Dermatology News™

News from the European Academy of Dermatology and Venereology annual congress.

LATEST NEWS

New genetic causes of ichthyoses likely to emerge

Publish date: August 11, 2017

By: Doug Brunk, Dermatology News

AT WCPD 2017

CHICAGO– The way Keith Choate, MD, PhD, sees it, he and other clinicians are only beginning to scratch the surface on their understanding of the genetic causes of ichthyosis and ichthyosis syndromes.

"Despite the fact that we now understand that there are about 21,000 genes in the genome, we have very superficial understanding and functions known for only about 4,000 genes," Dr. Choate of the departments of dermatology and genetics at Yale University, New Haven, Conn., said at the World Congress of Pediatric Dermatology. "Clinical insight is what's driving all of the discovery. We continue to find new disorders, and these next-generation technologies really permit us to find the genetic basis for those disorders. I like to say that it's the disorders that we don't read about in the textbook that end up being the ones that are most interesting."

Ichthyoses are cardinal disorders that occur when the normal pattern of epidermal differentiation is disrupted and leads to compensatory hyperproliferation. Clinically, ichthyoses present in a variety of ways, and more than 50 genes can cause them.

Dr. Keith Choate

"These genes encode proteins of diverse function, from enzymatic proteins to membrane transporters to structural proteins," Dr. Choate <http://www.dermatology.yale.edu/people/keith_choate.profile> said. "I think the question we have is, is there anything left to discover? What is the potential for gene discovery? We and others have found that there are new causes of ichthyosis, and in clinical practice, we've come to understand that there are many disorders for which we really don't have any known genetic causes. This includes many palmoplantar keratodermas and erythrokeratodermas, syndromic cases, and subtypes of congenital ichthyosis, particularly milder types, and unusual or unique cases."

Dr. Choate is the principal investigator of the National Registry for Ichthyosis and Related Skin Types <http://www.firstskinfoundation.org/national-registry-for-ichthyosis-and-related-disorders> , which has been recruiting kindreds of ichthyosis patients within the United States and internationally. To date, they have provided genetic diagnoses for 674 of the 880 cases enrolled. The process involves phenotyping with a clinical history and photography, obtaining DNA from blood or saliva, and prescreening the DNA samples for mutations in 51 genes currently implicated in ichthyosis. Subjects without known mutations undergo whole exome or genome sequencing.

"We have created a unique resource in doing this," he said. "Genotyped/phenotyped patients provide a resource for clinical and translational studies in disorders of keratinization."

When the researchers examined patients from the registry who have epidermolytic presentations, 100% had mutations in the known genes, “so the biopsy is diagnostic,” Dr. Choate said. “About 80% have mutations in keratin 10, about 13% have mutations in keratin 1, and another 6% have mutations in keratin 2.”

About 85% of patients with recessive and syndromic disorders have mutations in this same 51-gene panel; 15% of cases don’t have mutations in those genes. “This is a similar fraction to what my colleagues have found at a variety of institutions around the world,” Dr. Choate said. “What’s fascinating is that this 15% has been the source of remarkable discovery.”

He then discussed three cases of a novel erythrokeratoderma phenotype that were referred to the registry. In one case, a boy had pervasive intellectual disability, congenital alopecia, and absence of the eyebrows. “Within the first days of life, he developed a significant erythroderma with copious scaling of the skin that persisted throughout life and that was unresponsive to a variety of different therapeutic interventions, including immunosuppressant medications,” Dr. Choate said. “He had nail dystrophy and progressive enamel decay with severe caries, leading to loss of all of his teeth by the age of 6.”

Another case was a child who died of cardiomyopathy at about 3 years of age. He had congenital absence of the eyebrows and eyelashes, nail dystrophy, and scaling. “About 2 weeks before his death, he had a skin biopsy that we would ultimately repurpose to identify a new genetic cause of what we would call the erythrokeratodermia-cardiomyopathy syndrome,” Dr. Choate said. “It included features of congenital erythroderma, defective dental enamel, abnormal nails, and progressive and lethal cardiomyopathy. When we did exome sequencing, we found that all three of these patients showed tightly clustered de novo mutations in a gene called desmoplakin (DSP). Other DSP mutations do not cause erythrokeratoderma.”

Electron microscopy showed aggregates of desmosomes, normal corneodesmosomes, widening of intercellular spaces, and abnormal lipid secretion. The finding led the researchers to conclude that clustered DSP mutations cause a novel cutaneous phenotype with erythrokeratoderma and progressive cardiomyopathy. “The next time an insurer refuses to do genetic testing for you in a patient who has erythrokeratoderma, this is the disorder that you want to cite as the reason why you need to do genetic testing,” he said.

In a recent study, Dr. Choate and his associates identified the genetic cause for a rare subtype of progressive symmetric erythrokeratoderma (PSEK), a disorder that features thick facial plaques and thickened palms and soles (Am J Hum Genet. 2017 Jun 1;100[6]:978-84 <http://www.cell.com/ajhg/fulltext/S0002-9297(17)30190-8>). Histology reveals a thickened epidermis, loss of granular layer, and retention of nuclei in the stratum corneum. They discovered that PSEK was caused by mutations in 3-ketodihydrosphingosine reductase (KDSR), an enzyme that is central to de novo ceramides in skin.

“Ceramides are secreted by keratinocytes with cholesterol and free fatty acids to form the cutaneous lipid barrier,” he explained. “They also regulate cutaneous proliferation and differentiation. One of the things this story in particular told us was, when you find just one mutation and a compelling candidate gene and can’t find the other, it’s often because of how you’re approaching detection. In two of our cases, genome sequencing was necessary to find a large inversion, which disrupted the encoded protein. Finally, the challenge of studying ceramides is that it’s hard to get cells in culture to produce them. Therefore, we had to work with collaborators in yeast biology to prove pathogenesis.”

Dr. Choate cited other recent developments, including the discovery that familial pityriasis rubra pilaris is caused by mutations in CARD14, which is a known activator of nuclear factor kappa B signaling (Am J Hum Genet. 2012 Jul 13;91[1]:163-70 <http://www.cell.com/ajhg/fulltext/S0002-9297(12)00266-2>). This led to the subsequent use of ustekinumab for patients with familial pityriasis rubra pilaris. Another group of researchers found that SULT2B1 encodes sulfotransferase family 2B member 1 and is central to epidermal cholesterol metabolism (Am J Hum Genet. 2017 Jun 1;100[6]:926-39 <http://www.cell.com/ajhg/fulltext/S0002-9297(17)30194-5>).

“There are still new genetic causes of ichthyosis to be found, particularly cases that don’t meet the textbook criteria for the disorder,” he concluded. “Severe, dominant disorders primarily due to de novo mutations are fertile ground for discovery. Genetic investigation is critical to our understanding of disease biology and biology of the skin. It’s also potentially relevant to outcomes of therapy. [Erythrokeratodermia-cardiomyopathy syndrome] highlights the potential for comorbidities, and the efficacy of ustekinumab in familial [pityriasis rubra pilaris] highlights the therapeutic importance of understanding the pathway underlying the disease.”

Dr. Choate reported having no financial disclosures.

dbrunk@frontlinemedcom.com <http://www.nationalmssociety.org>

Related Articles

VIDEO

VIDEO: N-acetylcysteine for ichthyosis, OCD behaviors

Whitney McKnight, Dermatology News

Publish date: January 28, 2016

CONTINUE READING ARTICLE ›