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Novel homozygous *KREMEN1* mutation causes ectodermal dysplasia

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Tooth agenesis is one of the most common dental genetic disorders. Single or combination of multiple genetic factors is believed to be involved in the molecular pathogenesis in addition to the various harmful environmental factors (Thesleff, 2003). Hypodontia or oligodontia can occur as an isolated form or syndromic phenotype (Song et al., 2020; Yang et al., 2020). Because the tooth organ is ectodermally derived, the most frequent manifestation of tooth agenesis is as a syndromic phenotype of ectodermal dysplasia (ED). ED is a collection of genetic disorders affecting more than two tissues with ectodermal origin (Wright et al., 2019), and the current search in the Online Mendelian Inheritance in Man database resulted in 233 EDs of which 65 EDs have tooth agenesis.

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AUTHOR CONTRIBUTIONS

Yejin Lee: Formal analysis; Methodology; Writing-review & editing. **Hong Zhang:** Formal analysis; Methodology; Writing-review & editing. **Figen Seymen:** Conceptualization; Investigation; Project administration; Writing-original draft; Writing-review & editing. **Mine Koruyucu:** Data curation; Investigation; Methodology; Writing-review & editing. **Yelda Kasimoglu:** Data curation; Formal analysis; Investigation; Writing-review & editing. **Zang Hee Lee:** Data curation; Investigation; Writing-review & editing. **Jan Hu:** Conceptualization; Funding acquisition; Investigation; Project administration; Writing-original draft; Writing-review & editing. **JP Simmer:** Conceptualization; Funding acquisition; Investigation; Project administration; Writing-original draft; Writing-review & editing.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

EDA/NF-κB and WNT/β-catenin pathways are important signaling pathways involved in tooth development (Yu et al., 2018). Mutations in genetic factors involved in these pathways, such as *WNT10A, WNT10B, LRP6*, and *AXIN2*, have been identified and characterized. Recently, a homozygous recessive mutation in the gene encoding kringle-containing transmembrane protein 1 (*KREMEN1*) has been determined to be responsible for ED with tooth agenesis in an extended Palestinian family (Issa et al., 2016). Clinical features were reported as oligodontia affecting both the primary and permanent teeth, abnormal hair distribution and brittle scalp hair, thin eyebrows and eyelashes, soft and glossy facial skin, and some dysmorphic features. Subsequently, two homozygous mutations of *KREMEN1* in Turkish families (Dinckan et al., 2018) and compound heterozygous mutations in a Thai family (Intarak et al., 2018) have been reported to be involved with oligodontia with ED phenotype (Table S1).

In this study, we identified a novel homozygous mutation (c.97+2T>A) in a consanguineous Turkish family by whole-exome sequencing (Figure S1). The mutation destroyed the splicing donor site of intron 1 and would lead to a frameshift and a premature stop codon (Figure 1). This mutation would result in a lack of functional KREMEN1 due to the nonsense-mediated mRNA decay. The affected daughter was first evaluated at age 26 months with multiple missing teeth. At age 8, it was apparent that she has curly fluffy hair, thin eyebrows and eyelashes, mildly dry skin, and perioral pigmentation, but no dysmorphic facial features. The parents and the first unaffected child in this study were carriers but have no missing tooth or other features related to ED.

