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Identification of *de novo* LRP6 (c.1846A>G, p.Ile616Val) mutation in Saudi family with a rare selective tooth agenesis-7

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Abstract:

Congenital dental anomalies with abnormal number, structure and position are a major problem in humans, where identifying causative variants is a concern. Whole-exome sequencing was performed to detect disease associated variants in Saudi patient with dental anomalies in Saudi Arabia and validated by Sanger sequencing. We identified a *de novo* heterozygous variant in the LRP6 gene (c.1846A>G, p.Ile616Val) in a thirteen-year-old Saudi girl with dental anomalies with classical selective tooth agenesis-7. Evolutionary conserved analysis showed presence of detected mutation in a conserved area and 3D analysis revealed structural changes because of the mutation. Thus, data show a clinically significant variant in the LRP6 gene associated with selective tooth agenesis-7 in a patient, representing the first such report from Saudi Arabia.

Keywords: Selective tooth agenesis-7, whole exome sequencing, LRP6, bioinformatics, mutation, annotation, features, including hypodontia involving the permanent dentition, ankylosed primary teeth, rootless upper first and second premolars bilaterally

Background:

Human dentition results from a complex developmental process that begins during embryogenesis and continues until facial growth is complete [1]. Tooth formation progresses from crown development to root completion, while the jaws undergo continuous growth during this period [2]. Owing to the complexity of tooth development and eruption, dental anomalies are common and are classified into anomalies of number, shape, structure and position, with a predominantly genetic origin [3]. Dental agenesis, defined as the congenital absence of one or more teeth, is one of the most frequent dental anomalies and may occur alone or in association with craniofacial abnormalities [4]. The most primitive classifications of tooth agenesis include (i) anodontia, complete absence of teeth; [5] oligodontia, absence of at least half of the expected number of teeth and hypodontia, absence of fewer than half of the normal dental complement [5]. Recently, the classification has been revised and hypodontia is now defined as the absence of fewer than six teeth [6, 7], excluding the third molars. Hypodontia can be further classified as non-syndromic (the most common presentation of hypodontia) or syndromic when associated with systemic conditions such as ectodermal dysplasia and more severe dental abnormalities [8]. Anodontia is a failure of tooth development [9]. Oligodontia is defined as the congenital absence of six or more permanent teeth [10]. Orodental anomalies can significantly impact both function and aesthetics, affecting the number, size, shape and position of teeth in both primary and permanent dentitions [11]. The main genes implicated in tooth

agenesis include EDA, MSX1, WNT10A, PAX9, LRP6, KREMEN1, PITX2, SMOC2, SHH, GREM2 and TSPEAR, each of which contributes to dental development through distinct biological functions [12]. In non-syndromic forms, these genes are primarily associated with selective tooth agenesis, oligodontia, or variations in tooth size and structure [13]. In syndromic cases, mutations in these genes are linked to broader systemic conditions, most notably ectodermal dysplasia and its variants, as well as disorders such as Axenfeld-Rieger syndrome, coronary artery disease, holoprosencephaly and craniofacial abnormalities [14]. While some genes (*e.g.*, PAX9, SMOC2 and GREM2) show no reported extraoral involvement, others show significant associations with both dental and extraoral phenotypes, highlighting the genetic and clinical heterogeneity of tooth agenesis [15]. Selective tooth agenesis (STHAG) is a genetically heterogeneous group of non-syndromic dental anomalies characterized by the congenital absence of one or more teeth in dentition. It is classified in the Online Mendelian Inheritance in Man (OMIM) database into at least ten autosomal forms (STHAG1-STHAG10) and one X-linked form (STHAGX1) [16]. These subtypes are associated with pathogenic variants in key developmental genes including MSX1 (STHAG1; MIM:106600), chromosome 16q12.1 (STHAG2; MIM:602639); PAX9 (STHAG3; MIM 604625), WNT10A (STHAG4; MIM:150400), chromosome 10q11 (STHAG5; MIM:610926), LTBP3 (STHAG6; MIM:602090), LRP6 (STHAG7; MIM:616724), WNT10B (STHAG8; MIM:617073), GREM2 (STHAG9; MIM:617275), TSPEAR (STHAG10; MIM:620173) and EDA

