Genetics of human isolated hereditary nail disorders

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Summary

Human hereditary nail disorders constitute a rare and heterogeneous group of ectodermal dysplasias. They occur as isolated and/or syndromic ectodermal conditions where other ectodermal appendages are also involved, and can occur associated with skeletal dysplasia. 'Nail disorder, nonsyndromic congenital' (OMIM; Online Mendelian Inheritance in Man) is subclassified into 10 different types. The underlying genes identified thus far are expressed in the nail bed and play important roles in nail development and morphogenesis. Here, we review the current literature on nail disorders and present a coherent review on the genetics of nail disorders. This review will pave the way to identifying putative genes and pathways involved in nail development and morphogenesis.

Nails are specialized epithelial miniorgan structures designed to protect the soft tissues of the distal digits of the fingers and toes from environmental assault and injury. In addition to this basic function, the nail apparatus—a modified ectodermal appendage—contributes to the sensory perception of fingertips, fine manipulation of small objects with refined dexterity, is a tool for scratching and grooming, and can be utilized as a natural weapon. Finally, well manicured, embellished nails can enhance the aesthetic appeal of the hands and feet.

Human nail development starts around the ninth week of gestation and is completed during the fifth month of pregnancy, with development of the toenails lagging approximately 4 weeks behind the fingernails.1 Nail is produced by the matrix and grows over the nail bed. The mature nail plate grows continuously through life as a result of matrix epithelial cell differentiation, and consists of a number of hard and soft keratin molecules embedded in an amorphous matrix.

Inherited anomalies of nail are rare and represent a heterogeneous group of genodermatoses. Nail disorders can occur as rare isolated conditions or as a part of ectodermal syndromes involving anomalies in other epidermal appendages (e.g. hair, teeth and sweat glands) and skin, or are associated with skeletal deformity. Most inherited nail disorders manifest either with nail hypertrophy or nail hypoplasia.2 Nail hypertrophy includes pachyonychia congenita type 1 [Online Mendelian Inheritance in Man (OMIM) 167200], type 2 (OMIM 167210), type 3 (OMIM 615726) and type 4 (OMIM 615728), which are caused by mutations in KRT16 (OMIM 148067), KRT17 (OMIM 148069), KRT6A (OMIM 148041) and KRT6B (OMIM 148042), respectively. Nail patella syndrome and isolated congenital nail dysplasia are examples of nail hypoplasia disorders.

Defects in genes involved in nail development/homeostasis are underlying causes of nail abnormalities. Disruption in the normal process of dorsoventral patterning of the distal limb also upsets nail development.3 Despite considerable advances in the diagnosis and management of nail disorders, knowledge of the molecular developmental pathways of nail growth and morphogenesis is relatively limited. The molecular basis of some nail disorders has only been elucidated during the last few years.

This review is an account of recent updates in the genetics of 'nail disorder, nonsyndromic congenital' (NDNC), which are classified in the literature into 10 different types and included in OMIM. These are described in the following sections along with the available information on the genetic defects associated with them.
Nail disorder, nonsyndromic congenital, 1

NDNC-1 (OMIM 161050) is also termed ‘twenty nail dystrophy’ (TND) or trachonychia. It is characterized by excessive longitudinal striations and numerous superficial pits on the nails, which have a distinctive rough, sand paper-like appearance. Nails are variably involved and may show thinning, thickening, pitting, ridging, koilonychias, opalescence and loss of lustre, or may be spared.\(^4\) NDNC-1 segregates in an autosomal dominant manner.

At least three familial cases and one sporadic one showing NDNC-1 phenotypes have been reported. The various phenotypes observed include the absence of thumb nails; thin, fragile nails split at the ends; longitudinal ridges; ragged distal edges; and discolored TND.\(^5\)–\(^8\) To date, the gene/loci causing NDNC-1 is unknown.

Nail disorder, nonsyndromic congenital, 2

NDNC-2 is described in the literature as koilonychia or spoon-shaped nails. This is a very rare disease in which the nails are abnormally thin and concave from side to side, with turned up edges. The mode of inheritance of NDNC-2 is dominant.

