Research letter

A novel *de novo* mutation substantiates *KDF1* as a gene causing ectodermal dysplasia

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Dear Editor, Ectodermal dysplasia (ED) is a group of more than 200 disorders caused by mutations in approximately 50 genes that affect ectodermal organs.[1,2] Keratinocyte differentiation factor (KDF)1 plays a role in the proliferation and differentiation of epidermal progenitor cells.[3] In 2017, a heterozygous missense mutation, c.753C>A, p.F251L, in *KDF1* (NM_152365·2) was found to segregate with hypohidrotic ED (ECTD12, OMIM 617337) in a Saudi family, suggesting *KDF1* as a probable disease gene for ED.[4] Recently, another heterozygous mutation, c.908G>C, p.R303P, in *KDF1* was found in two members of a Chinese family with nonsyndromic tooth agenesis (NSTA).[5]

Here we describe a 5-year-old Thai boy with ED and a *de novo* mutation in *KDF1*. The proband was born at 36 weeks' gestation weighing 2010 g. Punctal agenesis, bilateral complete cleft palate, bilateral athelia, neonatal sepsis and hypospadias were noted at birth. At 5 years of age he showed sparse hair, hypertelorism, flat nasal bridge, low-set ears, short philtrum and absence of eyebrows, eyelashes and nipples. He had delayed speech, probably due to the cleft palate. However, his general development was appropriate for his age. He did not sweat and his skin was very dry. Generalized lentigines, freckles and rashes were present on his scalp, face, arms and legs. Superficial skin sloughing and erosions at areas of friction were observed. His nails were brittle, hypoplastic and convex. They showed pits, subungual hyperkeratosis and ridges in the longitudinal, transverse and angular directions. Only a root of a deciduous molar was shown radiologically (Fig. 1a–c). Scanning electron microscopy showed his hair to be twisted, and the nail plates were irregular, showing several ridges. He also had urethral meatal stenosis. Cystourethrogram showed narrowing of the urethral opening with penile torsion (3-o'clock position) and diffused bladder-wall thickening (further images available on request).

Exome and Sanger sequencing were performed as previously described.[6] The proband was found to be heterozygous for a missense mutation, c.823A>C, p.Ile275Leu, in exon 2 of *KDF1*. It is evolutionarily conserved, predicted to be damaging, and absent from the ExAC and 1000 Genomes Project databases and our in-house database. The boy's parents were

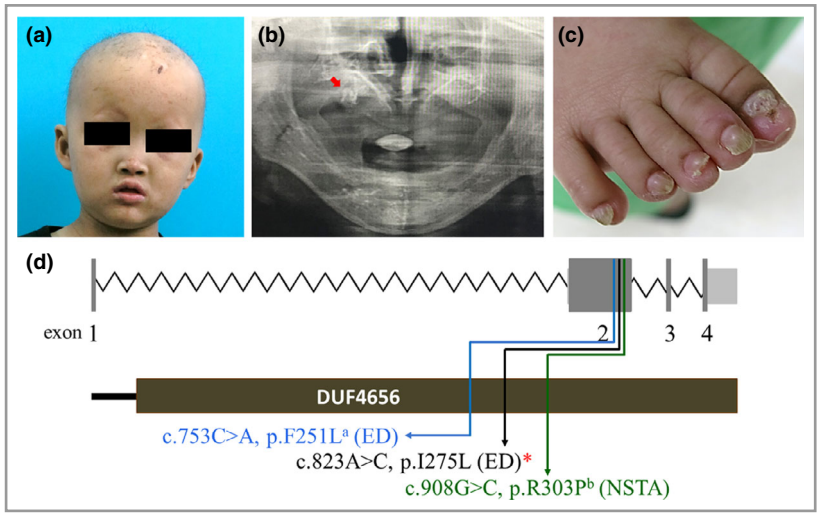

Fig 1. Phenotype and genotype of the patient. (a–c) A 5-year-old boy had sparse hair, eyebrows and eyelashes, saddle-shaped nose, low-set ears, dry skin with pigmentation and freckles, and dysplastic nails with ridges and pits. Absence of almost all primary and permanent teeth except the root of the primary molar (red arrow) was found at 5 years of age. (d) The proband had the mutation c.823A>C, p.I275L, in *KDF1* (*). Previously identified mutations in *KDF1* are shown, associated with hypohidrotic ectodermal dysplasia (ED)[a] (Shamseldin *et al.*)[4] and nonsyndromic tooth agenesis (NSTA)[b] (Zeng *et al.*).[5]

healthy and nonconsanguineous and did not harbour the mutation.

To our knowledge, our proband is the first patient with a *de novo* mutation in *KDF1*. On average, the *de novo* mutation rate for single-nucleotide variants is around $1{\cdot}0–1{\cdot}8 \times 10^{-8}$ per nucleotide per generation, or 44–82 mutations in the genome of an individual. Of those, only one to two mutations affect the coding sequence.[7] The rate is increased with advanced parental age.[8] The proband's father was 39 and mother was 36 years of age at the time of conception. As only a few *de novo* mutations affect coding regions, these highly suggest the causative role of the gene for a phenotype.[7] Our finding of a *de novo KDF1* mutation in a patient with ED, combined with the previously reported *KDF1* mutation in a multigenerational Saudi family with ED,[4] substantiates its causal role for ED.

Among the seven patients with ED reported to have *KDF1* mutations, the overlapping features include tooth absence, cleft palate, short philtrum, nail dystrophy, subungual hyperkeratosis, decreased sweating, eczema, keratosis pilaris and lustreless hairs with a decrease in number. The athelia, hypospadias, urethral stenosis, absent lacrimal system and generalized lentigines found in our patient have not previously been reported in patients with ED with *KDF1* mutations.

All three *KDF1* mutations reported to date are in exon 2 and the DUF4656 domain of the protein, suggesting the functional significance of this region (Fig. 1d). Interestingly, the two mutations causing ED, p.F251L and p.I275L, are substitutions of hydrophobic amino acids, namely phenylalanine and isoleucine. These residues are likely to embed in the protein hydrophobic core and be important for the function of epidermal cells. In contrast, the p.R303P mutation found in NSTA changes the charged amino acid arginine, which is located further towards the carboxyl terminus of the protein. This is expected to have a smaller effect on the function of KDF1. Whether this genotype–phenotype correlation holds true awaits more cases.

Interestingly, mice with heterozygous loss-of-function mutations in *Kdf1* did not show obvious defects.[3] This suggests that the human mutations could result in a gain-of-function or dominant negative function. Alternatively, humans may be more susceptible to haploinsufficiency of *KDF1*.

In conclusion, our proband is the first patient with a *de novo KDF1* mutation, substantiating the causal role of *KDF1* for ED. Some of his clinical features and the identified mutation have not previously been reported. This study expands the phenotypic and mutational spectra and proposes a genotype–phenotype correlation.

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