

Filaggrin Plays Critical Role in Skin Barrier Health

BY BRUCE JANCIN
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KYOTO, JAPAN — Filaggrin mutations are potent risk factors for allergic rhinitis and eczema-related asthma, the results of two large population-based studies have shown.

Loss-of-function mutations in the filaggrin gene have previously been found to be the cause of ichthyosis vulgaris, as well as being a predisposing factor in atopic dermatitis. (See related story below.)

Filaggrin is an abundant protein that plays a critical role in the formation of a healthy stratum corneum.

It is thus a key contributor to the skin's barrier function, and it also regulates stratum corneum hydration, W.H. Irwin McLean, Ph.D., noted in his René Touraine Lecture at an international investigative dermatology meeting.

The filaggrin gene is part of the epidermal differentiation complex located on chromosome 1q21. Recently, it has become evident that mutations causing low or no filaggrin expression are found the world over and are particularly prevalent in individuals of European ancestry, added Dr. McLean, professor of human genetics at the University of Dundee (Scotland).

Dr. McLean was the senior author of



two landmark papers first linking filaggrin mutations to ichthyosis vulgaris (Nat. Genet. 2006;38:337-42) and atopic dermatitis (Nat. Genet. 2006;38:441-6). He was also a coauthor of the recent population-based studies that identified filaggrin mutations as conferring significant risks for allergic rhinitis and eczema-related asthma.

The first study involved 3,099 German children aged 9-11 years recruited as part of phase II of the International Study of Asthma and Allergies in Childhood. Investigators headquartered at the Technical University of Munich assessed the children for two common filaggrin null mutations—R501X and 2282del14—and three other recently identified rare ones.

The presence of a target filaggrin mutation was associated with a 3.1-fold increased risk of atopic dermatitis, which is similar to previous results in other studies, he noted. In addition, filaggrin mutations independently conferred a 2.6-fold increased risk for allergic rhinitis and a 3.5-fold risk of asthma with a history of eczema. However, filaggrin mutations were not associated with an increased risk of asthma alone.

The population-attributable risk of atopic dermatitis associated with the filaggrin mutations—that is, the proportion of cases of the skin disease believed

to be due to these genetic variants—was 13.5%, said Dr. McLean. The population-attributable risk was estimated at 10.8% for allergic rhinitis, 15.6% for atopic dermatitis plus asthma, and 20.1% for atopic dermatitis plus allergic rhinitis.

Nasal biopsies showed strong expression of filaggrin in the anterior vestibular lining of the nose, but not in transitional and respiratory nasal epithelia (J. Allergy Clin. Immunol. 2008;121:1203-9).

In another large study, Dr. McLean and his coworkers at the University of Bristol (England) reported on the impact of the same two common filaggrin null mutations in 7,000 participants in the Avon Longitudinal Study of Parents and Children who were born in 1990-1991.

In this cohort, having either mutation was associated with a highly significant 1.8-fold increased risk of childhood asthma, a 3.0-fold risk of eczema plus early wheezing, and a 3.2-fold risk of atopic dermatitis plus asthma. Children with atopic dermatitis related to either of the filaggrin null alleles also tended to have markedly more persistent eczema than atopic dermatitis patients without a filaggrin mutation (J. Allergy Clin. Immunol. 2008;121:872-7).

The hope is that once treatments designed to correct filaggrin deficiency are

available, early identification and treatment of children with filaggrin-associated atopic dermatitis will prevent the other atopic outcomes. Dr. McLean and his coworkers at the University of Dundee are now attempting to develop such therapies.

“My motto for the next few years is, ‘Enough genetics—let’s cure something.’” he said at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

He and his colleagues have identified one molecule he declined to name that more than doubles filaggrin expression in vitro in the setting of a single mutation with one normal and one silent allele. And aminoglycosides such as gentamicin can inhibit mutations in homozygous individuals who make no filaggrin at all and who therefore have particularly severe atopic disease, he said.

“When we treat human skin cells containing filaggrin mutations with gentamicin, we recover gene expression. We see improvement in the granular layer. Gentamicin is not an ideal drug ... I think we can find a better one,” Dr. McLean added.