To date, three families showing typical features of koilonychias of fingernails and toenails have been reported.\(^9\)–\(^11\) The gene/loci underlying NDNC-2 is yet to be discovered.

Nail disorder, nonsyndromic congenital, 3

NDNC-3, or leuconychia, is the most familiar form of nail discoloration abnormality, marked by white discoloration of the nails (Fig. 1). Based on the distribution of the white tone, leuconychia is classified into three different types: (i) true leuconychia, with the involvement of the nail plate originating in the matrix; (ii) apparent leuconychia, involving subungual tissue; and (iii) pseudoleuconychia, when the matrix is not responsible for the nail plate alteration. True leuconychia is further separated into total and subtotal or partial, the latter occurring as leuconychia punctata, leuconychia striata and leuconychia distal.\(^12\) The inheritance patterns of hereditary leuconychia can be both autosomal recessive and dominant.\(^13\)

Leuconychia (OMIM 151600) was mapped to chromosome 3p21.3-p22 with pathogenic mutations in PLCD1 (OMIM 6022142), detected in several Pakistani families, inherited both in autosomal dominant and recessive fashion.\(^13\) Affected individuals had chalky white nails (complete leuconychia) along with translucency and yellowish coloration in the distal parts of the nail plate (incomplete leuconychia).\(^13\),\(^14\)

To date, two mutations in families showing autosomal dominant inheritance and four mutations in isolated families showing a recessive mode of inheritance have been reported (Table 1).\(^13\)–\(^15\)

PLCD1 consists of 15 exons, spanning 22 17 kb and encodes two isoforms containing 777 and 756 amino acids, respectively. Phospholipase C, 61 is a member of a large superfamily of phosphoinositide-specific phospholipase C (PLC) enzymes, which are involved in the hydrolysis of phosphatidylinositol 4,5-bisphosphate to produce second messengers including dia-cylglycerol and inisitol trisphosphate (IP3). Disruption of PLCD1 results in a significant reduction of inositol monophosphate, a downstream metabolite of IP3.\(^13\) High expression of PLC-61 has been reported in nail matrix, hair follicles, hair matrix and the nail bed.\(^13\),\(^16\)

It has been suggested that PLC-61 functions downstream of the forkhead box N1 transcription factor that regulates hard keratin gene expression, essential for nail differentiation.\(^17\) Interestingly, loss-of-function mutations in FOXN1 result in defects of onycholemmal differentiation and severe onychodystrophy in mice and humans.\(^18\) Therefore, loss of PLC-61 function may result in abnormal keratinization of the nail plate owing to aberrant expression of hard keratins causing the leuconychia phenotype.

Nail disorder, nonsyndromic congenital, 4

Complete absence or severe hypoplasia of all fingernails and toenails without significant bone anomalies is the characteristic feature of NDNC-4 (OMIM 206800), also termed anonychia/hyponychia congenita. Hyponychia is the milder phenotypic variant of anonychia. Isolated anonychia is a rare dysplasia that usually follows autosomal recessive inheritance with variable expression, even within members of the same family.\(^19\) Affected individuals either show complete absence of the nail

Fig 1. Clinical presentation of an individual with leuconychia showing white discoloration of the nail plate, involving all 20 nails. Note yellow pigmentation of the second nail of the right toe (nail disorder, nonsyndromic congenital, 3).
plate and matrix, with only the nail bed present, or hyponychia, with some remnants of rudimentary, fragile nail plates (Fig. 2).12,20

RSPO4 (OMIM 610573) has been identified as an underlying gene in anonychia/hyponychia congenita and is the first gene reported for isolated nail dysplasia.21,22 The encoded RSPO4 protein acts as an agonist for the Frizzled (FZD) family of receptors, which is involved in activation of the Wnt/β-catenin signalling pathway that is crucial for the formation of ectodermal appendages like nails.21

To date, 18 mutations in RSPO4 causing isolated anonychia/hyponychia congenita have been identified in different populations of the world (Table 1).19-22 So far, no correlation has been established between mutations detected in RSPO4 and the specific phenotype observed.

