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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Letter to the Editor

Recessive mutations in the gene encoding frizzled 6 cause twenty nail dystrophy—Expanding the differential diagnosis for pachyonychia congenita

To the Editor,

Nail dystrophy is a hallmark of the autosomal dominant disorder pachyonychia congenita (PC), accompanied by keratoderma and other ectodermal defects [1]. We recently analysed three cases initially diagnosed as PC, but who presented with nail dysplasia only. None had mutations in any of the four keratin genes associated with PC (KRT6A, KRT6B, KRT16 & KRT17) [2] or in KRT6C (associated with keratoderma and trivial changes) nor in GJB6 (Clouston syndrome is in the differential diagnosis for PC). The frizzled 6 gene (FZD6) was analysed because mutations in this gene were shown to cause autosomal recessive nail dysplasia [3,4]. FZD6 mutations were identified in these three unrelated families with clinically similar nail dystrophy, where all fingernails and toenails were discoloured and thickened from birth.

An affected boy in family 1 was born to healthy consanguineous parents and had symmetrical involvement of all finger and toenails which were thickened and discoloured since birth (Fig. 1a, c and d). The palms, soles, oral cavity and scalp were normal. By direct DNA sequencing (see supplementary material) he was shown to be homozygous for mutation p.Arg509Ter in FZD6; his unaffected parents and sibling were heterozygous carriers of the mutation (Fig. 1e–g).

In the second family, a 10 year old girl presented with nail dystrophy involving all 20 nails. Thickening of the nails on the hands and feet began in infancy; the toenails were affected first, quickly followed by the fingernails. She developed onycholysis in 3 nails on each hand but no onycholysis on feet. Nails with onycholysis “crack” in the middle and are painful if filed too thin. She was also homozygous for p.Arg509Ter mutation; her unaffected parents and unaffected siblings were all heterozygous for the mutation (Fig. 1b). Residue p.Arg509 is conserved across several species as shown in the multiple alignment, Fig. 1h.

The proband of a third family was a 6-year-old girl born to unaffected parents; her older brother is unaffected. A dark purple discolouration of the fingernails was noted at birth. Toenails were also discoloured but to a lesser degree (Fig. 2a–c). The nails became progressively thicker but did not seem to grow out. The thumb and radial nails were most affected, as were the great toes and the adjacent nails. On several occasions the nails have fallen off at the cuticle, revealing a thick stub of a nail on the proximal third of the nail bed. There have never been blisters nor frank infections. Mild inflammation has occurred as the “new” nail grows out; a change likened to ‘ingrown’ nails. By mutation analysis we identified compound heterozygous mutations p.Arg96Cys/p.Glu438Lys in this individual; her unaffected mother was heterozygous for p.Arg96Cys and unaffected father was heterozygous for p.Glu438Lys (Fig. 2d–g). Her unaffected brother and 100 unrelated control samples were wild type for both mutations. Both p.Arg96 and p.Glu438 are conserved across several species (Fig. 2h). None of the FZD6 variants that we identified are listed on dbSNP database (version 135).

Frizzled 6 belongs to a family of receptors in the Wnt pathway and is a receptor for the Wnt-4 ligand [5]. Wnt signaling is important for the development of ectodermal appendages including nails and it is known that FZD6 is expressed in the ventral nail matrix and nail bed. Mutations in another gene, frizzled agonist R-spondin4, also in the Wnt pathway, cause another nail disorder, autosomal recessive anonychia [6]. The frizzled 6 gene contains 7 exons including a 5’ untranslated exon. At the protein level there is a signal peptide, a cysteine-rich domain in the N-terminal extracellular region and seven transmembrane domains. Mutation p.Arg509Ter is in the 3’ cytoplasmic domain and is predicted to lead to a truncated protein or loss via nonsense mediated decay. Mutation p.Arg96Cys is located in the cysteine-rich Wnt-binding domain and p.Glu438Lys is in the putative frizzled/smoothened family membrane region. Both these mutations are predicted to result in defective frizzled 6 thereby affecting normal nail development and maintenance. Both mutations, p.Arg96Cys and p.Glu438Lys, were analysed using PolyPhen-2 [7] (Polymorphism-Phenotyping v2, http://genetics.bwh.harvard.edu/pph2/index.shtml) to look at the possible impact of these amino acid substitutions, which are predicted pathogenicity.

Fröjmark et al. [3] were the first to show mutations in FZD6 cause autosomal recessive nail dysplasia. They identified mutations in two large Pakistani consanguineous families; in one family affected individuals were homozygous for missense mutation p.Arg511Cys and in the second family affected individuals were homozygous for nonsense mutation p.Glu584Ter. Naz et al. [4] reported 2 further families, also of Pakistani origin, where affected individuals were also homozygous for mutation p.Glu584Ter, indicating a common ancestor. While it was known that frizzled 6 is important in hair patterning in mice [8], on re-examination of the Fz6ds/–– mouse model Fröjmark et al. [3] found some male mice showed absent or abnormal claws compared to wild type mice. They also showed that in mouse embryos, at E16.5, there was expression of Fzd6 in the epidermis of the digital tip in the region corresponding to the developing nail bed and ventral part of the digit. Further evidence of involvement of FZD6 in the nail was shown by immunohistochemical studies of nail sections from healthy humans by Naz et al. [4]. They showed strong expression of FZD6 in the ventral nail matrix and some FZD6 staining in the nail bed.

Several rare variants have recently been identified in FZD6 in a cohort with neural tube defects and it is suggested that these variants may contribute to neural tube defects in humans [9].

These cases highlight the difficulty in diagnosing rare disorders where clinical features overlap. We conclude that FZD6 should be added to the screening panel for PC and should especially be considered in sporadic or confirmed recessive cases of isolated nail dysplasia where all nails are discoloured and thickened from birth.
The Wnt pathways have an important role in nail development and therefore further Wnt signaling molecules are possible candidate genes for hereditary nail dystrophies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2012.12.005.

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