A novel LRP6 variant in a Japanese family with oligodontia

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Tooth agenesis is one of the most common developmental anomalies in humans; however, its underlying cause is complex and remains largely unknown. We have previously reported that the prevalence rates of hypodontia and oligodontia, which are subtypes of the condition, in the Japanese population are 6.8% and 0.1%, respectively; we also found that sibling recurrence risks corresponded to 25.0% and 43.8%, respectively. These observations suggest that oligodontia, the more severe tooth agenesis phenotype of the two subtypes, is mostly inherited in a dominant manner. Multiple congenitally missing teeth have been associated with abnormalities in several genes encoding Msh homeobox box 1, 5, ectodysplasin A, axin inhibition protein 2, paired box gene 9, Wnt family member 10A (WNT10A), and low-density lipoprotein receptor-related protein 6 (LRP6).

To date, 12 functionally null variants of the LRP6 gene have been identified in families with congenital tooth agenesis. In this study, we performed whole-exome sequencing (WES) as previously described using genomic DNA from a Japanese family with congenital tooth agenesis and identified a novel frameshift mutation in LRP6. This study was approved by the Aichi-Gakuen University Committee on the Ethics of Human Experimentation (Nagoya, Japan; approval no. S8), the Institute for Developmental Research (Kasugai, Japan; approval no. 13-07) and IRB of Yokohama City University Graduate School of Medicine (Yokohama, Japan, approval no. A201200014).

A 48-year-old Japanese woman diagnosed with familial oligodontia was referred to our hospital (II-2, Fig. 1A). Clinical examination, including radiographic analysis, confirmed the diagnosis of oligodontia in the proband with 23 missing permanent teeth (Fig. 1B). Subsequently, three other members of her family (I-1, II-1, and III-3) were analyzed, and one of her children (III-3) was diagnosed with oligodontia. However, we could not definitively diagnose her father with congenital tooth agenesis because of severe tooth loss. All of the family members had normal primary dentition, nails, skin, and hair.

WES detected a heterozygous single-nucleotide insertion in exon 9 of LRP6 (NM_002336.2: c.1924dup) (Fig. 2). The variant is not present in Exome Aggregation Consortium or the 1000 Genome database. Polymerase chain reaction and Sanger sequencing confirmed that our index case patient’s child, III-3, and father, I-1, also carried this insertion. The mutation is predicted to generate a protein with a truncated extracellular domain (NM_002336.2: c.1924dup; p.Ile642AsnfsI11*).

The Wnt family consists of 19 secreted glycoproteins that regulate homeostasis in various adult tissues and are related to various diseases via the actions of several signaling molecules, such as frizzled receptors and LRP coreceptors. WNT10A is the causative gene for rare autosomal recessive ectodermal dysplasia presenting with syndromic tooth agenesis. Disruption of WNT10A is associated not only with recessive syndromic congenital anomalies but also with a dominantly inherited form of selective tooth agenesis. The LRPS and LRP6 genes are crucial for various Wnt/β-catenin signaling pathways. Several studies have revealed that loss-of-function mutations in LRP6 cause the autosomal dominant form of selective tooth agenesis. Therefore, the Wnt/β-catenin signaling pathway is considered to be associated with tooth development.

In conclusion, we identified a novel LRP6 variant, c.1924dup, in a Japanese family with tooth agenesis. The gene product of the p.Ile642AsnfsI11* variant is a truncated form of the protein lacking transmembrane and cytoplasmic domains. Moreover, we attempted to screen shared gene variations among case patients using WES data, but promising candidate genes other than LRP6 variant were not identified. Therefore, c.1924dup appears to be a novel causative variant for tooth agenesis in the family investigated. Further studies are needed to clarify the role of LRP6 in tooth agenesis.
are needed to determine the precise molecular pathology of Wnt-signaling-related diseases.

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COMPETING INTERESTS
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