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Conflicts of interest

None to declare.

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Supporting Information

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Stopping pachyonychia congenita plantar pain with a statin?

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Linked Article: Abdollahimajd *et al.* Br J Dermatol 2019; **181**:584–586.

Pachyonychia congenita (PC) is a rare autosomal dominant disorder classified into five subtypes based on mutations in keratin genes (*KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17*).[1] The main clinical features include the triad of severe debilitating plantar pain, plantar keratoderma and hypertrophic nail dystrophy usually apparent by the age of 10. At present, there are limited treatment options for PC and the majority of patients perform mechanical debridement of calluses to manage their disease. As there is no cure for PC, novel treatment strategies are necessary to relieve pain and improve patient's quality of life. Current treatment options under investigation include topical sirolimus, botulinum toxin injections, small interfering (si)RNA targeting mutant keratin and statins.[1]

In 2011, Zhao *et al.*[2] performed a drug screen using a *KRT6A*-promoter-driven firefly luciferase construct in HaCaT keratinocytes and identified that statins, drugs commonly used to reduce cholesterol levels, inhibited *KRT6A* expression. The experience of physicians collaborating with the Pachyonychia Project in using statins in PC is mixed, with a few patients experiencing improvement in plantar pain and some experiencing no change.[1] In this issue of the *BJD*, Abdollahimajd and colleagues from the Shahib Beheshti University of Medical Sciences in Iran, report a case study of an 8-year-old female patient with PC with a mutation in *KRT6A* treated with rosuvastatin 5 mg daily with a reduction in both plantar hyperkeratosis and pain.[3] The patient was treated for 6 months with a nine-point drop in Children's Dermatology Life Quality Index score and a reduction in hyperkeratosis and blistering. The rosuvastatin was stopped for 3 weeks and pain recurred, but this improved on reintroducing rosuvastatin.

Statins are inhibitors of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme. Rosuvastatin is a more potent inhibitor of HMG-CoA, with a half maximal inhibitory concentration (IC_{50}) of 0·16 nmol L^{-1}, compared with atorvastatin or simvastatin, with IC_{50} of 1·16 and 1–2 nmol L^{-1}, respectively.[4] It is possible that rosuvastatin worked well in this case as it is a more potent statin and it may also be more effective in a child as the plantar pain is generally not as severe. Other possible mechanisms include reduction in inflammation and moderation of endoplasmic reticulum stress, a known pathomechanism in many genetic skin diseases.[5]

Patients with PC need long-term treatment. Although use of statins has resulted in a reduction in cardiovascular and cerebrovascular disease, there are concerns about increased diabetes mellitus and cataracts with long-term use.[4] Statins are also contraindicated during pregnancy and breastfeeding, so they would need to be used intermittently by women of childbearing age. Paediatric data in familial hypercholesterolaemia indicate that statins are safe, but the data and follow-up are limited. Our opinion is that although rosuvastatin worked well in this case, a placebo-controlled clinical trial would be necessary to prove the efficacy of oral statins and it is likely that there will be better treatments for PC.

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Conflicts of interest

E.A.O.'T. is a consultant to Palvella Therapeutics a company that is developing topical sirolimus as a treatment for PC (fees go to university).

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Mosaicism: time matters

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In this issue of the BJD, Reinders *et al.* report two patients with multiple basal cell carcinomas (BCCs), in whom postzygotic mosaic mutations were responsible for phenotypes resembling those resulting from germline mutations.[1]

Postzygotic mutations occurring during embryonic development are responsible for most mosaic phenotypes.[2] In recent years, advances in genetic testing have revealed that mosaicism is not just a rare phenomenon responsible for unusual phenotypes, but a common event, even in early embryogenesis,[3] that explains congenital anomalies and acquired lesions, and may have unforeseen consequences.

The site of the mutation within the gene, the cell(s) affected and the mode of inheritance and lethality determine the nature and extent of the mosaic condition. However, timing, the exact moment in life when the mutation occurs, is a key variable influencing the phenotype.[4] Mosaic mutations in postnatal life will cause a more limited phenotype than those occurring prenatally. Postzygotic mutations occurring during or shortly after organ differentiation will usually cause a mosaic phenotype with a recognizable Blaschkoid pattern of skin disease.[2] Because the skin, the central nervous system and the eye are ectoderm-derived organs, an early ectodermal mutation can cause a neurocutaneous syndrome when tissues affected by the mutation are located on the cephalic pole.[5] Also, an early mutation in a yet undifferentiated, pluripotential ectodermal stem cell can cause a phenotype with two or more different skin naevi or malformations.[6] However, when the mutation is even earlier than the formation of the embryonic layers, the mosaicism may extend to cells derived from layers other than the ectoderm, for example, a variable percentage of blood cells. Very early postzygotic mutations in an autosomal dominant, nonlethal gene, can cause a phenotype resembling a prezygotic, germline mutation; because many cells in the individual will be affected by the mutation, where the disease manifestations reflect a second hit mutation, the mosaic condition may appear generalized (as occurs in the second patient in the report by Reinders *et al.*).

Timing of mosaicism is also a key determinant of disease transmission to offspring: the earlier the parental mutation the more likely it is to involve the gonads, with a higher chance of transmission of the full-blown disease. Mosaicism can theoretically be classified into three types: (i) somatic, if it affects only somatic but not gonadal tissues; (ii) gonadal, if it affects only gonadal tissue but not other organs; and (iii) gonosomal, when both are affected. Only types (ii) and (iii) can be transmitted to the offspring, but in practice it is rarely possible to exclude gonadal involvement completely. The presence or degree of gonadal mosaicism cannot be predicted on phenotypic grounds, although it is perhaps more likely in the presence of extensive somatic disease. This has seldom been studied at the genetic level.[7]

Genetic advances are solving many puzzles, but also raising new questions and opportunities in the field of mosaicism, which may be responsible for many more diseases and phenotypes than we formerly suspected. Hopefully these advances will provide targeted therapies and strategies for genetic counselling and prevention of disease anticipation and disease complications in the near future.

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