

Congenital Hyponychia without *RSPO4* Mutation

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Sir,

Congenital anonychia or its milder phenotypic variant hyponychia is a disorder with total or partial absence of finger- and toe-nails (1). Some congenital anonychia or hyponychia is associated with skeletal, limb and ectodermal developmental abnormalities, such as nail-patella syndrome, Coffin-Siris syndrome and ectodermal dysplasias. However, other patients show only anonychia or hyponychia without any associated disorder. Recently, homozygous and compound heterozygous mutations in the secreted Wnt signalling component R-spondin 4 (*RSPO4*) gene have been identified as responsible for autosomal recessive congenital anonychia or hyponychia (1–3). We report here a case of congenital hyponychia in a patient whose mother showed a similar hyponychia. However, the patient had no mutation in *RSPO4*.

CASE REPORT

A 33-year-old man presented with hyponychia. Partial absence of nails was noted at birth on the right third, left second and third fingers and the right second and left first, second and third toes. The proportional size and distribution of hyponychia had remained unchanged (Fig. 1). He had no ab-

normality in limb or skeletal development. A plane radiograph examination in another hospital revealed no abnormality in terminal phalanges. Sweating and teeth formation was normal. His mother showed similar hyponychia from birth; however, his younger sister and nephew had no nail abnormalities. The patient's mother had no sibling and it was unclear whether her parents suffered from nail disorders. There was no family history of consanguineous marriage. Congenital onychodysplasia of the index fingers (COIF) was first reported from Japan (4); however, nail changes were not limited to index fingers in our case. Autosomal dominant inheritance was reported in isolated congenital nail dysplasia (5, 6), but our case lacked the thinning and longitudinal streaks in the nail plates or small reddish dome-shaped prominence adjacent to the proximal nail fold existing in isolated congenital nail dysplasia. Taken together, a diagnosis of hereditary congenital hyponychia was established.

After obtaining approval from the ethics committee of the university and informed consent from the patient, genomic DNA was extracted from the patient's blood (Qiagen, Hilden, Germany). The coding exons and flanking regions of *RSPO4* were amplified by PCR using the specific primers described previously (2). PCR



Fig. 1. (a) Partial absence of nails on the right third, left second and third fingers. (b) Partial absence of nails on the right second and left first, second and third toes. The patient's mother has a similar hyponychia. (c) Polyonychia on the right third finger.

products were purified using QIAquick gel extraction kit (Qiagen) and directly sequenced. We could not identify any mutation in 5 exons and flanking regions of *RSPO4*. However, sequencing *RSPO4* does not exclude deletions. Unfortunately, the patient's mother did not consent to genetic evaluation.

DISCUSSION

RSPO4 is a member of R-spondin family proteins that binds to frizzled homolog 8 (*Drosophila*) (FZD8), and low-density lipoprotein receptor-related protein 6 (LRP6), and augments the signal by catenin (cadherin-associated protein) β 1 (CTN β 1) (7). Recently, in mice, we identified the expression of *RSPO4* not only in the embryos but also in the adult digits (8). Moreover, Fzd8 and Lrp6 expression was found in the same region as label-retaining cells, one of the features of the stem cells. Label-retaining cells reside in the basal layer of the nail matrix adjacent to the nail matrix in mice (8). The expression pattern of Fzd8 and Lrp6 suggested that mesenchymal–epithelial interactions through RSPO4–FZD8–CTN β 1 might control both development and postnatal growth of nails. Lack of mutation in *RSPO4* and the autosomal dominant-like inheritance in our patient may suggest the existence of a dominant-negative type mutation in a receptor or another molecule in signalling cascades for RSPO4.

In summary, our patient had no mutation in *RSPO4* and may be classified as having another type of congenital onychychia caused by an unidentified gene.

The authors declare no conflicts of interest.

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