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

Emma K. Wedgeworth[1], Nikoletta Nagy[2], Jonathan M. L. White[1], Andrew C. Pembroke[3] and John A. McGrath[1,2,4]*

*St John's Institute of Dermatology, [1]The Guy's and St Thomas' NHS Foundation Trust and [2]King's College London, London, [3]Department of Dermatology, Sevenoaks Hospital, Kent, and [4]Dermatology Research Laboratories, Floor 9 Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK. *E-mail john.mcgrath@kcl.ac.uk*

Accepted September 27, 2010.

WNT10A is a member of the wingless 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 SI (http://adv.medicaljournals.se/article/abstract/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://adv.medicaljournals.se/article/abstract/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.

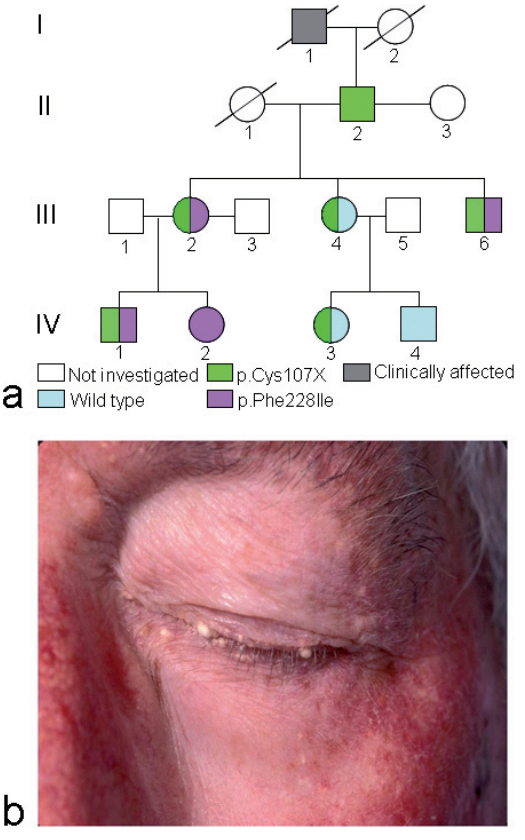

Fig. 1. (a) Pedigree details showing carrier status for the nonsense/missense mutations in *WNT10A*. (b) Prominent eyelid cysts (apocrine hidrocystomas) in individual II-2 characteristic of Schöpf-Schulz-Passarge syndrome.

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 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, 5). 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).

ACKNOWLEDGEMENTS

The authors acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust.

REFERENCES

1. Bolognesi R, Beermann A, Farrana L, Wittkopp N, Lutz R, Balavoine G, et al. Tribolium Wnts: evidence for a larger repertoire in insects with overlapping expression patterns that suggest multiple redundant functions in embryogenesis. Dev Genes Evol 2008; 218: 193–202.
2. Adaimy L, Chouery E, Megarbane H, Mroueh S, Delague V, Nicolas E, et al. Mutation in WNT10A is associated with an autosomal recessive ectodermal dysplasia: the odonto-onycho-dermal dysplasia. Am J Hum Genet 2007; 81: 821–828.
3. Castori M, Ruggieri S, Giannetti L, Annessi G, Zambruno G. Schopf-Schulz-Passarge Syndrome: further delineation of the phenotype and genetic considerations. Acta Derm Venereol 2008; 88: 607–612.
4. Bohring A, Stamm T, Spaich C, Haase C, Spree K, Hehr U, et al. WNT10A mutations are a frequent cause of a broad spectrum of ectodermal dysplasias with sex-biased manifestation pattern in heterozygotes. Am J Hum Genet 2009; 85: 97–105.
5. Nawaz S, Klar J, Wajid M, Aslam M, Tariq M, Schuster J, et al. WNT10A missense mutation associated with a complete odonto-onycho-dermal dysplasia syndrome. Eur J Hum Genet 2009; 17: 1600–1605.
6. Nagy N, Wedgeworth E, Hamada T, White JM, Hashimoto T, McGrath JA. Schöpf-Schulz-Passarge syndrome resulting from a homozygous nonsense mutation in WNT10A. J Dermatol Sci 2010; 58: 220–222.
7. van Geel M, Gattas M, Kesler Y, Tong P, Yan H, Tran K, et al. Phenotypic variability associated with WNT10A nonsense mutations. Br J Dermatol 2010 February 15 [Epub ahead of print].
8. Visinoni AF, Lisboa-Costa T, Pagnan NAB, Chautard-Freire-Maia EA. Ectodermal dysplasias: clinical and molecular review. Am J Med Genet Part A 2009; 149A: 1980–2002.
9. Starink TM. Eccrine syringofibradenoma: multiple lesions representing a new cutaneous marker of the Shöpf syndrome, and solitary nonhereditary tumors. J Am Acad Dermatol 1997; 36: 569–576.
10. Lapébie P, Gazave E, Ereskovsky A, Derelle R, Bézac C, Renard E, et al. WNT/beta-catenin signalling and epithelial patterning in the homoscleromorph sponge Oscarella. PLoS One 2009; 4: e5823.
11. Tauriello DV, Haegebarth A, Kuper I, Edelmann MJ, Henraat M, Canninga-van Dijk MR, et al. Loss of the tumor suppressor CYLD enhances Wnt/beta-catenin signaling through K63-linked ubiquitination of Dvl. Mol Cell 2010; 37: 607–619.