Kremen has a context-dependent biphasic Wnt signaling activity: Kremen potentiates Wnt/β-catenin signaling by maintaining LRP5/6 at the plasma membrane in the absence of Dickkof1 (Dkk1); however, Kremen increases Dkk1-mediated Wnt inhibition in the presence of Dkk1 (Cselenyi & Lee, 2008). The mutation identified in this study would result in a lack of functional KREMEN1 at the plasma membrane. This report will not only expand the mutational spectrum of rare *KREMEN1* mutations but also provide further evidence to support the idea of *KREMEN1* as a candidate for oligodontia with mild-to-moderate ED symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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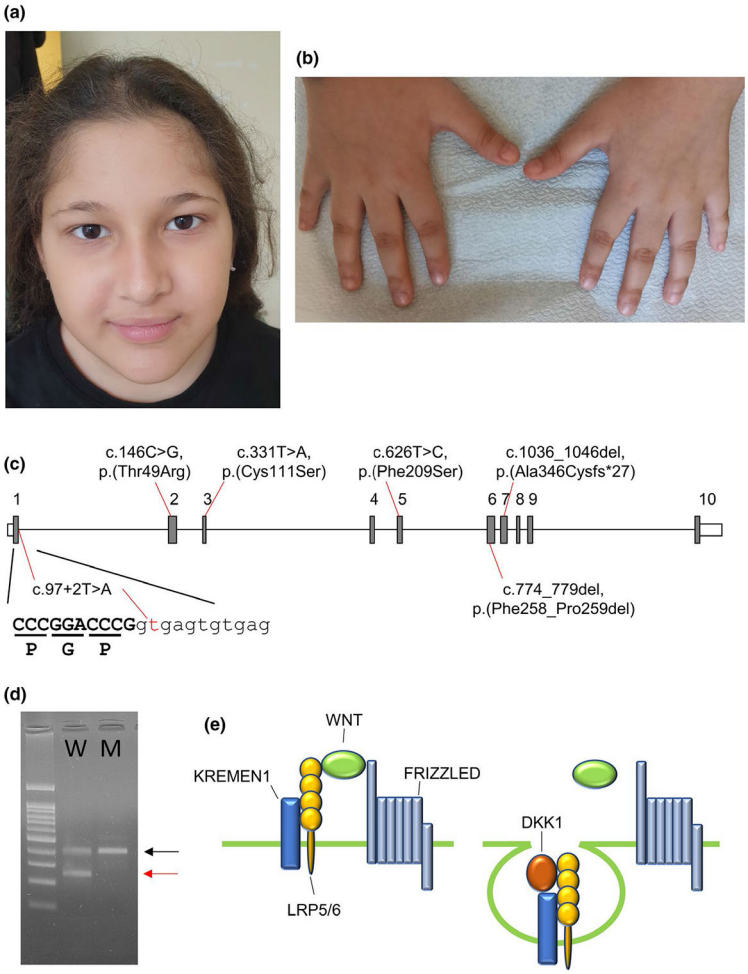

FIGURE 1.

Clinical photographs of proband, gene diagram, and mutations of *KREMEN1*, a minigene splicing assay, and an illustration of KREMEN1 function. (a) Facial photograph of the proband at age 8 years. Curly fluffy hair, thin eyebrows and eyelashes, mildly dry skin, and slight perioral pigmentation, but no other dysmorphic facial features can be seen. (b) Hands of the proband at age 8 years. No abnormality can be seen. (c) Gene diagram of *KREMEN1*. Gene structure (NM_032045.5) shows 10 exons. White boxes indicate UTRs, and gray boxes indicate coding exons. Exon numbers are shown above the boxes, and previously reported mutations are shown. The mutation (c.97+2T>A) identified in this study is shown below the diagram. Nucleotide sequences with capital letter in bold are exon 1, and sequences with lower cases are intronic sequences. Amino acids encoded are indicated with black underlines in the exonic sequence. Mutated nucleotide is shown in red color. (d) In vitro splicing assay with a minigene showed a 251 bp normal splicing product (red arrow) only in the wild-type (W) vector not in the mutant (M) vector. Black arrow indicates a band with vector sequence. Intron 1 retention due to the disruption of the splicing donor site would result in the premature translation termination in the intron 1 [p.(Glu33Glyfs*316)]. However, mutant mRNA would be degraded by nonsense-mediated mRNA decay, resulting in a lack of functional KREMEN1 (Appendix S1 materials and methods). (e) KREMEN1

binding to LRP5/6 potentiates WNT signaling at the plasma membrane in the absence of DKK1 (left illustration). However, KREMEN1 increases DKK1-mediated WNT signaling inhibition by promoting the endocytosis of the KREMEN1-DKK1-LRP5/6 complex (right illustration)