

Intra-familial Variability of Ectodermal Defects Associated with *WNT10A* Mutations

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WNT10A is a member of the wntless signalling pathway that has a fundamental role in skin and appendageal morphogenesis (1). Moreover, naturally occurring *WNT10A* gene mutations have been identified in the autosomal recessive human ectodermal dysplasia syndromes odonto-onycho-dermal dysplasia (OODD; OMIM277980) and Schöpf-Schulz-Passarge syndrome (SSPS; OMIM224750) (2–7). These disorders show considerable phenotypic overlap, with hypodontia, nail dystrophy, hypotrichosis and palmoplantar keratoderma common to both, although eyelid cysts (apocrine hidrocystomas) are thought to be characteristic for SSPS (8). Furthermore, variable ectodermal defects (teeth, nails, hair) have also been noted in heterozygous carriers of *WNT10A* mutations, with some phenotypic differences between males and females: dental anomalies predominate in males, whereas hair and nail pathology is more common in female heterozygotes (4, 7).

CASE REPORTS

In this study we undertook genotype-phenotype correlation in a British family with OODD/SSPS, spanning four generations and containing seven individuals with diverse ectodermal abnormalities (Fig. 1a). One individual (II-2) had the typical clinical features of SSPS, including eyelid cysts (Fig. 1b), whereas the others had variable ectodermal defects, which are detailed in Table S1 (<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1028>). Following ethical approval, informed consent, and in accordance with the principles of the Declaration of Helsinki, genomic DNA from eight available family members was amplified and screened for mutations in the *WNT10A* gene, as described previously. Two potentially pathogenic mutations were identified, p.Cys107X and p.Phe228Ile (Fig. S1) (<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1028>), both of which have been documented previously in other individuals and families with OODD/SSPS. The carrier status for these mutations is depicted in Fig. 1a.

DISCUSSION

Homozygosity for p.Cys107X was detected in individual II-2 (male) with clinical features of SSPS. This particular mutation appears to be the most common recurrent nonsense mutation, as it has been reported in nine other pedigrees with OODD/SSPS (4, 6, 7). Indeed, it is the most frequent molecular pathology in SSPS, notwithstanding that it can also underlie OODD, an observation that underscores OODD and SSPS being variable manifestations of the same clinicopathological and molecular entity. Three individuals in our family who were compound heterozygotes for p.Cys107X/p.Phe228Ile showed similar

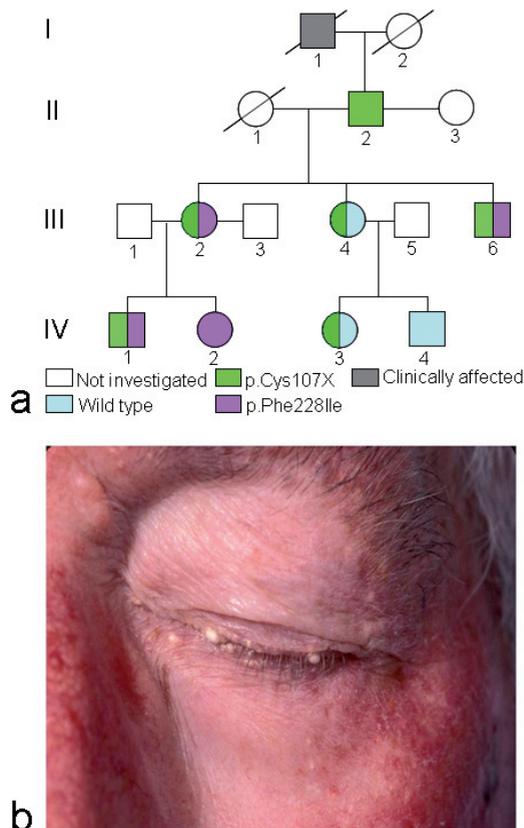


Fig. 1. (a) Pedigree details showing carrier status for the nonsense/missense mutations in *WNT10A*. (b) Prominent eyelid cysts (apocrine hidrocystomas) in individual II-2 characteristic of Schöpf-Schulz-Passarge syndrome.