The mammalian family of RSPO proteins includes four independent gene products (RSPO1–RSPO4), which share 40–60% pairwise amino acid sequence identity and similar domain architecture.26 RSPO4 encodes a secreted protein of approximately 35 kDa, containing 234 amino acids. Like other

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<th>Effect</th>
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RSPO proteins, RSPO4 contains an N-terminal signal peptide encoded by exon 1 for secretion, followed by two furin-type cysteine-rich domains encoded by exons 2 and 3, a thrombospondin-type domain encoded by exon 4 and a C-terminal basic region that scores highly as a nuclear localization signal. The furin-like repeats are believed to be required for activation and stabilization of \(\beta\)-catenin.\(^{27}\)

Briefly, the RSPO family of proteins regulates Wnt signalling, resulting in a wide range of biological processes such as cell proliferation, differentiation, stem cell maintenance and mature tissue homeostasis. Secreted RSPO proteins interact synergistically with the Wnt family of ligands, causing activation of the canonical Wnt signal pathway induced by binding of the Wnt ligands to FZD receptors and low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6) co-receptors.\(^{28}\)

As a consequence, it stimulates cytoplasmic accumulation and translocation of the \(\beta\)-catenin protein to the nucleus. In the nucleus, \(\beta\)-catenin associates with the T-cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factor complex that controls target gene activation.\(^{29,30}\) Recently, three reports identified leucine-rich repeat-containing G-protein-coupled receptor (Lgr)4, Lgr5 and Lgr6 as the receptors of the RSPO proteins.\(^{31}\) The Lgr proteins are believed to be physically coupled with the FZD/LRP complex. So the RSPO component in Wnt signalling may consequently be mediated by the activated FZD–LRP5/6 co-receptors.\(^{27}\)

RSPO4 is expressed in mesenchyme from which the digit tips and nails are developed.\(^{20}\) Additionally, RSPO4 transcripts have been identified in human primary fibroblasts but not in keratinocytes. Hence, RSPO4 might function in the activation of Wnt/\(\beta\)-catenin signalling during ectodermal–mesenchymal crosstalk at the early stages of nail development.\(^{21}\) As the nail bed is intact in affected individuals with RSPO4 mutations, it has been suggested that RSPO4 might be involved in the advanced stages of nail morphogenesis.\(^{32}\)

**Nail disorder, nonsyndromic congenital, 5**

Hereditary distal onycholysis is grouped as NDNC-5 (OMIM 1648000). It is characterized by a decreased growth rate, thick and hard nails, and a straight or concave proximal edge of detachment. The mode of inheritance of NDNC-5 is autosomal dominant. In 1966, Schulze reported a family showing onycholysis, slow nail growth, thick and hard nails.\(^{33}\) Some nails also had increased transverse curvature and absent lunulae. Several other families, of different ethnicities, reported as showing dominant inheritance, had onycholysis, thickening and discoloration of the finger- and toenails.\(^{34–36}\) The causative gene/loci for NDNC-5 is yet to be reported.

**Nail disorder, nonsyndromic congenital, 6**

Congenital absences of nails are of two types: (i) complete and (ii) partial. Complete absences of nails were discussed earlier and are categorized as NDNC-4. Partial absences of nails are cases where the thumbs and big toes are more severely affected, while the remaining digits are less affected. Several cases of the partial absence of nails are referred to here as NDNC-6 (OMIM 107000).

So far, several familial cases have been reported involving partial absences of nails. The mode of inheritance is dominant. Several reports from different ethnic groups revealed anonychia of the thumbs and toenails, and onychodystrophy. Abnormalities in the nails of digits other than thumbs and big toes are of varying degrees of severity.\(^{37–41}\) The gene underlying NDNC-6 has not been identified yet.

