo} ZDHHC9 mutation identified by targeted next-generation sequencing.

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1. Introduction

Intelectual disability (ID), primarily defined by low cognitive ability in pediatric population, can be caused by environmental and/or genetic backgrounds. Its worldwide prevalence in children is estimated to be 1–8\% with a high degree of variation (Ropers, 2010). Because of unbalanced sex ratio (1.3–1.4 to 1) observed in ID and the identification of large ID-affected families revealing X-linked segregation, much attention has been focused on the genetics of X-linked ID (XLID) (Piton et al., 2013). One of the first genes identified to be involved in XLID was FMR1 (MIM: 309550). Since then, the number of mutations in genes involved in XLID has grown exponentially. Up to date, more than 100 genes have been described (Gécz et al., 2009; Lubs et al., 2012).

Childhood speech and language deficits are highly prevalent and common features of neurodevelopmental disorders. However, it is difficult to investigate the underlying causal pathways because many diagnostic groups have heterogeneous etiologies. Several studies have attempted to identify genes and associated causative mutations responsible for XLID (Lubs et al., 2012). In the meantime, Sanger sequencing has been performed to identify causative variants of candidate genes with function or expression pattern that suggests a role in cognition or fits with metabolic or clinical observations in affected subjects (Callier et al., 2013; Gécz et al., 2009). Recently, high-throughput next-generation sequencing (NGS) has allowed for screening of mutations in all protein-coding regions of the genome or mutations specifically on the X chromosome (Hu et al., 2016; Niranjany et al., 2015; Redin et al., 2014; Tzschach et al., 2015). Among XLID-related genes, Zinc finger DHHC domain-containing protein 9 (ZDHHC9) is located on Xq26.1. Recent reports have indicated that ZDHHC9 mutations are associated with susceptibility to ID. ZDHHC9 is a palmitoyltransferase that catalyzes posttranslational modification of NRAS and HRAS.

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(Swarthout et al., 2005). The extent of palmitoylation influences both temporal and spatial location of these proteins in the trans-membrane region and Golgi complex. ZDHHC9 mutations suggest that alterations in concentration and cellular distribution of target proteins are sufficient to cause disease.

Several ZDHHC9 mutations have been reported (Masurel Paulet et al., 2014; Mitchell et al., 2014; Raymond et al., 2007; Tzschach et al., 2015). The distribution of clinical presentations associated with ZDHHC9 is currently unclear. After the first report of ZDHHC9 mutations in patients with ID and Marfanoid habitus, several studies have screened patients with ID and some patients have been found to have Marfanoid habitus, structural brain abnormalities, or epilepsy. Only X-linked recessive inheritance of ZDHHC9 mutations has been reported in the literature. Currently there are no specific clinical criteria that determine which patients should be screened for mutations in this gene. Here, we first report a Korean infant with a de novo missense mutation in ZDHHC9. We also provided detailed clinical phenotypes, including neurological and behavioral assessment.

2. Clinical report

A 4-month-old male infant was referred to the Department of Pediatric Neurology of Daejeon St. Mary’s Hospital with a diagnosis of congenital hypotonia. He was born via caesarean section to non-consanguineous parents at 38 weeks of gestation. The pregnancy was uneventful with normal amniotic fluid and fetal movements. His birth weight was 3200 g (50th percentile). His occipitofrontal circumference was 31 cm (50th percentile). He was the second child of his parents. There was no family history of genetic or neurologic diseases. His elder sister was healthy. She appeared to be normal. His early signs of hypotonia and developmental delay were noticed by his parents. The patient could not control his head or hold objects. He showed some difficulties sucking and swallowing. He laid in a frog-like position and showed weak developmental reflexes, including Moro, grasp, and suckling reflexes. His deep tendon reflexes were normal. No fasciculation of the tongue was seen. He had neither facial dysmorphism nor Marfanoid habitus (Fig. 1A). Brain magnetic resonance images showed an appropriate myelination pattern for his age (Fig. 1B and C) without obvious structural abnormalities. Nerve conduction tests and electromyography results were normal. Visual and auditory provoked potential tests were also normal. He had no skeletal abnormalities on radiologic findings.

During late infancy, the patient showed gradual improvements in motor function. He could control his head well at the age of 6 months. He rolled over at the age of 10 months. He sat independently at 14 months, crawled at 18 months, and stood at 22 months. Examination using Bayley scale of infant and toddler development, third edition (Bayley-III) at age of 2 years and revealed marked global developmental delays. His cognitive, motor, and language developmental ages were 8–9 months, 12 months, and 9 months, respectively. At the age of 2 years, his weight was 14.9 kg (50th percentile) with head circumference of 50.7 cm (75th percentile) and height of 50 cm (50th percentile). Physical findings revealed a well-nourished boy without microcephaly at the age of 2 years. Walking was accomplished at the age of 2.5 years. The patient’s speech was limited to just pronouncing his parents’ names at the age of 3 years. He frequently smiled upon kinesthetic and tactile stimulation. Despite his language deficits, he liked to be in touch with friends. He attended a kindergarten for normal children. However, he received additional educational programs, including speech therapy and exercise.

3. Methods

3.1. Genetic analysis

Study subjects provided written informed consent for clinical and molecular analysis. The study protocol was approved by Institutional Review Board of the Catholic University of Korea. Genomic DNA was extracted from the peripheral blood of the proband and his parents. Peripheral blood G-banding karyotyping and genomic microarray analysis were performed using SurePrint G3 Human CGH + SNP microarray 4 × 180 k Kit (Agilent Technologies, Inc., Santa Clara, CA, USA). They revealed no abnormal findings. No mutation was identified by fragment analyses for CGG triplet repeat of FMR for fragile X syndrome or CTG trinucleotide repeat of DMPK associated with myotonic dystrophy.

Since no definite diagnosis was made, we opted to perform targeted NGS to reveal the underlying genetic cause of the patient’s condition. Library preparation was conducted using TruSight One Sequencing Panel (Illumina, Inc., San Diego, CA, USA) to enrich 12 Mb region spanning 4813 genes with clinical relevance. Massively parallel sequencing was performed on Illumina NextSeq platform (Illumina, Inc.). Sequence reads were aligned to human reference genome hg19 with Burrow-Wheeler Aligner 0.7.12. Duplicate reads were removed using Picard-tools 1.96. Local realignment and base quality recalibration were performed using Genome Analysis Tool Kit 3.5 according to GATK’s best practice guidelines. Variants were called by GATK HaplotypeCaller and annotated with Variant Effect Predictor and dbNSFP 2.4, a database developed for functional prediction and annotation of all potential non-synonymous single-nucleotide variants in the human genome (Liu et al., 2013). Common variants with >1% minor allele frequency (MAF) were filtered out using public databases, including the 1000 Genomes Project, Exome Variant Server, and Exome Aggregation Consortium.

Fig. 1. (A) Photograph of the patient at age of 2 years showing no specific dysmorphic features. (B and C) Coronal and sagittal brain MRI of the patient showing normal corpus callosum without other structural abnormalities.

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