Table SI. *Clinical features of family members with* WNT10A *gene mutations*

Pedigree number	II-2	III-2	III-4	III-6	IV-1	IV-2	IV-3
Sex	M	F	F	M	M	F	F
Age	83	53	51	47	24	21	22
Genotype							
p.Cys107X	+/+	+/–	+/–	+/–	+/–	–/–	+/–
p.Phe228Ile	–/–	+/–	–/–	+/–	+/–	+/+	–/–
Phenotype							
Eyelid cysts	Yes	Yes*	Yes*	No	No	No	No
Palmoplantar keratoderma	Yes	Yes	Mild	Yes	No	No	No
Dystrophic fingernails	Yes Pterygium	Fragility Poor growth	No	Fragility	No	No	No
Dystrophic toenails	Yes	Yes	Mild onycholysis	Mild	No	No	No
Deciduous dentition	Microdontia	Microdontia	Normal	Microdontia Widely spaced	Microdontia	Widely spaced	Normal
Permanent dentition	Oligodontia Conical teeth Dentures aged 14 years	Widely spaced Retained deciduous dentition	Normal	Widely spaced teeth Hypodontia Conical teeth	Oligodontia Conical teeth Dental implants	Mild hypodontia Retained deciduous teeth	Normal
Hypotrichosis (head)	Androgenetic alopecia present – Hamilton VI	No	No	No	No	No	No
Hypotrichosis (other)	Sparse eyelashes	No	Sparse eyebrows	Sparse body hair	No	No	No
Abnormalities of sweating	Hyperhidrosis	Hyperhidrosis	No	Hyperhidrosis	No	None reported, but easy overheating	No
Benign adnexal tumours	Multiple seborrhoeic keratoses Eccrine hidrocystoma	Multiple seborrhoeic keratoses	No	Yes	No	No	No
Malignancies	Cutaneous: Malignant melanoma Squamous cell carcinoma Basal cell carcinomas	No	No	No	No	No	No
Photophobia	Mild	Mild	No	Mild	No	No	No
Retinal abnormalities	Retinal detachment (aged 78 years; cause unknown)	No	No	No	No	No	No
Other features	Absent dermatoglyphics Facial erythema and easy flushing Smooth tongue	Facial erythema and easy flushing	Facial erythema Telangiectasia	No	No	No	No

*Suspected apocrine hidrocystomas, but not histologically proven.

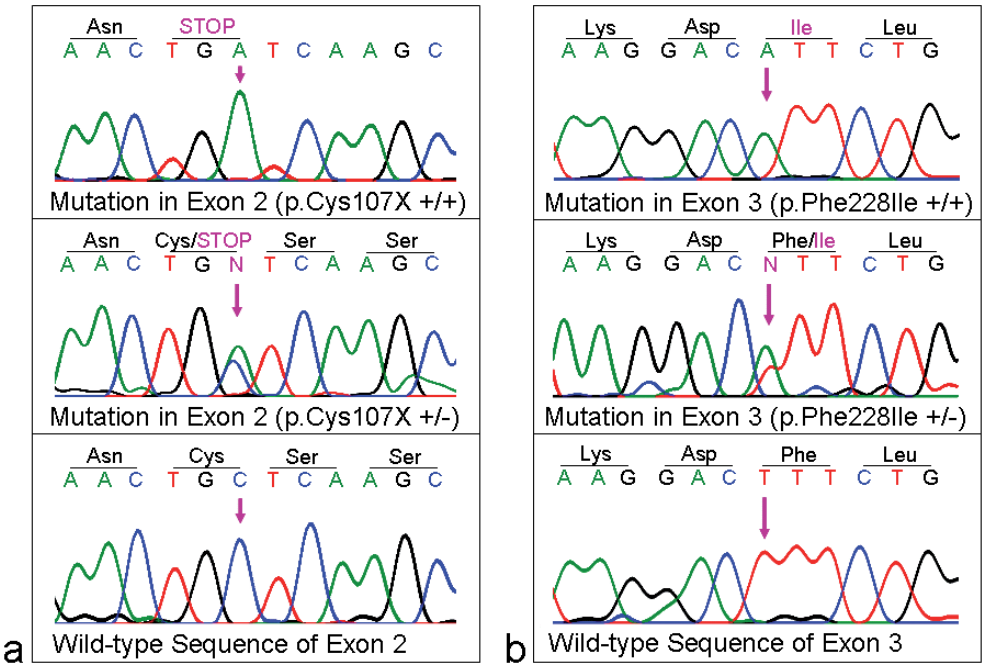

Fig. S1. Genomic DNA sequencing. (a) Sequencing of family member DNA reveals a C>A transversion at nucleotide 321 that converts cysteine (TGC) to a stop codon (TGA): the mutation is designated p.Cys107X and homozygous, heterozygous and wild-type sequences are illustrated; (b) Sequencing of family member DNA reveals a T>A transversion at nucleotide 682 that converts phenylalanine (TTT) to isoleucine (ATT): the mutation is designated p.Phe228Ile and homozygous, heterozygous and wild-type sequences are illustrated.