Letter to the Editor

Two families confirm Schöpf-Schulz-Passarge syndrome as a discrete entity within the WNT10A phenotypic spectrum

To the Editor:

Schöpf-Schulz-Passarge syndrome (SSPS; OMIM 224750) is a rare ectodermal dysplasia which combines classical features of defective skin organogenesis with facial telangiectases and adnexal tumors, often presenting as palmoplantar keratoderma (PPK) and multiple eyelid cysts (1–3). Although SSPS follows autosomal recessive inheritance (1, 4–7), apparent vertical transmission has been reported (3, 8, 9), probably related to pseudodominance and/or incomplete disease expression in heterozygote carriers (7, 10). Odonto-onycho-dermal dysplasia (OODD) is an autosomal recessive ectodermal dysplasia which shares with SSPS features like PPK and facial telangiectases, but lacks eyelid cysts. Recently, a homozygous non-sense mutation in the WNT10A gene has been identified in three inbred Lebanese families with OODD (11). Further reports expanded the mutational and clinical spectrum of WNT10A to include three sporadic patients with features compatible with SSPS (10, 12–14).

We ascertained two consanguineous Italian families with SSPS (Fig. 1a). Family 1 consisted of a sporadic 65-year-old female (II,3), whereas family 2 comprised a 73-year-old man (II,4) and his two older affected brothers (II,2 and II,3). Clinical features of both families were previously reported (7). In brief, all patients displayed PPK, nail dystrophy, rosacea-like lesions on the face, universal hypotrichosis and multiple eyelid cysts (Fig. 1b–h). Oligo/hypodontia and hypoplastic nipples were additional findings. In the proband of family 2 punch biopsies of an eyelid lesion and foot keratoderma were consistent with apocrine hidrocystoma (Fig. 1i) and eccrine syringofibroadenoma (data not shown), respectively. In family 1, the mother (I,2) of the proband who died by that time was reportedly affected by similar eyelid lesions. In family 2, two additional subjects (III,4 and III,7) showed hypodontia with four missing non-molar teeth, whereas II,10 had mild, finely desquamating, hyperkeratosis of palms. All these individuals were offspring of affected family members and, thus, according to autosomal recessive inheritance, obligate heterozygote carriers.

A genomic search using a high density Illumina SNP chip, Human Hap 370K Quad followed by microsatellite analysis (data not shown) showed in both families homozygosity at the WNT10A locus. The 2 families did not share a common haplotype. Mutation analysis of WNT10A, performed as described (10), revealed two novel homozygous missense mutations: p.Gly266Cys (resulting from the c.796G>T transversion) in family 1 and p.Ala131Thr (resulting from the c.391G>A transition) in family 2 (Fig. 2a,b). Both mutations were absent in a panel of 270 ethnically matched control chromosomes. Tested siblings resulted heterozygote for the respective mutations (Fig. 1a). In silico analysis revealed that both mutated residues are highly conserved among WNT10A orthologs (Fig. 2c) and human paralogs of WNT family (Fig. 2d).

Present and previously reported WNT10A mutations are scattered throughout the coding region of the gene (Fig. 2e). However, specific amino-acidic residues represent true hot-spots. In particular, p.Cys107X affects 15 of the 42 mutated alleles (35.7%) and, although it originates from a common ancestor in some families, it is not always associated with the same haplotype. The second most common alteration is p.Phe228Ile, occurring in 11.9% alleles (5/42), while codon Ala131 is affected in family 2 and in the OODD pedigree reported by Nawaz et al. (12). Overall, these three residues, namely Cys107, Phe228 and Ala131, are mutated in 57.1% alleles reported to date.

