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Conflict of interest: the authors declare that they have no conflicts of interest.
Accepted for publication 21 April 2017

References

A recurrent mutation in the KRT17 gene responsible for severe steatocystoma multiplex in a large Chinese family

doi: 10.1111/ced.13311

Steatocystoma multiplex (SM; OMIM 184500) is a rare autosomal dominant cutaneous disorder, which is characterized by multiple cutaneous nodules of variable size, and is most commonly found on the sternal areas, upper extremities, face and anterior trunk. The lesions usually start to develop in adolescence or early adult life.1 These nodules may present as an isolated feature, and can also be found in conditions such as pachyonychia congenita type II, LEOPARD syndrome and Alagille syndrome.1–3 SM results from a mutation of the keratin 17 gene (KRT17; OMIM 148069) within the type I keratin cluster on chromosome 17q21.2,4 Keratin 17 is expressed in the sebaceous glands, nail bed, hair follicle and other epidermal appendages.5 In the present work, we report a recurrent KRT17 gene mutation responsible for severe steatocystoma multiplex in a Chinese family.

In this study, we investigated a four-generation family from Henan province in China. The family was comprised of 40 individuals, including 7 with typical severe SM features (Fig. 1). The condition showed an autosomal dominant inheritance pattern with full penetrance. The proband (II:10 in the pedigree) was a 53-year-old man who had a history of subcutaneous nodules, varying in size from 2–80 mm, over almost his whole body since puberty. The numbers of lesions had gradually increases in diameter with age (Fig. 2a–e). Multiple subcutaneous nodules were fluctuating but not painful. No inflammation was found.

Histological examination of a lesional skin biopsy from a 10-mm cyst on the patient’s right forearm revealed an unfolded round cystic wall and the absence of a granular layer. Sebaceous gland lobules were adjacent to the cyst lining (Fig. 2f).

All affected individuals in this family had similar manifestations, but the proband’s brothers (II:7 and II:11) presented milder clinical features. The proband’s condition was the most severe in the family. None of the affected individuals had any evidence of nail changes, plantar keratoderma or plantar pain, or any other skin, hair, sweat or mucosal abnormalities.

Figure 1 Pedigree of a Chinese family with steatocystoma multiplex. Arrow indicates the proband.
Figure 2 Clinical characteristics of the proband: multiple subcutaneous nodules on (a) the upper trunk and shoulders (b) back, shoulders and buttocks, (c) arms, (d) legs, and (e) face and head. (f) Histology showed an unfolded round cystic wall and the absence of a granular layer, while sebaceous gland lobules were adjacent to the cyst lining ((haematoxylin and eosin, original magnification × 40). (g) Mutation analysis of the KRT17 gene showed a heterozygous transition mutation c.280 C>T, resulting in the missense mutation p.Arg94Cys. (h) Part of the normal sequence from exon q of the KRT17 gene, with the red arrow indicating the mutation in this family.
We carried out a genetic study on the family. The study was approved by the ethics committee of Henan Provincial People’s Hospital, and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided informed consent.

Peripheral blood was collected from each participant. Genomic DNA was extracted from lymphocytes and used as a template for PCR amplification. The primer sequences are shown in Table 1. The DNA template (100 ng) was mixed in a solution containing 1× PCR buffer, consisting of 100 mmol/L Tris-HCl (pH 8.3) and 500 mmol/L KCl, 1.5 mmol/L MgCl₂, 2.5 µmol/L dNTPs, 10 pmol of each primer, and 2.5 U of Taq DNA polymerase (Promega Corporation, Madison, WI, USA), in a final reaction volume of 30 µL. Amplification was performed using an initial denaturation at 95 °C for 1 min, followed by 35 cycles of denaturing at 95 °C for 40 s, annealing at 58 °C for 40 s and extension at 72 °C for 1 min, with a final extension at 72 °C for 3 min. The resulting product was sequenced on an automated sequencer (ABI PRISM 3730; Applied Biosystems, Foster City, CA, USA). Sequence comparisons and analysis were performed using Phred-Phrap-Consed program (v12.0; http://www.phrap.org/phredphrapconsed.html), and mutations were identified by comparing the sequence with the reported cDNA reference sequence (GenBank accession no. NM_000422.2).

Mutation analysis of the proband’s genomic DNA revealed a recurrent mutation, c.280C>T (p.Arg94Cys), in the KRT17 gene (Fig. 2g,h), which is the hotspot mutation for SM. This mutation segregated clearly with the disease phenotype within the family members, and it was not detected in 100 unrelated healthy Chinese individuals.

SM is a rare genetic skin disease that usually presents in adolescence. It always presents with multiple cutaneous cysts on the trunk, axilla, groin and proximal extremities because of the high density of the developed pilosebaceous units. The multiple cutaneous lesions are generally 1–20 mm in size.6 SM lesions occurring as multiple nodules > 20 mm in size are very rare.6 Jeong et al. reported a patient with four cystic masses varying in size from 10 to 40 mm and located on the scalp.6 Yonekura et al. also reported a giant steatocystoma, around 60 mm in size, which was located on the patient’s scalp.7 Our case is interesting in that the proband had multiple nodules varying in size from 20 to 80 mm on the face, trunk and proximal extremities.

In the current study, we identified a heterozygous missense mutation c.280 C>T (p.Arg94Cys) in the 1A domain of the KRT17 gene. The possible arginine substitution can result from deamination mutation of this codon. This mutation is predicted to be detrimental to the keratin cytoskeleton, producing cell fragility and hyperkeratosis in tissues expressing dkeratin 17,8 and it has been reported previously in several families with SM or pachyonychia congenita type 2.8,9 In our family, the patients had severe typical epidermal cysts, but no changes in mucous membranes, hair or nails. SM was the only phenotype found. Compared with the patients reported previously, all affected members with SM in this family have a more severe form. The same mutation will lead to different phenotypes even in the same family, which suggests that the genotype–phenotype correlation of SM may be determined not only by the site and type of the KRT17 gene mutation, but also by other modifying factors, androgenic stimulation and even environmental factors.10

In conclusion, we report a recurrent mutation in the KRT17 gene found in a family with severe SM, which provides further evidence that some factors such as modifiers, androgenic stimulation and/or environment influence the phenotypes, and other genetic or proteomic conditions might also influence the final manifestations of the disease.

Acknowledgements

We thank all subjects for their ongoing participation in this study. This study was funded by grants from the National Nature Science Foundation of China (81472867) and Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20161417).

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Conflict of interest: the authors declare that they have no conflicts of interest.

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Accepted for publication 17 April 2017

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