(STHAGX1; MIM:313500) [17]. Among them, MSX1 has the annotation “with or without orofacial cleft,” which refers to the rare combination of tooth agenesis and different types of orofacial clefting in the affected members of two families identified to date [18, 19]. Tooth agenesis causing genes converge on critical signaling networks, particularly the WNT/ β -catenin pathways, bone morphogenetic protein (BMP) pathways and EDA/NF- κ B pathways, which regulate epithelial-mesenchymal interactions essential for odontogenesis [20]. Here, WNT signaling networks initiate tooth development, BMP refines morphogenesis and EDA regulates ectodermal appendage formation and patterning [20-22]. Overall, these pathways determine tooth number, position and morphology, which are highly relevant to syndromic and non-syndromic presentations [23]. LRP6 mutations impair receptor complex formation and disruption in the WNT/ β -catenin signaling pathway typically leading to arrest at the bud-to-cap stage, explaining oligodontia phenotypes [24]. The BMP signaling pathway regulates epithelial-mesenchymal crosstalk and tooth shape determination, whereas dysregulation leads to defective tooth patterning and arrested morphogenesis, often affecting posterior teeth [25]. Advances in genetic research have enhanced the understanding of dental anomalies and their etiology and pathogenesis [26]. Next-generation sequencing-based genetic testing enables the identification of variants associated with disease in *de novo* or inherited conditions [27]. Therefore, it is of interest to show the whole-exome sequencing approach to identify and characterize the pathogenic variants associated with tooth agenesis in a Saudi family.

Materials and Methods:

Pedigree ascertainment and clinical findings:

A Saudi family was recruited with clinical features of tooth disorders from King Abdulaziz University Hospital in 2025. Detailed medical/dental and family histories of the patient and his/her family members up to three generations were obtained by interviewing the guardian and reviewing the patient's hospital medical records for the pedigree analysis. Clinical examination, intraoral photographs and panoramic radiography were used to evaluate dental anomalies, including tooth agenesis, conical teeth, delayed eruption and ectopic tooth positions. This study was approved by the Institutional Review Board of King Abdulaziz University, Jeddah (approval no. 45128516). Written informed consent was obtained from all participating families according to the Declaration of Helsinki after explaining the study aims in Arabic (if needed). All experiments conducted in this study were performed in accordance with the guidelines of the ethical committee.

DNA extraction and quantification:

Five milliliters of blood were collected in ethylene diamine tetraacetic acid (EDTA) tubes from the affected child and the parents and immediately transferred and stored at 4°C for further investigation at the Institute of Genomic Medicine Research, King Abdulaziz University, Jeddah. Genomic DNA was extracted using the QIAamp Blood Mini Kit (Qiagen, Cat. No:

51104) according to the manufacturer's instructions. The quantity and quality of DNA were assessed using a Nanodrop 2000c spectrophotometer, with the elution buffer used as a blank. DNA purity was evaluated by calculating the absorbance ratio at 260 nm to 280 nm (A260/A280). Samples with ratios between 1.7 and 1.9 were considered pure DNA. To further confirm DNA integrity, we ran the gel on 1% agarose horizontal gel electrophoresis using SYBR Safe dye (Thermo Fisher, USA).

Whole exome sequencing and bioinformatics analysis:

Whole exome sequencing was performed for the affected child using the Illumina NovaSeq6000 platform with a minimum average coverage depth of 100X. Library preparation was done using the Illumina DNA Prep and Enrichment Kit. Raw sequence reads were converted to FASTQ format and aligned to the human reference genome (GRCh37/hg19) using the Burrows-Wheeler Aligner (BWA). Variant calling and base quality recalibration were conducted using the Genome Analysis Toolkit (GATK). Annotation and interpretation were performed using Franklin by QIAGEN and classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines [28]. Variants were filtered based on inheritance pattern, read depth, mapping quality and minor allele frequency (gnomAD < 0.001).

PCR and sanger sequencing:

The identified variants were confirmed using an ABI 3500 Genetic Analyzer (Thermo Fisher, USA) following a standard protocol. Primer pair set: forward (5'-AGCTTCCTTGACACCAGTGAG-3') and reverse (5'-CAATGTGTGTGTCCTTCTGTG-3'), were used for amplification and sequencing of the detected variant (LRP6, c.1846A>G) for confirmation. The reference sequence for the LRP6 gene was downloaded from the University of California, Santa Cruz (UCSC) genome browser (<https://genome-euro.ucsc.edu> accessed on 5 January 2025). Chromatogram peaks were visualized and analyzed using the Bio Edit Sequence Alignment Editor (v7.2.5) and Finch TV.

