NEWS

ASPRV1 variants lead to dominantly inherited ichthyosis

Liam Norris/Getty

Lamellar ichthyosis causes the skin on most of the body to become dry and scaly and the skin on the palms and soles to become thickened. Variants in many genes that encode epidermal proteins lead to the recessive condition. Now, however, Boyden and colleagues report in a recent article in the *American Journal of Human Genetics* (https://www.cell.com/ajhg/pdfExtended/S0002-9297(20)30160-9) that variants in aspartic peptidase retroviral-like 1 (*ASPRV1*) cause a dominantly inherited form of ichthyosis that presents with the same characteristic features as those of lamellar ichthyosis. The researchers exome sequenced a cohort of subjects with cornification disorders that were negative for pathogenic variants in genes known to cause such conditions. The investigation revealed that five affected members of a family were heterozygous for c.932G>C in *ASPRV1*, encoding p.Arg311Pro. The scientists then discovered that members of three unrelated families were heterozygous for two other *ASPRV1* variants: c.595A>G encoding p.Lys199Glu and c.940C>A encoding p.Pro314Thr. The three variants occur at highly conserved residues and are predicted to be damaging. All of the subjects with the missense *ASPRV1* variants displayed a consistent phenotype, presenting with large, plate-like scales on most of the body since infancy, thickened skin of the soles and palms with deep creases, and mild or absent erythema. The single-exon *ASPRV1* gene, first characterized by research and development scientists at the cosmetic company L'Oreal and its former subsidiary, Galderma, is unique to mammals and encodes an enzyme that is critical to epidermal integrity. Autocleavage produces a 14-kDa active form of ASPRV1 that directly processes a protein called filaggrin, a central scaffolding component of the uppermost epidermal layer. Three-dimensional structural modeling suggests that the three *ASPRV1* variant sites are tightly clustered on the same surface of the active enzyme. When the researchers expressed the variant forms in human keratinocytes, they found that cells transduced with each of the variants produced a 20 kDa form of ASPRV1, whereas nontransduced cells or cells transduced with wild-type *ASPRV1* did not. Additionally, high–molecular weight filaggrin accumulated only in cells expressing the *ASPRV1* variants. The results suggest that the *ASPRV1* variants impair filaggrin processing. Immunostaining skin from an affected subject revealed strong filaggrin expression in an expanded granular layer, whereas expression remains tightly bound in the granular layer of an age-matched control. The authors conclude that variants in *ASPRV1* cause this dominantly inherited ichthyosis that is phenotypically indistinguishable from the recessively inherited condition. —*V. L. Dengler, News Editor*

Altering sorbitol metabolism to treat hereditary neuropathy

FotoDuets/Getty

One of the ways in which the body processes glucose, a sugar found in many foods, is to convert it to fructose via the polyol pathway. First, aldose reductase reduces glucose to sorbitol, which is then oxidized to fructose by sorbitol dehydrogenase (SORD). Although the two-step process is straightforward, the second and last step is critical, as sorbitol does not metabolize well. In a recent study published in *Nature Genetics* (https://www.nature.com/articles/s41588-020-0615-4), Cortese and colleagues report that biallelic variants in *SORD* cause a common hereditary neuropathy and outline a potential therapeutic pathway. The researchers searched through a collection of sequencing results from 1100 patients with hereditary neuropathy for overrepresented and potentially pathogenic variants. The analysis uncovered 12 individuals from 11 unrelated families with a homozygous variant in *SORD*, c.757delG encoding p.Ala253GlnfsTer27. Another four affected individuals from three unrelated families were found to be compound heterozygous for this variant. Drawing on two other independent sets of recessive, sporadic, or unresolved neuropathies, the team identified 45 individuals from 38 unrelated families with biallelic *SORD* variants in total. The researchers determined that all but one of the identified *SORD* variants were loss-of-function. All of the patients exhibited clinically diagnosed, slowly progressing neuropathy that was mild in distal upper limbs and mild to nearly completely paralyzing in the lower distal limbs. Close to 70% of the cases were sporadic. When the researchers assessed SORD protein expression in patient fibroblasts, they found that SORD levels were absent in homozygous and compound heterozygous patient cells and reduced in unaffected carriers cells compared with levels in cells from healthy control subjects. Intracellular sorbitol levels were also 10 times higher in patients' cells than in controls'. Additionally, fasting sorbitol levels in serum from homozygous patients were more than 100 times higher than in unrelated healthy controls. Together these results indicate that patients lack SORD enzymatic activity. Next, the team tested a potential therapeutic pathway. They treated patient-derived fibroblasts with two commercially available aldose reductase inhibitors: epalrestat and ranirestat. Both compounds significantly reduced sorbitol levels in patient cells. Treatment was also able to rescue locomotor and synaptic defects in two *Drosophila melanogaster* models of SORD deficiency that recapitulated the progressive, age-dependent phenotype of patients. The authors conclude that together the results demonstrate that biallelic *SORD* variants are a novel cause of inherited neuropathy with great potential for treatment. —*V. L. Dengler, News Editor*

Genetics in Medicine (2020) https://doi.org/10.1038/s41436-020-0902-6