but somewhat milder clinical features that were more akin to OODD. The missense mutation p.Phe228Ile, which is located within a conserved alpha-helix domain of the protein, has previously been demonstrated to occur in ~0.5% of control chromosomes and its occurrence in this family appears to have been acquired both through the deceased spouse of individual II-2 and the first spouse of individual III-2 (individual III-1). There is no history of consanguinity in this family, and thus the entrance of this mutation at two separate points of the pedigree supports the published data that p.Phe228Ile may be a common finding in the general population (4). In previous reports, homozygosity for p.Phe228Ile has been associated with OODD in one individual, but approximately 50% of heterozygotes may show variable abnormalities of skin, hair, teeth or nails (4, 5). This observation, based on an assessment of 15 individuals heterozygous for p.Phe228Ile and the published control population data, suggests that

approximately 1 in 400 of the general population may manifest some developmental ectodermal defects that are directly attributable to this particular missense mutation in *WNT10A*. In our pedigree there were no individuals who were solely heterozygous for this mutation, but one subject was homozygous for p.Phe228Ile (female, IV-2); clinically, there were widely spaced deciduous teeth in childhood, but only mild hypodontia and a persisting tendency to overheat as an adult. Two individuals who were heterozygous for p.Cys107X (but no other *WNT10A* mutation) displayed very different features: one (female, III-4) had eyelid cysts, sparse eyebrows, mild hypodontia and slight palmoplantar keratoderma, whereas the other (female, IV-3) had no apparent clinical anomalies. Although eyelid cysts are a typical feature of autosomal recessive SSPS, we noted their presence in two other family members, one of whom (III-4) was only heterozygous for p.Cys107X and no other mutation in *WNT10A*. Individual III-4 reported multiple eyelid cysts similar to those experienced by subject II-2. However, these cysts, which developed in her early 30s, lasted for only approximately two years and resolved spontaneously before detailed clinical or histological assessment was feasible. Thus, this clinical feature should perhaps be regarded as just one physical sign in the OODD/SSPS spectrum rather than a pathognomonic hallmark of SSPS. Individuals with SSPS have also been reported to have a higher incidence of malignancies, particularly skin cancers, although this has not been a universal finding (9). In our pedigree, individual II-2 had a history of superficial spreading malignant melanoma, cutaneous squamous cell carcinoma and basal cell carcinomas, but not internal malignancies. No other family member had any history of cancer. Dental changes were the most common clinical pathology in our pedigree and were detected in the permanent dentition of all homozygotes, all compound heterozygotes, and one of the two heterozygotes. The severity of the dental abnormalities was more marked in males. Individuals II-2 and IV-I had severe hypodontia, which was evident in their permanent dentition. Of note, subject II-2 required dentures from the age of 14 years and subject IV-I retained several deciduous teeth, many of which showed extensive root resorption. Individual IV-1 also required multiple implant replacement of his deciduous teeth, as well as maxillary advancement due to mid-facial hypoplasia. Individual III-6 reported hypodontia and wore an upper dental plate. All 3 of these family members had conical-shaped teeth. More variable and less frequent symptoms/signs in these and other family members included hyperhidrosis, nail dystrophy, facial erythema and photophobia. Overall, our single pedigree study provides a detailed illustration of the phenotypic spectrum of ectodermal abnormalities associated with *WNT10A* gene pathology. The findings demonstrate that OODD and SSPS are essentially part of the same disorder and that the actual clinical manifestations depend not only

on the presence of one or two mutations in *WNT10A*, the nature of the mutation (nonsense or missense), and the sex of an individual, but also on other currently unknown influences (genetic, epigenetic or environmental) that may be relevant to WNT signalling and ectodermal homeostasis (10, 11).

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