

Schöpf-Schulz-Passarge Syndrome: Previously Unreported *WNT10A* Genotype and Phenotypes in 9 Family Members

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Schöpf-Schulz-Passarge Syndrome (1) (SSPS, ORPHA: 50944; OMIM: 224750; ICD-10: Q82.8) is a rare genodermatosis characterized by multiple cysts on the eyelids (apocrine hidrocystomas), palmo-plantar keratoderma, hypodontia, hypotrichosis, and nail dystrophy. While hypodontia can be diagnosed during childhood, the hallmark of SSPS (2, 3), hidrocystomas of the eyelids, develop at an advanced age, and, thus, SSPS may occasionally be underdiagnosed. The mode of inheritance and the underlying genetic fundamentals have not been completely identified. Most of the 38 documented cases of SSPS are single or within 1 generation.

Recently, mutations of the WNT family member (*WNT10A*) gene have been linked to various ectodermal dysplasias (ED), e.g. odonto-onycho-dermal dysplasia (OODD) (4), including SSPS (3, 5). The *WNT10A* gene is expressed during multiple developmental processes including skin, tooth, hair, and nail embryogenesis. In adult tissues, *WNT10A* is involved in tooth and hair follicle morphogenesis by inhibiting the β -catenin degradation pathway.

We recruited 14 family members from 2 generations for clinical and genetic analysis of symptoms of SSPS (Fig. S1¹). Patient examination included medical history and physical examination. Informed consent for DNA analysis, publication of data and photographs was obtained from all patients. Ethical aspects were in accordance with the principles outlined in the Declaration of Helsinki. Blood samples of all 14 participants were taken and analysed in the same manner. For molecular genetic analysis patients' DNA was extracted and all coding exons of the *WNT10A* gene were amplified by PCR and Sanger sequenced in forward and reverse directions in all family members. Database searches for variant analysis were performed in the Human Gene Mutation Database (HGMD public), Exome Variant Server (EVS), Ensembl and ExAC.

CASE REPORTS

Patient 1. A 53-year-old man (IV.2 in the pedigree, Fig. 1A) presented with multiple cystic lesions along the margins of his eyelids since his mid-40s. Histological examination revealed apocrine hidrocystoma. He reported severely callused skin of palms and soles with painful fissuring since his early 20s. His finger nails, and particularly his toe nails, were fragile and malformed. He denied excessive sweating. At age 17 years, he received partial dentures, because only 6 permanent tooth had developed. His primary dentition had been normal. No permanent teeth had been removed. From the same age onwards, he noticed decreased growth of hair. Three years before presentation, a basal cell carcinoma of the right

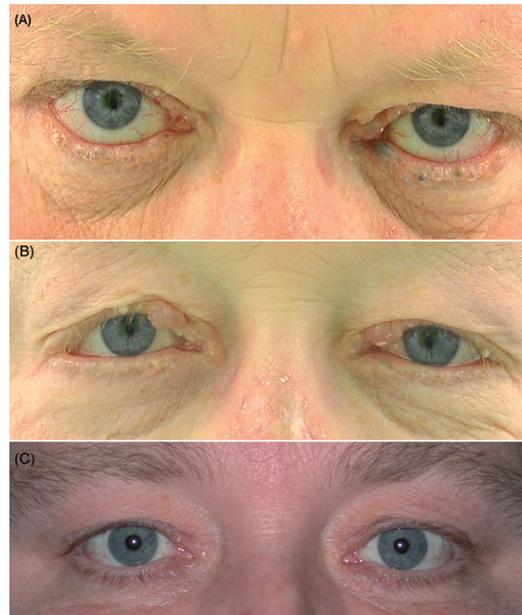


Fig. 1. Patients 1 (IV.2) (A), 2 (IV.3) (B) and 3 (IV.7) (C) with numerous (recurrent) 1–2 mm clear or bluish cystic lesions of translucent or milky opacity bilaterally on the upper and lower eyelid margins.

cheek had been removed. Genetic analysis identified 2 heterozygous nonsense mutations in exon 2 (c.321C>A;p.Cys107*) and exon 3 (c.742C>T;p.Arg248*) of the *WNT10A* gene (Fig. S2¹).

Patient 2. The 51-year-old sister (IV.3) of patient 1 showed similar symptoms including eyelid cysts (Fig. 1B), keratoderma of the palms and soles, and oligodontia with only 8 permanent teeth present. For the past 1.5 years her nails had become dystrophic with hypoplasia, splitting, longitudinal furrows, and ridging. Her scalp hair was dry; she had sparse eyebrows and no hair on the legs and axillae. She reported not sweating at all and having xerostomia. Genetic analysis identified the same nonsense mutations as in patient 1.