Evolutionary conservation analysis:

Multiple sequence alignment approach was applied for LRP6 protein sequence conservation analysis amongst eight different species. LRP6 reference protein sequence for human and other species like *Mus musculus*, *Bos taurus*, *Heterocephalus glaber*, *Canis lupus familiaris*, *Felis catus*, *Macaca mulatta* and *Pan troglodytes* were retrieved from the UniProt database. All sequences were aligned using Clustal Omega alignment from EMBL-EBI with default parameters. The alignment result was visualized using MView, where residues were colored based on the percentage identity to highlight conserved regions.

Protein structural analysis:

The protein sequence was downloaded from UniProt database (O75581) in FASTA format. Bioinformatics-based mutational analysis for the specific mutation I616V was carried out using HOPE, a web-based service [29]. The 3D structural information

was obtained from the analysis of PDB 8FFE. Structural visualization and I616V mutagenesis were done using PyMOL 2.3.3.

Results:

A Saudi family with a history of consanguinity and having an affected child was recruited for genetic analysis. The parents were clinically healthy, while a 13-year-old daughter (proband) presented with hypodontia involving the permanent dentition (upper and lower laterals, four lower first and second premolars), ankylosed primary teeth and rootless upper first and second premolars bilaterally (**Figure 1**). A three-generation pedigree of the family showing first-degree consanguinity in the parents of the affected child (**Figure 2**). The WES results of the family for the proband revealed a heterozygote missense mutation in the LRP6 gene (c.1846A>G) located on chromosome 12:12317413, resulting in the substitution of isoleucine by valine 616 (p.I616V) at the 9th exon with dbSNP number (rs201504354). According to the ACMG guidelines, the missense variant was classified as a variant of uncertain significance (VUS) [28]. Sanger sequencing confirmed WES result (LRP6, c.1846A>G) in affected child. Segregation analysis showed that parents were normal with wild type gene sequence whereas affected child had a heterozygous mutation indicating *de novo* mutation and following autosomal dominant mode of inheritance (**Figure 3A**). Multiple sequence alignment of the LRP6 protein from amino acid position 600 to 630 across eight species (*Homo sapiens*, *Mus musculus*, *Bos taurus*, *Heterocephalus glaber*, *Canis lupus familiaris*, *Felis catus*, *Macaca mulatta* and *Pan troglodytes*) showed a high degree of sequence conservation within the analyzed region (**Figure 3B**). The alignment showed a high level of conservation with 100% identity scores of seven species except *Mus musculus* (96.7%). The original wild-type residue and the newly introduced mutant were compared. The mutation is located within the EGF-like 2 domains, which is important for the binding of other molecules and for the activity of the protein. The mutation introduces an amino acid with different properties, which can disturb this domain and abolish its function. The wild-type and mutant amino acids differ in size, with the mutant residue being smaller than the wild-type residue. This might cause a possible loss of external interactions. I616 was mutated to V616 using the ‘mutagenesis wizard’ in PyMOL 2.3.3 (**Figure 4**). Based on the STRING database interaction network for the human LRP6 protein (9606.ENSP00000261349), the network highlights a core interaction group of 11 nodes (proteins) connected by 55 edges (**Figure 5**). Key interacting partners usually include LRP5 (a homolog that acts as a co-receptor), Frizzled family receptors (FZD), Wnt ligands (WNT1, WNT3A), DKK1 (a Wnt inhibitor that interacts with the LRP6 ectodomain) and AXIN1 (a downstream signaling component). The network centers on the canonical Wnt signaling pathway, LDL receptor-related protein 6 and their role in transmembrane signaling.