**Nail disorder, nonsyndromic congenital, 7**

NDNC-7 (OMIM 605779) is characterized by nails with longitudinal streaks, thinning of the nail plate, poorly developed or absent lunulae, along with variously disturbed formation of the nail plate leading to increased vulnerability of the free nail margins. The mode of inheritance is autosomal dominant. NDNC-7 was described by Hamm et al.\(^{42}\) in a large German family of 22 individuals. All 22 affected members have defects in their toes and fingernails, which Krebsova et al.\(^{43}\) mapped to chromosome 17p13. The candidate gene for this locus is yet to be discovered.
Nail disorder, nonsyndromic congenital, 8

NDNC-8 (OMIM 607523) is also known as isolated toenail dystrophy. Affected individuals show dystrophy of the toenails only. The mode of inheritance of NDNC-8 is autosomal dominant.

Hammami-Hauasli et al. reported a family with affected toenail dystrophy, without any skin lesions. Sequence analysis of COL7A1 (OMIM 697523) showed a compound heterozygous mutation (p.Gly1519Asp; p.Gly2251Glu) in a girl affected by bullous dermolyis from this family; however, the mother was a heterozygous carrier of the p.Gly2251Glu mutation. Shimizu et al. reported a Japanese girl showing unusual epidermolysis bullosa dystrophica, having compound heterozygous missense mutations in COL7A1 (p.Gly2316Arg; p.Gly2287Arg). The girl’s mother was affected by mild toenail dystrophy without skin problems, and was a heterozygous carrier for the p.Gly2287Arg mutation. Her mother, maternal uncle and maternal grandmother were also heterozygous carriers of this mutation.

Two Japanese families with dystrophic toenails were studied. In affected members of the first family, the nail plates of the toenails were deformed and narrow. In the second family, a female patient had a shrunken big toenail, which was buried in the nail bed and severely deformed. Sequencing of COL7A1 identified two missense mutations in both families.

COL7A1 consists of 118 exons and is localized to chromosome 3p21.3. This gene encodes the alpha chain of type VII collagen. The type VII collagen fibril is composed of three identical α-collagen chains, which are restricted to the basement zone beneath stratified squamous epithelium. The main function of COL7A1 protein is to anchor the fibril between the external epithelium and the underlying stroma.

Nail disorder, nonsyndromic congenital, 9

A Pakistani family with an isolated autosomal recessive form of hereditary nail dysplasia (NDNC-9; OMIM 614149) has been reported by Rafiq et al. At birth, all affected members with the NDNC-9 phenotype had normal finger- and toenails. By the age of 7–8 years, they started to show onychodystrophy of the fingers and toes, which differentially affected the finger- and toenails (Fig. 3). Dystrophy of the finger- and toenails started at the same time but led to anonychia on the toenails and onycholyis on the fingernails. Through a genome-wide scan the NDNC-9 phenotype was localized to chromosome 17q25.1–17q25.3. The candidate gene for this locus is yet to be identified.

Nail disorder, nonsyndromic congenital, 10

In autosomal recessive nail dysplasia, affected individuals show thick, hard nails on the hands and feet. In the main, nails are shiny, hyperplastic and hyperpigmented from birth. A very slow rate of nail growth has been observed in affected individuals, and trimming of the nails was required only at intervals of a few years. At the age of about 10 years, the nails develop into a claw-like structure, which might represent an outgrowth from below the edge of the nail (NDNC-10; OMIM 614157) (Fig. 4).

The NDNC-10 phenotype was mapped to chromosome 8q22.3 and sequence analysis of FZD6 (OMIM 603409) revealed mutations in multiple families. To date, five mutations have been reported in FZD6, including three missense, one nonsense and one compound heterozygous (Table 1).

FZD6 consists of eight exons, spanning 3,719 kb, and encodes a 706-amino acid protein of 80 kDa in size. Frizzled class receptor (FZD)6 belongs to the heptahelical class of FZD receptors characterized by an extracellular cysteine-rich domain at the N-terminal region that forms the signal peptide sequence, followed by seven transmembrane domains and an internal PDZ-interacting motif at the C-terminal region necessary for the recruitment of the phosphoproteins dishevelled 1–3 and other signalling factors, as well as for trafficking of the receptor.

