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Nonsense variant in a consanguineous family expands the phenotype of *KPTN* gene-related syndrome to include hearing impairment

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Keywords

exome sequencing; hearing impairment; intellectual disability; KPTN; phenotype expansion

KPTN gene-related syndrome (MIM #615620) is a rare autosomal recessive disorder that is characterized by intellectual disability (ID), global developmental delay, language deficits, macrocephaly, epilepsy/seizures, hypotonia and behavioral issues with variable severity[1]. We report on a consanguineous Pakistani family, DEM4669 (Figure 1A) with ID, motor disability, language deficit, and hearing impairment (HI) due to a pathogenic homozygous variant in *KPTN,* which encodes kaptin protein, expressed in neuronal cells and stereocilia of hair cells.[1–3] Affected family members do not have macrocephaly or seizures. This study was approved by the Institutional Review Boards of Quaid-I-Azam University (QAU-153) and Columbia University, New York (AAAS3433 and AAAS2343). Written informed consent was obtained from all participating family members. DEM4669

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was ascertained from a rural area of Khyber Pakhtunkhwa province in Pakistan. The affected individuals have profound HI affecting all frequencies (Figure 1B, C). A homozygous variant [hg38; chr19:47479914; NM_007059, c.736C>T: p.(Gln246*)] in *KPTN* gene was detected through the analysis of exome sequence data that were generated using a DNA sample from affected family member IV:1. Sanger sequencing confirmed segregation of the variant in family DEM4669 (Figure 1A). No variants were identified in genes implicated in HI. The variant p.(Gln246*) identified in this study lies within the fourth α helix of kaptin protein (Figure 1D), due to the location of the nonsense variant, the mutant mRNA is predicted to be targeted by nonsense-mediated decay. The variant is absent in various public databases, e.g., gnomAD, ToPMed, is predicted to be damaging by various bioinformatics tools, and 3D modeling suggests that the variant disrupts protein structure (Figure 1E, F).

The Kaptin is located on the tips of the elongating stereocilium and has unique role in the actin rearrangements that leads to stereocilia formation[2] and that variants in *KPTN* may underlie HI in humans. *KPTN* was previously considered as a candidate for autosomal dominant nonsyndromic HI, DFN4A and the gene was screened for potentially causal variants but none were identified in the family understudy[3]. None of the previously reported patients with *KPTN* variants, presented with HI.

For *KPTN* gene-related syndrome all reported patients have the common phenotypes of ID with language deficits, but for additional phenotypes there is a high level of heterogeneity[4]. Ohio Amish patients with *KPTN* gene-related syndrome have phenotypes that were unique to this population which included hooded eyelids, broad nasal tip, and fifth finger clinodactyly. These finding suggest that phenotypic variability should be expect in patients with *KPTN* gene-related syndrome.

In summary, we report on a new pathogenic loss of function variant [c.736C>T: p.(Gln246*)] in *KPTN* and expand the phenotypic spectrum of *KPTN* gene-related syndrome. This is also the first report of *KPTN* gene-related syndrome in patients from the Asian subcontinent.

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We thank the family members for participating in this study. Author contributions: T.B. and A.A. performed laboratory experiments. K.L. performed data analysis and drafted the manuscript, I.S. oversaw the laboratory and data analyses. K.S., S.K., and I.U. collected the samples. A.N. performed the protein modeling. W.A. and S.M.L. designed and funded the study. S.M.L. edited the manuscript.

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DATA AVAILABILITY STATEMENT

The identified variant has been submitted to ClinVar database [Accession number: VCV002446053.1]

