MedicalXpress

Scientists discover genetic cause of rare allergy to vibration

February 3 2016

Scientists at the National Institutes of Health (NIH) have identified a genetic mutation responsible for a rare form of inherited hives induced by vibration, also known as vibratory urticaria. Running, hand clapping, towel drying or even taking a bumpy bus ride can cause temporary skin rashes in people with this rare disorder. By studying affected families, researchers discovered how vibration promotes the release of inflammatory chemicals from the immune system's mast cells, causing hives and other allergic symptoms.

Their findings, published online in the *New England Journal of Medicine* on Feb. 3, suggest that people with this form of vibratory urticaria experience an exaggerated version of a normal cellular response to vibration. The study was led by researchers at the National Institute of Allergy and Infectious Diseases (NIAID) and the National Human Genome Research Institute (NHGRI), both part of NIH.

"Investigating rare disorders such as vibratory urticaria can yield important insights into how the immune system functions and how it reacts to certain triggers to produce allergy symptoms, which can range from mild to debilitating," said NIAID Director Anthony S. Fauci, M.D. "The findings from this study uncover intriguing new facets of mast cell biology, adding to our knowledge of how allergic responses occur."

"This study illustrates the power of a multidisciplinary team, involving clinicians, geneticists and basic immunologists, to get to the heart of a medical mystery," said Dan Kastner, M.D., Ph.D., scientific director of

the Intramural Research Program at NHGRI and a co-author of the study. "It also underscores the tremendous potential of new genomic techniques."

In addition to itchy red welts at the site of vibration on the skin, people with vibratory urticaria also sometimes experience flushing, headaches, fatigue, blurry vision or a metallic taste in the mouth. Symptoms usually disappear within an hour, but those affected may experience several episodes per day.

The current study involved three families in which multiple generations experienced vibratory urticaria. The NIH team evaluated the first family under an ongoing clinical protocol investigating urticarias induced by a physical trigger.

Mast cells, which reside in the skin and other tissues, release histamine and other inflammatory chemicals into the bloodstream and surrounding tissue in response to certain stimuli, a process known as degranulation. To assess potential mast cell involvement in vibratory urticaria, the researchers measured blood levels of histamine during an episode of vibration-induced hives. Histamine levels rose rapidly in response to vibration and subsided after about an hour, indicating that mast cells had released their contents. The researchers also observed increased tryptase, another marker of mast cell degranulation, in skin around the affected area.

"Notably, we also observed a small increase in blood histamine levels and a slight release of tryptase from mast cells in the skin of unaffected individuals exposed to vibration," said Hirsh Komarow, M.D., of NIAID's Laboratory of Allergic Diseases, the senior author of the study. "This suggests that a normal response to vibration, which does not cause symptoms in most people, is exaggerated in our patients with this inherited form of vibratory urticaria."

The NIH team realized that the first family's symptoms matched those of a different family described by researchers at Yale University in 1981. Through a collaboration with Yale, the NIH team obtained DNA samples from 25 members of that family. Two family members came to NIH for evaluation, and they put the scientists in contact with a third family with similar symptoms.

To identify the genetic basis of the disorder, the scientists performed genetic analyses, including DNA sequencing, on 36 affected and unaffected members from the three families. They found a single mutation in the *ADGRE2* gene shared by family members with vibratory urticaria but not present in unaffected people. The scientists did not detect the *ADGRE2* mutation in variant databases or in the DNA of more than 1,000 unaffected individuals with a similar genetic ancestry as the three families.

"This work marks, to the best of our knowledge, the first identification of a genetic basis for a mast-cell-mediated urticaria induced by a mechanical stimulus," said Dean Metcalfe, M.D., chief of NIAID's Laboratory of Allergic Diseases and a study co-author.

The *ADGRE2* gene provides instructions for production of ADGRE2 protein, which is present on the surface of several types of immune cells, including mast cells. ADGRE2 is composed of two subunits—a beta subunit located within the cell's outer membrane, and an alpha subunit located on the outside surface of the cell. Normally, these two subunits interact, staying close together.

People with familial vibratory urticaria produce a mutated ADGRE2 protein in which this subunit interaction is less stable, the investigators found. After vibration, the alpha subunit of the mutant protein was no longer in close contact with the beta subunit. When the alpha subunit detaches from the beta subunit, the researchers suggest, the beta subunit

produces signals inside mast cells that lead to degranulation, which causes hives and other allergy symptoms.

The research suggests that the ADGRE2 subunit interaction plays a key role in the mast cell response to certain physical stimuli, which could have implications for other diseases in which mast cells are involved. Next, the scientists plan to study what happens to the alpha subunit post-vibration and to unravel the cellular signaling leading to degranulation. They also plan to recruit more families with vibratory urticaria to further study the disorder and look for additional mutations in *ADGRE2* and other genes.

More information: Steven E. Boyden et al. Vibratory Urticaria Associated with a Missense Variant in , *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMoa1500611

Provided by NIH/National Institute of Allergy and Infectious Diseases