The FZD family of proteins, including FZD6, serve as receptors for the Wnt ligand family. LRPS and LRPs serve as coreceptors with FZD proteins. The best-known signalling pathway downstream of FZD is the canonical Wnt/b-catenin pathway, leading to the stabilization of b-catenin, nuclear translocation and subsequent TCF/LEF-dependent transcription of Wnt target genes. Besides Wnt–FZD signalling it has been revealed that FZD6 has the ability to transduce the ß-catenin-dependent WNT3A and ß-catenin-independent WNT5A pathways. Wnt–FZD signalling is vital for numerous develop-
mental processes such as tissue morphogenesis, differentiation and regeneration in all animals.\textsuperscript{55}

It has been shown that FZD6 is involved in the transcriptional regulation of 63 genes essential for epidermal differentiation, including keratins, keratin-associated proteins, and transglutaminases and their substrates.\textsuperscript{56}

Isolated congenital nail clubbing

Hereditary nail clubbing (or digital clubbing) is a distinct rare genodermatosis entity characterized by enlargement of the nail plate and terminal segments of the fingers and toes, resulting from proliferation of the connective tissues between the nail matrix and the distal phalanx.\textsuperscript{57} In nail clubbing there is a clear loss of the normal angle between the nail and the posterior nail fold. Involvement of different fingers and toes varies. Some fingers or toes are spared but the thumbs are almost always involved.\textsuperscript{58} Nail clubbing may be isolated or associated with other disorders like primary hypertrophic osteoarthropathy. Bilateral symmetric nail clubbing in all finger- and toenails by birth without any associated abnormality is named isolated congenital nail clubbing (ICNC; OMIM 119900). A condition related to this was first described by Von Eiselsberg in 1911 (in Horsfall).\textsuperscript{59} The nails are usually shiny, hypoplastic, thickened, long, broad and more curved from cuticle to tip.\textsuperscript{59}

HPGD consists of seven exons spanning 31 kb and encodes a 266-amino acid protein. 15-Hydroxy prostaglandin dehydrogenase (15-PGDH), a member of the short-chain nonmetalloenzyme family of dehydrogenases, is a dimeric enzyme composed of two identical subunits approximately 28-9 kDa in size, with a variety of substrates such as prostaglandins, lipoxins and hydroxyl fatty acids.\textsuperscript{62}

15-PGDH, residing in the cytosol, catalyses the first step in catabolism of prostaglandin and related eicosanoids – the oxidation of the 15-hydroxyl group, which results in a reversible inactivation of these biologically active compounds into their inactive 15 keto-metabolites, which exhibit greatly reduced biological activity.\textsuperscript{63} Coggins et al.\textsuperscript{64} generated Hpgd-deficient mice (\textit{hpgd}^{−/−}), demonstrating the involvement of 15-PGDH in regulating the metabolism of prostaglandins.
Conclusion

The last decade has witnessed incredible progress in elucidating the molecular genetics of many rare genetic skin disorders, including nail abnormalities. Recent advances in high-throughput technologies, such as next-generation sequencing and computational biology, have sped up the process of gene discovery for rare genetic diseases. Owing to these technological innovations, it is predicted that by the year 2020 most genes underlying genetic factors in families with nail defects. 

Further research efforts to uncover the functional role of the genes for various genetic nail disorders in defining nail structure are needed to fill the gaps. An understanding of the function of these genes will provide novel clues in designing molecular diagnostic/therapeutic methods/procedures not only for nail and other ectodermal appendages, but also for tissues that share particular signalling pathways. In this context, the importance of genomic approaches based on already identified and newly discovered genes underlying nail disorders needs to be emphasized. Understanding of the genetics of nail disorders will help in early diagnosis of the disease and direct clinical care of family members.

References

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