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A novel homozygous *PTH1R* variant identified through whole-exome sequencing further expands the clinical spectrum of primary failure of tooth eruption in a consanguineous Saudi family

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ABSTRACT

Objectives: The present study aimed to identify the genetic cause of non-syndromic primary failure of tooth eruption in a five-generation consanguineous Saudi family using whole-exome sequencing (WES) analysis.
Design: The family pedigree and phenotype were obtained from patient medical records. WES of all four affected family members was performed using the 51Mb SureSelect V4 library kit and then sequenced using the Illumina HiSeq2000 sequencing system. Sequence alignment, variant calling, and the annotation of single nucleotide polymorphisms and indels were performed using standard bioinformatics pipelines. The genotype of candidate variants was confirmed in all available family members by Sanger sequencing.
Results: Pedigree analysis suggested that the inheritance was autosomal recessive. WES of all affected individuals identified a novel homozygous variant in exon 8 of the parathyroid hormone 1 receptor gene (*PTH1R*) (NM_000316: c.611T>A: p.Val204Glu).
Conclusion: To the best of our knowledge, this is the first report of primary failure of eruption caused by a homozygous mutation in *PTH1R*. Our findings prove the application of WES as an efficient molecular diagnostics tool for this rare phenotype and further broaden the clinical spectrum of *PTH1R* pathogenicity.

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1. Introduction

Primary failure of eruption (PFE; OMIM 125350) is observed as a defect in the tooth eruption mechanism causing complete failure of eruption or the cessation of initial eruption, resulting in non-ankylosed teeth (Ahmad, Bister, & Cobourne, 2006; Raghoebar, Boering, Vissink, & Stegenga, 1991). The clearance of eruption pathways leads to the development of normal dentition, and a failure to do so causes this rare phenotype. The primary retention of permanent teeth is an isolated condition associated with a localized failure of eruption with no other identifiable local or systemic involvement (Raghoebar, Boering, Vissink, & Stegenga, 1991). Secondary retention involves an unexplained cessation of further eruption after a tooth has penetrated the oral mucosa (Raghoebar, Boering, & Vissink, 1991). Tooth involvement might be unilateral or bilateral in origin, considering the anterior–posterior

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axis as the main target. PFE predominantly affects molar dentition rather than anterior teeth.

The observation of affected individuals experiencing a high frequency of hypodontia and with a family history for tooth eruption problems suggests a genetic involvement in the etiology of PFE (Ahmad et al., 2006). This has been assigned to heterozygous mutations in the parathyroid hormone receptor gene on chromosome 3p21.31 (*PTH1R*, OMIM 168468) (Decker et al., 2008). *PTH1R* is associated with five clinically overlapping human disorders, depending on the type of mutation. Dominant mutations in *PTH1R* cause Jansen's metaphyseal chondrodysplasia, a disorder of bone and cartilage leading to severe metaphyseal alterations (Schipani, Kruse, & Juppner, 1995; Schipani et al., 1996). Recessively inherited, loss-of-function variations in *PTH1R* cause the skeletal disorders Eiken syndrome (Duchatelet, Ostergaard, Cortes, Lemainque, & Julier, 2005) and Blomstrand osteochondrodysplasia (BOCD) (Karperien et al., 1999; Zhang, Jobert, Couvineau, & Silve, 1998). Additionally, heterozygous mutations in *PTH1R* have been reported in patients with Ollier disease (Couvineau et al., 2008; Hopyan et al., 2002).

Saudi Arabia has a high incidence of autosomal recessive disorders because of the high rate of consanguinity (56%) in this population (Al-Owain, Al-Zaidan, & Al-Hassnan, 2012). The successful molecular diagnosis of recessive disorders in these families has been achieved using whole-exome sequencing (WES) and genome-wide single nucleotide polymorphism (SNP) microarray analysis followed by candidate gene sequencing (Ahmed et al., 2015; Alrayes et al., 2015; Jelani, Ahmed et al., 2015). The PFE phenotype has previously been considered to be a non-syndromic autosomal dominant disorder of dentition (Decker et al., 2008; Pilz et al., 2014; Risom et al., 2013; Roth et al., 2014; Yamaguchi et al., 2011); however, in this study we used the WES strategy for causative gene identification in an autosomal recessive family with the PFE phenotype from Saudi Arabia.