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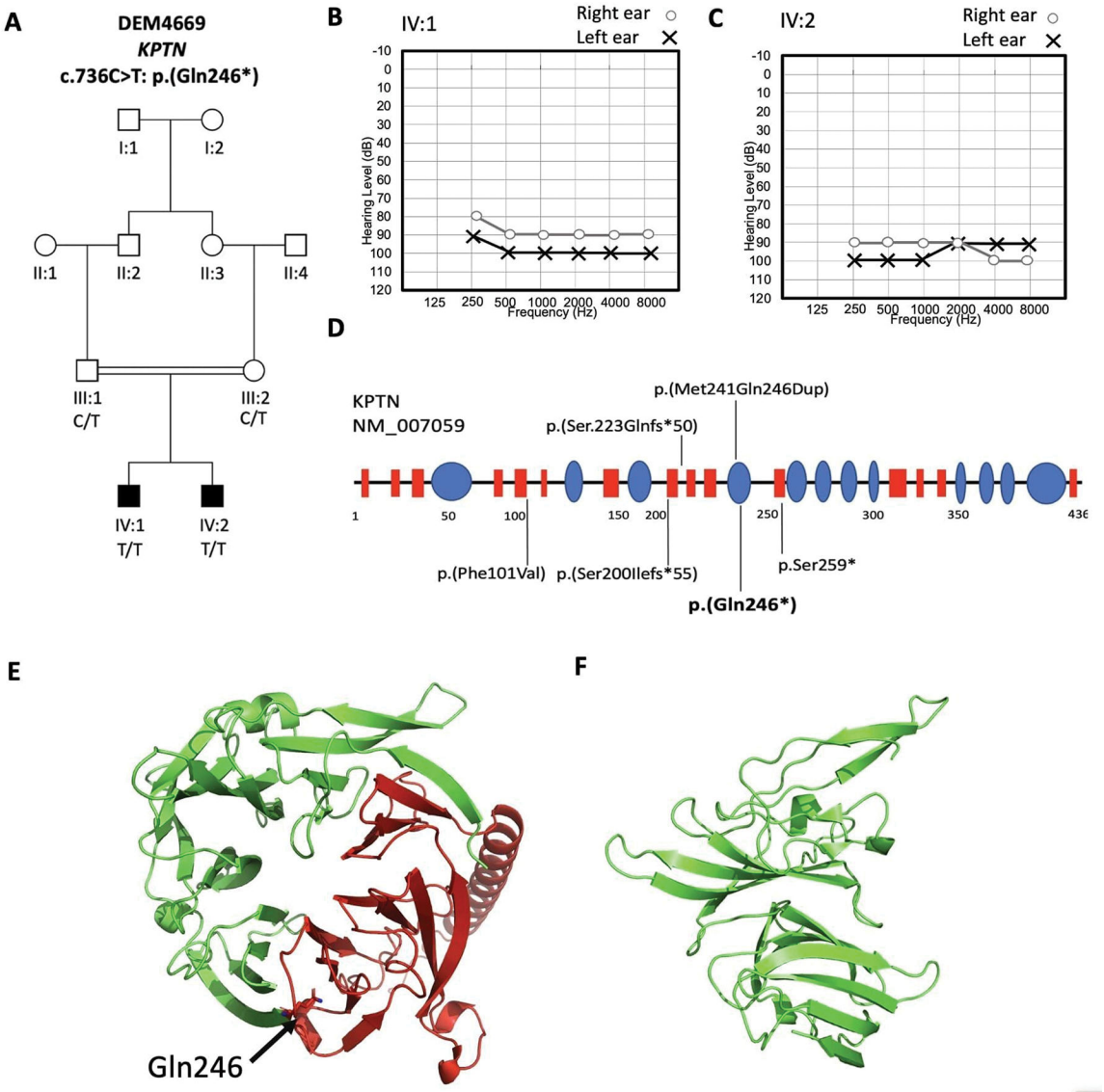

Figure 1.

Information on the DEM4669 family, KPTN protein, and identified variant. (a) Pedigree drawing of family DEM4669 with segregation of c.736C>T: p.(Gln246*). (b) Audiograms for the affected family members IV:1 and (c) IV:2. (d) Schematic representation of the kaptin protein domains, β sheets are shown as red boxes, and α-helices are shown as blue ellipsoids. Shown in bold is p.(Gln246*), the other variants were previously identified for *KPTN* gene-related syndrome. (e) Predicted model of wild type kaptin protein. The Gln246 residue is represented with a stick model. (f) The red color ribbon is lost in the p.Gln246* mutant form.