His filaggrin research is funded by the British Skin Foundation, the National Eczema Society, and the Medical Research Council. ■

The population-attributable risk of atopic dermatitis believed to be due to filaggrin mutations was estimated to be 13.5% in the study.

Atopic Dermatitis: Filaggrin-Barrier Defect Story Continues

BY BRUCE JANCIN
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KYOTO, JAPAN — Children heterozygous for a filaggrin gene loss-of-function mutation are at an 8.2-fold increased risk for moderate to severe atopic dermatitis, while those who are homozygous for the defect carry a staggering 169-fold elevated risk, according to a case-control study.

This Irish study of mutations in the gene expressing filaggrin, a key skin barrier function protein, involved 262 children with dermatologist-diagnosed moderate to severe atopic dermatitis and 736 matched controls. As in other studies of people of Northern European ancestry, almost one-half of the atopic dermatitis patients possessed a filaggrin mutation, Dr. Gráinne M. O’Regan reported at an international investigative dermatology meeting.

The study also turned up three previously unknown filaggrin mutations, noted Dr. O’Regan of Our Lady’s Children’s Hospital, Dublin.

Her coinvestigator, W.H. Irwin McLean, Ph.D., noted that this brings the total num-

ber of filaggrin loss-of-function or null mutations identified to 39, mostly in the European and Far Eastern populations where studies thus far have been concentrated.

“The mutations are completely ethnic specific. The mutations you find in white people are not found in Japan, for example, with very, very few exceptions,” he explained in his René Touraine Lecture at the meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

There is little doubt that other skin barrier genes just as replicable as filaggrin will emerge in the future. And additional filaggrin mutations await discovery, added Dr. McLean, professor of human genetics at the University of Dundee (Scotland).

“We don’t know much yet about filaggrin mutations in black populations,” he noted. “It’s very difficult to analyze populations. It takes probably a year to do each ethnic group.”

Heterozygotes for a filaggrin null mutation make half the normal amount of filaggrin. Homozygotes make none. In heterozygotes the penetrance is 40%, meaning

40% of bearers of one mutant allele have atopic dermatitis. The penetrance in homozygotes is 90% or more, and they tend to have the most severe skin disease.

The newest data on the prevalence of filaggrin null mutations in the general population come from an epidemiologic study in the north of England, where 1 in 7 individuals was found to carry one mutation and 1 in 90 carried two.

Two years ago, Dr. McLean and his coworkers shook up the dermatology world with their landmark discovery that filaggrin mutations strongly predispose to atopic dermatitis.

Their report brought forth a new appreciation of impaired skin barrier function as a driving force in the pathophysiology of this common inflammatory skin disease.

Since then, Dr. McLean said, one of the most common questions physicians ask him is this: Is atopic dermatitis fundamentally a skin barrier problem or an immunologic disorder?

“I think that’s too simple a question,” he added. Instead, the Irishman drew an analogy between atopic dermatitis and the St. Patrick’s three-leafed shamrock. The “leaves” of atopic dermatitis are the skin barrier, the immune system, and the environment.

“If you have no barrier, every environmental trigger is going to cause eczema.

And you can have some people who have a good barrier and a very, very sensitive immune system, so the environmental trigger gets through. But I think a lot of people will fall in the middle, where there’s a barrier defect, there’s something going on with the immune system, and there’s an environmental trigger. The incidence of atopic dermatitis has increased over the years, and that’s due to the changed environment. The genes controlling these two other things have stayed the same,” Dr. McLean said.

His filaggrin research is funded by the British Skin Foundation, the National Eczema Society, and the Medical Research Council. ■

AAD Launches Rare Disease Web Forum

The American Academy of Dermatology has launched a new program called DermBase that will help members collaborate on research into rare diseases from multiple sites. The Web-based tool provides an online forum for dermatologists to submit ideas for clinical studies, receive feedback for those studies, conduct studies, and publish findings. For more information, visit www.dermbase.com. ■