2. Materials and methods

2.1. Ethical approval

The work was carried out in accordance with the Declaration of Helsinki, and ethical approval (project ref. 24-14) was granted from the Medical Research and Ethics Unit, King Abdulaziz University (Jeddah, Saudi Arabia). Each participant above 18 years of age signed an informed written consent form to participate in the study and to publish clinical photographs and research for academic purposes. The legal guardian of participants below 18 years of age signed the consent letter.

2.2. Study subjects

The five-generation family (Fig. 1) resided in a remote southwestern region of Saudi Arabia. Consanguinity details and disease history were obtained from the family elders. Affected individuals were examined at the Oral and Maxillofacial Prosthodontics Department, Faculty of Dentistry and Department of Genetic Medicine, King Abdulaziz University. Four sisters (V-2, V-3, V-4, and V-5) affected with PFE fulfilled the previously defined diagnostic criteria for the PFE phenotype (Pilz et al., 2014; Sharma, Kneafsey, Ashley, & Noar, 2015). Venous blood samples from four affected and two unaffected (V-1 and V-6) siblings as well as the unaffected mother (IV-2) were collected in EDTA tubes. Genomic DNA was extracted using standard methods. The father (IV-1) of the affected siblings had died before the start of this study, therefore, his DNA was not available for analysis.

2.3. Whole-exome analysis

A total of 2 μg genomic DNA from all four affected patients was subjected to human whole-exome analysis with paired-end sequencing at 100× coverage. Whole exomes of four affected individuals (V-2, V-3, V-4 and V-5) were captured using SureSelect V4 kits (Agilent Technologies, Santa Clara, CA), and sequenced as 100-bp paired-end reads on the HiSeq 2000 platform (Illumina, San Diego, CA).

For bioinformatic analyses we used Lasergene Genomic Suite V.12 software package (DNASTAR, Madison, WI, USA). Briefly, FASTQ files were aligned to hg19 (NCBI build GRCh37) using SeqMan NGen 12, and ArrayStar v.12 was employed to annotate variant alleles based on dbSNP 142. The mapped variants were compared with dbSNP (http://www.ncbi.nlm.nih.gov/snp/) and the 1000 Genomes(http://www.1000genomes.org/) databases. All homozygous variants including single nucleotide variants shared by the four affected individuals were filtered by using ArrayStar v.12. The obtained variants were further narrowed down using various prediction software: Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/), MutationTaster (http://www.mutationtaster.org/), and PROVEAN (http://provean.jcvi.org/

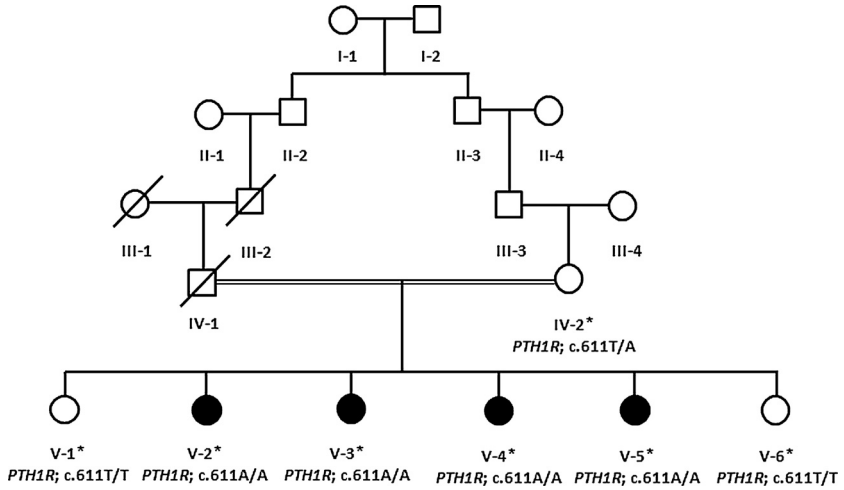

Fig. 1. Pedigree analysis of a consanguineous Saudi family showing the disease phenotype segregating in an autosomal recessive fashion. The available samples for Sanger sequencing are marked with '*' and their *PTH1R* genotypes are also mentioned.

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