Figure 1: A panoramic radiograph in the mixed dentition stage, revealing hypodontia involving the permanent dentition (upper and lower laterals, four lower first and second premolars), ankylosed primary teeth and rootless upper first and second premolar bilaterally

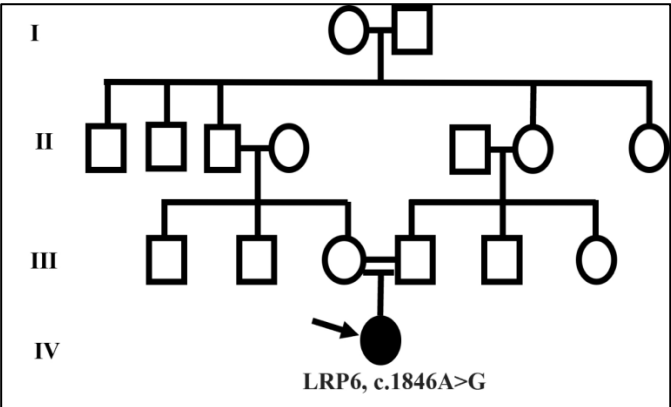


Figure 2: Three-generation pedigree of the family with the LRP6 Mutation

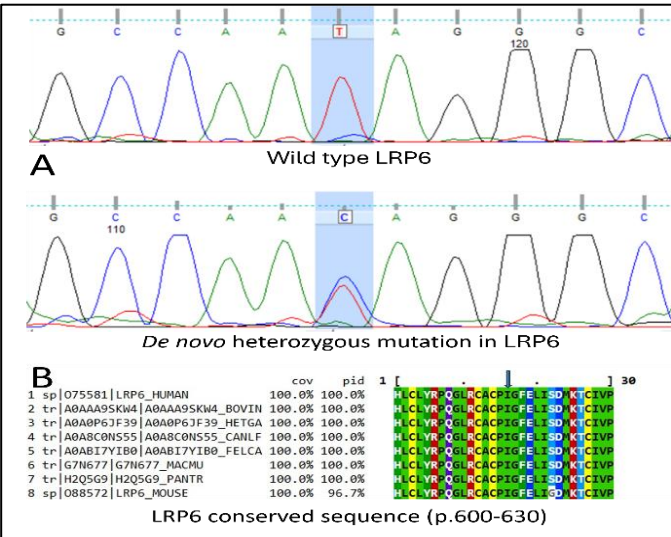


Figure 3: A. Chromatograms of LRP6 heterozygote missense mutation (c.1846A>G) detected in a 13-year-old girl but both parents were wild type. B. Evolutionary conservation analysis showed a conserved area for LRP6 p.600-630, including isoleucine at p.616

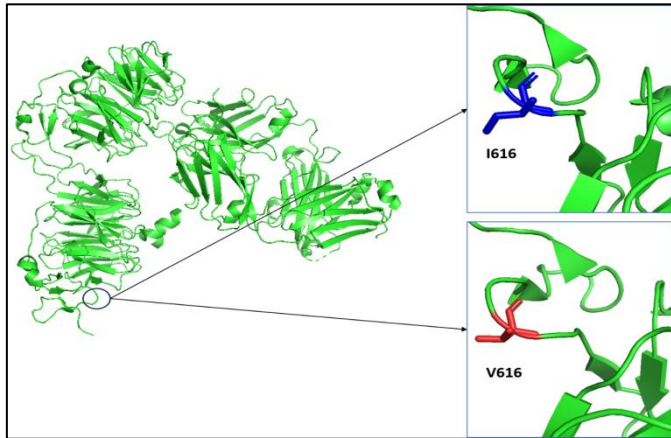


Figure 4: Three-dimensional structure of LRP6. Close-up view of the wild-type and mutant residue shown in blue and red respectively. Figures were made using PyMOL 2.3.3

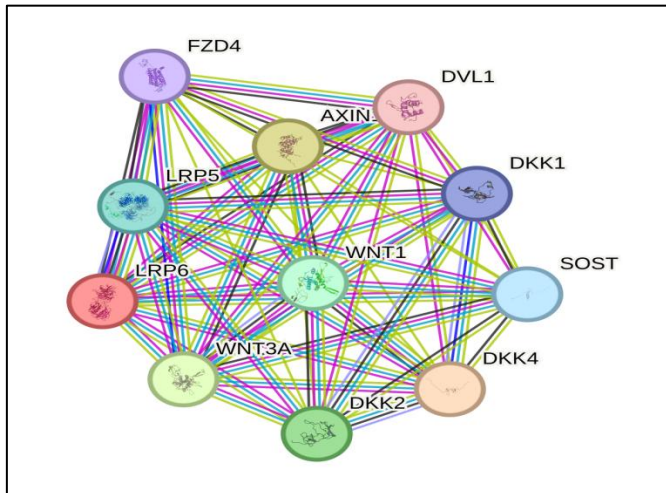


Figure 5: Interaction network of LRP6, as depicted by STRING version 12.0.