Patient 3. The 46-year-old sister (IV.7) of patient 1, reported callused skin of the palms and soles with painful fissures, agenesis of 3 permanent teeth, and recurrence of previously removed eyelid cysts (Fig. 1C). Genetic analysis identified a nonsense mutation of only 1 allele (p.Arg248*).

Patient 4. The 25-year-old daughter (V.3) of patient 1 exhibited no eyelid cysts, but mild keratoderma, nail dystrophy, and agenesis of 5 permanent teeth. She reported that her scalp hair never became greasy. Genetic analysis identified the same nonsense mutation as in patient 3.

Patient 5. The 8-year-old daughter (V.7) of patient 3 had very dry, slowly growing scalp hair and agenesis of 5 permanent teeth. Genetic analysis identified the same nonsense mutation as in patient 3 (for phenotypes see Fig. S3¹).

Four further family members were heterozygous carriers of one of the 2 mono-allelic nonsense mutations, but showed no features of SSPS. In the remaining 5 family members no mutations of the *WNT10A* gene were detected (wild type) and no symptoms were noted.

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DISCUSSION

Early diagnosis of SSPS is rare, because the cardinal symptom, eyelid cysts, develops at a mean age of 50 years, resulting in late diagnosis at a mean age of 60 years (Table SI¹). However, the onset of hypotrichosis, palmoplantar keratoderma and nail dystrophy is reported to range from early childhood to early adulthood. While the deciduous dentition in SSPS can be normal, tooth agenesis within the permanent dentition can be diagnosed during the mixed dentition stage (age 6–12 years). In the 5 patients with hypodontia presented here, there seems to be a symmetrical pattern of permanent tooth agenesis. The reason may be a differential temporal expression of signalling pathways, including WNT 10A, during tooth development.

The studies by Bohring et al. (5) and Nagy et al. (3), for the first time, linked SSPS to mutations in the *WNT10A* gene, which are also observed in OODD, hypohidrotic ectodermal dysplasia (HED), and isolated hypodontia (4–8). In SSPS, to date, 11 different mutations have been reported in 18 patients with SSPS (3, 5, 6, 9–13). The most commonly seen mutations in these studies were the nonsense mutation p.Cys107*, also identified in our study, and the missense mutation p.Ala131Thr (Table SII¹).

We identified 2 nonsense mutations in patients 1 and 2, most probably inherited from both parents. These were a mutation in exon 2 (c.321C>A;p.Cys107*) and a second rare mutation in exon 3 (c.742C>T;p.Arg248*) of the *WNT10A* gene, which so far has been reported only once in the apparently homozygous state in one individual with HED (14), but was not observed in the data set of 60,706 unrelated individuals of the Exome Aggregation Consortium. Both nonsense mutations introduce premature termination codons, which are predicted not to result in any normal full-length protein.

The SSPS phenotype was clearly more pronounced in the 2 patients harbouring both mutations compared with the 7 mono-allelic heterozygous carrier patients confirming the role of *WNT10A* mutations in SSPS. Among mono-allelic carriers, phenotypic expression varied considerably from symptoms (3 patients) to no symptoms (4 patients). It is remarkable that patient 3, carrying only one mutation, developed not only keratoderma and agenesis of permanent teeth, but also recurrent eyelid cysts, the pathognomonic symptom of SSPS. One reason for this might be the presence of another mutation, not uncovered by the Sanger sequencing strategy employed.

Except for age, the reason for the variability in phenotypic expression in heterozygous carriers in SSPS remains unclear. In other ED genotype-phenotype correlations could not fully be established (6, 8, 15). Incomplete phenotype manifestation and sex-specific differences in *WNT10A* expression in OODD (5) have been suggested. Our study does not allow further gender-specific analysis, because all heterozygous carriers were females.

Some authors suggested that OODD and SSPS are 2 variants of the same entity as they may harbour the same

WNT10A mutations (7, 9, 10). This implies that phenotypic expression is not a result of the mutation alone, but is influenced by other currently unknown factors. The variety of possible *WNT10A* mutations in cases of SSPS and the variation in phenotypic expression of SSPS symptoms in identical *WNT10A* mutations, as seen in our pedigree, leaves space for further genetic, epigenetic and environmental factors influencing WNT signalling and ectodermal homeostasis.

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