The WNT10A phenotypic spectrum observed in 25 patients from 21 pedigrees so far described is wide and includes not only SSPS and OODD but also incomplete odonto-onychial, tricho-odontal and tricho-odontal-onychial forms, according to
Fig. 1. (a) Pedigree of families 1 and 2. Affected individuals are indicated by full black symbols, obligate carriers by half black symbols and tested individuals by horizontal bars. (b) Foot keratoderma with desquamation and erythema. (c) Dystrophy of the fingernails. (d) Nose telangiectases. (e) Hypotrichosis. Variability of eyelid anomalies, ranging from multiple milia-like lesions (f) to milia intermingled with cysts (g) to isolated cysts filled with nearly clear fluid (h). (i) Light microscopy of an eyelid cyst reveals a wide cavity in the dermis, lined mostly by a double layer of epithelial cells with columnar inner layer cells showing decapitation secretion. Magnification: ×400.

Pinheiro and Freie-Maia’s classification of ectodermal dysplasias (15). We did not identify obvious genotype–phenotype correlations. Rather, the p.Cys107X mutation was associated with the entire spectrum of WNT10A phenotypes at homozygous or compound heterozygous states. Conversely, the missense alterations we report here caused SSPS, which may be considered as the most severe end of this spectrum. Further studies are warranted to identify the underlying modifier factors of this elevated variability. Interestingly, the very mild cutaneous and dental findings observed in some obligate carriers in our families appear as isolated features of SSPS. This is in line with previous studies (10) confirming the hypothesis of incomplete disease expression in heterozygotes.

Although the correlation between WNT10A germline mutations and increased risk for skin cancer is still questioned (14), it is of relevance that in addition to eccrine syringofibroadenomas skin neoplasms, such as porocarcinoma, eccrine poroma and basal cell carcinoma, have always been reported in association with eyelid cists (10, 13). Therefore, at present, it seems more prudent to consider OODD and SSPS as discrete entities within the WNT10A mutational spectrum. Eyelid lesions should be investigated with particular care in patients with WNT10A because their presence indicates a diagnosis of SSPS and, consequently, the possible need of increased care for adnexal skin tumors. Further studies on larger cohorts of patients are needed to confirm this thought.
Fig. 2. Molecular findings in Schöpf-Schulz-Passarge syndrome. (a) Direct DNA sequencing of exon 3 (upper panel) and exon 4 (lower panel) reveals homozygous c.391G>A (p.Ala131Thr) (upper right panel) and c.796G>T (p.Gly266Cys) mutations (lower right panel) in affected members of families 2 and 1, respectively. Involved codons are underlined. (b) Secondary structure of WNT10A predicted using the NetSurfP and Hierarchical Neural Network algorithms available in ExPASy proteomic server (http://www.expasy.ch/tools/#secondary). The WNT10A protein is composed of 10 α-helices (h1–h10, gray cylinders) and 9 β-strands (β1–β9, black arrows). Coils are represented as straight lines. Mutant residues are highlighted in pink, cysteine residues are bold and predicted N-glycosylation sites (identified by NetNGlyc 1.0 program available in http://www.cbs.dtu.dk/services/NetNGlyc/) are underlined. (c) Multiple species alignment of WNT10A in the regions spanning mutation sites (indicated at the top). Amino acid identity is highlighted in pink. (d) Multiple sequence alignments of all 19 human Wnt proteins encompassing mutation sites. Ala131 and Gly266 conservation is highlighted in pink. Pink shaded region shows the alignment of the Wnt family structural element embedding the glycine residue mutated in WNT10A (right panel). Sequences were taken from Swiss-Prot Q9ZT5 (WNT10A), P04628 (WNT1), P09544 (WNT2), Q93097 (WNT2B), P56703 (WNT3), P56704 (WNT3A), P56705 (WNT4), P41221 (WNT5A), Q9H1J7 (WNT5B), Q9Y6F9 (WNT6), Q93098 (WNT8A), Q93098 (WNT8B), Q93098 (WNT9A), O14904 (WNT9B), O00744 (WNT10B), O96014 (WNT11) and Q9UBV4 (WNT16). Protein sequence alignments were obtained by using ClustalW (http://myhits.isb-sib.ch/cgi-bin/clustalw). (e) Schematic representation of mutation sites in WNT10A described to date. Mutations reported in this study are shown in italics.
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