Discussion:

Tooth agenesis is a complex developmental disorder associated with multiple genetic variants playing a role in odontogenesis. Despite some reported LRP6 mutation in TA, it is important to expand the mutational spectrum to understand the molecular mechanism and genotype-phenotype relationship. In the present study, we identified a *de novo* missense variant of the LRP6 (c.1846A>G; p.Ile616Val) in a 13-year-old Saudi patient with hypodontia, indicating that dysfunction of LRP6 may disrupt tooth development as it is a causative for Selective Tooth Agenesis type 7 (STHAG7) [30]. Genotype-phenotype correlation studies have demonstrated that heterozygous LRP6

variants are recurrently associated with autosomal-dominant hypodontia, which perfectly aligns with the detected *de novo* heterozygous mutation [30-33]. The hypodontia affecting the maxillary and mandibular lateral incisors and premolars found in the patient is highly consistent with previously reported LRP6-associated tooth agenesis patterns, in which lateral incisors and premolars are among the most frequently missing teeth [20, 34 and 35]. Although truncating and frameshift variants constitute the majority of pathogenic LRP6 mutations, several missense variants have also been described in patients with isolated or syndromic tooth agenesis, indicating that single amino acid substitutions can be sufficient to impair LRP6 function [34, 36]. The identified LRP6 p.Ile616Val substitution is located within the extracellular domain, a region critical for ligand binding. This extracellular YWTD β -propeller and EGF-like domains bind with Wnt to activate signaling cascades. LRP6, a transmembrane cell surface protein and a member of the low-density lipoprotein receptor gene family, is a coreceptor for WNT/ β -catenin-TCF signaling cascade and plays role in differentiation, proliferation and migration processes during dental and orofacial development [37-39]. Additionally, LRP6 variants were reported to cause atherosclerosis/ coronary artery disease/cardiac problems [40], osteoporosis/low bone density [41, 42], spina bifida [43] and metabolic syndrome [44]. It can also affect skin appendage development and root formation, providing a combination of hypodontia, rootless premolars, ankylosed primary teeth and ectodermal features [45-47]. Missense variants in the extracellular domain have been implicated in tooth agenesis with variable clinical severity [34, 48 and 49]. However, according to ACMG guidelines, LRP6, p.Ile616Val still falls under the variant of uncertain significance (VUS) category, but a new finding, along with proper functional validation, might be helpful in re-classifying VUS to likely pathogenic [50]. Clearly, our findings add value to expand the clinical and genetic spectrum of LRP6-associated tooth agenesis, particularly in Middle Eastern populations and emphasize the importance of integrating detailed dental phenotyping with molecular analysis when evaluating patients with hypodontia [22]. The conservation of amino acid residues within the extracellular domain (LRP6, p.600-630) suggests a strong evolutionary constraint, supporting its structural, functional and pathogenic importance. Notably, the mutated residue (p.Ile616Val) is located within a fully conserved motif, indicating a significant impact on the protein structure and function. Based on LRP6 structure-function studies, mutations that alter the receptor's structure, particularly in key regulatory regions, can impair its function. The I616V mutation might affect protein-protein interactions and thereby disturb signal transfer from the binding domain to the activity domain. Therefore, the I616V mutation is likely to reduce the ability of LRP6 to act as a receptor, leading to diminished downstream Wnt signaling activation [51]. LRP6 mutations that interfere with the extracellular domain can result in loss-of-function phenotypes and causing diseases such as tooth agenesis, metabolic syndrome, or cardiovascular disease [52].

Conclusion:

De novo heterozygote missense mutation (LRP6, c.1846A>G; p.Ile616Val) in a thirteen-year-old Saudi girl with tooth agenesis expands the mutational spectrum of LRP6 and underscores its critical role in dental development. Despite the existing VUS classification of variant p.Ile616Val, matching clinical features of selective tooth agenesis type-7 in the patient and segregation analysis results clearly indicate its clinical significance in the pathogenesis of tooth agenesis. Whole exome sequencing-based approaches have shifted clinical practice from phenotype-based diagnosis to more precise and reliable genomic-based diagnosis and have showed utility in identifying genetic causes of rare inherited diseases.

Conflicts of interest: The authors declare no conflicts of interest.

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