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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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Researchers Identify Genetic Cause of Disfiguring Congenital Skin Disorder

A team of researchers at the National Institutes of Health (NIH), in a unique collaboration with Egyptian researchers, have found that genetic defects in a skin enzyme called transglutaminase 1 (TGM1) are the cause of lamellar ichthyosis—a severely disfiguring congenital skin disorder. TGM1 plays a role in formation of the outermost layer of skin, which develops abnormally in people with this disorder.

This finding provides much-needed insight into normal skin development as well as into what causes development of thickened, scaly skin over the entire body in this hereditary disorder. It also provides tantalizing clues to causes of the large number of other scaling skin disorders.

"This discovery raises the exciting prospect of being able to correct the underlying abnormalities that cause this severe skin disorder," said Dr. Michael D. Lockshin, acting director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at NIH. "Through their team approach, this interdisciplinary group of researchers is making impressive strides in understanding the genetic basis of a number of inherited skin disorders."

The research group included geneticist Dr. Sherri J. Bale from the NIAMS

Laboratory of Skin Biology, who developed a collaboration with Dr. Nemat Hashem and her staff at the Ain-Shams University Medical Genetics Center in Cairo, Egypt. The team also included National Research Council fellow Dr. Laura J. Russell, NIAMS molecular biologist Dr. John G. Compton, dermatologist Dr. John J. DiGiovanna of the NIAMS Dermatology Clinical Research Unit. Dr. Peter M. Steinert and Dr. Geraldine R. Rogers also contributed to this work. The group's results are reported in the March issue of *Nature Genetics*. Funding for this work was provided by NIAMS and the U.S. Agency for International Development (AID).

Lamellar ichthyosis (LI) is one of a group of acquired and inherited scaling skin disorders known as the ichthyoses. Babies with LI often are born encased in a thick, shiny membrane. This membrane soon dries and peels off, leaving the baby with bright red underlying skin. Over time patients develop large, brown, platelike scales all over their bodies, representing a thickening and scaling of the outermost layer of skin, known as the stratum corneum, or horny layer. People with LI may not tolerate heat and may have turned-out eyelids or lips due to tautness of facial skin. Some patients also suffer from scarring hair loss involving the scalp and eyebrows.

The stratum corneum consists of dry, flattened, dead cells that serve as a barrier, keeping the rest of the skin from drying out and protecting it against the environment. Normally, these cells continuously and invisibly flake off from the skin's surface to make room for new cells that come from layers deeper in the top layer of skin, or epidermis. This is part of the process by which the epidermis constantly renews itself. In ichthyosis, researchers believe the thickening and scaling are due either to runaway production of new stratum corneum cells or a defect in the process by which these cells slough off from the skin's surface.

"Dermatologists think of LI as the most typical type of ichthyosis," says DiGiovanna. "It's dramatic in appearance and common enough that it's the one thing dermatologists think of when they think of severe ichthyosis." LI is nevertheless a relatively rare disorder, occurring in about 1 of every 250,000 births. People with this scaling skin disease are often subjected to societal pressures that lead to isolation, ridicule, and misunderstanding. In the past, some people with LI even were exploited because of their appearance.

In visits to the Ain-Shams clinic in Cairo, Bale, Compton and DiGiovanna tapped into one of the largest genetic databases in the world. The database was assembled over the past 25 years by Hashem, director of the medical genetics center. It contains epidemiologic and demographic information on close to 4,000 families (more than 16,000 individuals) with inherited disorders, including several rare forms of ichthyosis.

Hashem used her database to locate several families with congenital ichthyosis and asked them to come to her clinic during the NIH team's visits. Compton set up a laboratory at the clinic to isolate genetic material (DNA) from blood samples from affected and unaffected individuals from these Egyptian families. The researchers also obtained DNA samples from U.S. families in which two or more members had LI, located with the aid of the Foundation for Ichthyosis and Related Skin Types.

