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Researchers Find Clue to Rare Skin Disease in Confetti-Like Spots

Dermatologists Keith Choate and Len Milstone dropped by the Yale University laboratory of Howard Hughes Medical Institute investigator Richard Lifton one day with a scientific challenge: Would it be possible to determine the genetic basis of an exceptionally rare skin disease that affected a patient, but neither of her parents or any other relatives?

Since the disease affected a single family member, Lifton said, there was not enough information to trace its genetic roots. Then Choate— a former M.D.-Ph.D. student in Lifton's lab—pulled out a photo of the patient, who had a condition called ichthyosis with confetti (IWC), which is marked by bright red skin speckled all over with pale “confetti” spots.

What causes the spots? Lifton asked. Choate replied that they had recently biopsied one and it appeared to be normal skin.

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- Richard P. Lifton

That answer yielded not only the genetic key to the disease, but also the first known example of an inherited disease that spontaneously corrects itself with high frequency. Lifton, Choate, Milstone and colleagues from California, Missouri, and Texas detail the work, which they say might someday be applied more broadly to reverse other genetic mutations, in a study published August 26, 2010, in the journal *Science*.

IWC is marked by red, scaly skin, thick patches on the palms and soles, and the paler confetti spots. The disease undermines the structural integrity of the skin, weakening it as a barrier between what's inside and outside the body.

Patients are vulnerable to frequent and dangerous bacterial infections; many face numerous hospitalizations, and some children with the disease do not survive through adolescence.

The finding that the thousands of confetti spots were normal skin led to the ‘aha’ moment, recalled Lifton. He speculated that the disease might be caused by a genetically dominant mutation – meaning just one copy of the mutation could cause the disease, even if cells also had a healthy version of the same gene – and that the mutation was spontaneously lost in the spots. Such widespread reversion of diseased cells back to normal was unheard of, Lifton said.

That idea led to a research plan. They would first biopsy multiple confetti spots, using samples from a handful of far-flung patients, then look to see whether the spots had lost a section of genetic material at any particular place. If a single gene was causing the disease, then any missing DNA in the confetti spots could pinpoint where the problem lay in the DNA of the diseased cells.

As it turned out, in all 32 spots the researchers checked, the same stretch of DNA on chromosome 17 was lost. This localized the presumed mutation to a segment of the chromosome that was 2 million base pairs long. They sequenced that piece and found that affected members of all of the seven families they studied had mutations in a gene called *keratin 10*. Although the mutations were diverse, they found that all caused the same problem: the tail of the gene’s protein product became loaded with the amino acid arginine, which led to mislocalization of the protein. Rather than being in the cell cytoplasm, it was tightly associated with the nucleolus, the site at which the protein-making ribosomes are assembled.

In the confetti spots, that missing stretch of DNA wasn’t simply being deleted. Rather, the whole arm of the chromosome was being swapped with that of its sister chromosome when the cells replicated—a process called mitotic recombination—leaving one daughter cell with two normal copies of the *keratin 10* gene. “When that happens, the cell reverts to normal and we see these spots of normal skin,” Choate explained.

Lifton noted that this type of gene swapping during mitotic recombination is better known for its detrimental effects, such as in some cancers caused by mutations in genes that normally suppress tumors. With one mutated copy and one normal copy of the gene, it’s the normal copy that gets thrown out and the mutated one that gives rise to a malignancy.

The sheer abundance of places where diseased skin has reverted to normal is remarkable, Lifton added. “Every patient with this disease has hundreds to thousands of revertant spots, and up to now there have been, in all of the world’s literature of skin diseases, only a handful of revertant spots that have been characterized.” What’s more, most of the spots are about the size of a

dime, each one containing thousands of healthy cells. Choate says that indicates that the recombination is occurring in the skin's precursor cells, or stem cells, rather than in mature epidermal cells. "If it just happened in one epidermal cell, you'd end up with maybe a couple of epidermal cells, but you'd never be able to see it."

The next step for the team is to understand why these mutations lead to such a high frequency of reversion, Lifton said. It's possible, they say, that mitotic recombination could be used to revert other genetic diseases.