"The Egyptian families were important for these studies because of the high rate of intermarriage in Egypt," explained Bale. "This results in increased prevalence of autosomal recessive diseases such as LI." Having DNA samples from these inbred families greatly facilitated the team's initial genetic analyses, which provided strong evidence that defects in the TGM1 gene were responsible for LI.

The researchers first used DNA from U.S. and Egyptian patients' blood samples to narrow down the location of the LI disease gene to a specific region of chromosome 14 that contains the gene encoding the TGM1 protein. They examined this region of the chromosome because they knew that TGM1 was one of a number of proteins involved in formation of the stratum corneum. TGM1 was the eighth such "candidate gene" that the researchers screened for a possible connection to the disease gene. Results of these initial genetic linkage studies were reported in the December 1994 issue of the *American Journal of Human Genetics.*

In further studies now reported in *Nature Genetics*, the researchers identified specific mutations in both copies of the TGM1 gene in U.S. and Egyptian patients with LI. "In each case, the same mutation was also seen in one of two copies of the gene in carrier members of these patients' families but not in any of more than 200 unrelated healthy individuals who were tested," said Russell. Carriers for the disease, who have a single defective copy of the TGM1 gene, do not themselves have LI. This is because both copies of a gene (one inherited from each parent) must be defective to cause an autosomal recessive disorder. Other TGM1 gene mutations in patients with LI have recently been reported by a European research group in the journal *Science.*

TGM1 serves to cross-link cellular proteins to form a rigid scaffold within the lifeless cells that form the stratum corneum. This molecular scaffold is an integral part of the cornified cell envelope, a specialized structure that replaces the cell membrane in cells of this outermost layer of the epidermis. The stratum corneum is formed as epidermal cells (keratinocytes) generated in the lowest layer of the epidermis move up toward the skin's surface, pushing older cells ahead of them. As these cells move upwards, they undergo a series of structural and functional changes. In the final stages of

this maturation process, known as terminal differentiation, the keratinocytes become more flattened, the cornified cell envelope forms, and the cells eventually die and slough off.

"The terminal differentiation process is somehow abnormal in people with LI," Compton said. "But how the production of scaling skin occurs is poorly understood and very important to study." This finding provides some insight into what goes wrong in this disease, Compton said, because "we now know a major cause of scaling is failure of this one component of the process. We know that the function of TGM1 is to produce crosslinks, and the importance of these crosslinks is now obvious." However, he added, "any particular specifics as to exactly what role these crosslinks play in producing a normal stratum corneum is still a mystery."

The research team plans to continue identifying and cataloging the different mutations that occur in the TGM1 gene in their patients. They also will work to understand what these mutations do to the TGM1 enzyme molecule itself and how this affects the normal formation of stratum corneum.

According to DiGiovanna, "the most important function of the skin is to make a normal stratum corneum, and we know very little about that process. Knowing more about this will not only increase our understanding of lamellar ichthyosis but also of many other skin diseases."

The researchers' collaboration with Ain-Shams University is one of 17 projects within the United States-Egypt Cooperative Health Program. This program was a collaborative effort between the U.S. Public Health Service and the Egyptian Ministry of Health, with support from the U.S. AID mission in Cairo. The Fogarty International Center of the NIH played a key role in managing and coordinating the nine NIH projects within the Cooperative Health Program.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases, a component of the National Institutes of Health, leads and coordinates the Federal biomedical research effort on the skin and skin diseases by conducting and supporting research projects, research training, clinical trials and epidemiologic studies, and by disseminating information on research results.

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Reference: Laura J. Russell, John J. DiGiovanna, Geraldine R. Rogers, Peter M. Steinert, Nemat Hashem, John G. Compton & Sherri J. Bale. Mutations of the gene for transglutaminase 1 in autosomal recessive lamellar ichthyosis. *Nature Genetics*, March 1995.

Sources of Further Information:

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For background information on lamellar ichthyosis and the other forms of ichthyosis, names of some experts available for comment and patient information:

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