Twin study surveys genome for cause of multiple sclerosis

Researchers looking for the genetic roots of disease have long dreamed of inspecting a patient's entire DNA sequence for telltale changes — now achievable thanks to the falling cost of sequencing. So the first in-depth comparison of the genomes of identical female twins — one with multiple sclerosis (MS) and the other free of the disease — is something of a milestone. But the study shows that even deep genetic analysis doesn't always yield clear answers.

There is no doubt that MS, which causes the body's own immune cells to attack the insulating sheath around nerve cells, has a genetic component. Relatives of people who have the disease have an increased risk of developing it; if a patient with MS has an identical twin, that twin's risk climbs to more than 25%. But when a team of US researchers compared the complete genomes of twin females with each other, they failed to find any genetic differences that might cause MS.

Reporting this week in *Nature*[1], the researchers, led by Sergio Baranzini at the University of California, San Francisco, and Stephen Kingsmore of the National Center for Genome Resources in Santa Fe, New Mexico, next looked for a difference in epigenetics — chemical modifications to DNA that affect gene expression but not genetic sequence — in the twins' immune cells and in cells of two other sets of similarly affected twins. But no differences were found in the expression levels of key genes, either.

Although they did not sequence the genomes of the other two sets of twins, they did compare 1 million specific 'spelling variations' (known as single nucleotide polymorphisms, or SNPs) in the sequences of twins with and without MS, confirming that their genomes were the same.

Because the study examined the genome so comprehensively, "it is an incredibly important negative", says David Hafler, a neurologist at Yale University in New Haven, Connecticut. The results indicate that there is no clear genetic reason to explain why one twin developed MS while the other did not.

Disease geneticists often survey large populations of patients to find SNPs that are associated with a disease. But sequencing offers a deeper analysis of the genome that can reveal overlooked differences in sets of twins in which one has a disease but one does not. Identical twins' genomes start off the same, but mutations in early development can occur in one and not the other.

Earlier studies had identified a handful of gene variants that are linked to a higher risk of getting MS, and all of the twins in the study had at least some of them. "Both twins came into the world with the same set of high risks for developing MS," says Kingsmore. But those genetic factors seem to have been insufficient to cause disease on their own: "There had to be some trigger that caused one to develop it and the other not," he adds. One possibility, says Baranzini, is that although both twins had the same predisposition for the disease, "one was exposed to the perfect combination of environmental triggers".

Comparing the complete genomes of family members to find the exact mutations responsible for disease is the new frontier, says Daniel Geschwind, a neurogeneticist at the University of California, Los Angeles. A study published earlier this month used complete genome sequences to identify a rare, patient-specific gene variant causing the neurological disorder Charcot–Marie–Tooth disease[2]; another study narrowed down the genetic cause of two more disorders[3]. The MS study is the first, however, to integrate studies of epigenetics and gene expression with whole-genome sequencing. "What they've done here is create a very nice template for others to follow," Geschwind says. "It isn't just sequence — they went from sequence to epigenome to expression. That's what really makes [the study] something special."

Yet scientists are unlikely to glean much immediate insight about MS from the work. One limitation, notes Geschwind, is that although Baranzini and colleagues examined epigenetics and gene expression in three twin pairs, they obtained the complete genome sequences of just one pair. "If we sequenced another dozen twin pairs we could make this much more definitive," says Kingsmore. And although the group targeted immune cells, "we really ought to look at sequencing of the brain tissue," he adds, as this might be an alternative site of genetic differences between the twins. ■

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1. Baranzini, S. E. *et al. Nature* **464,** 1351–1356 (2010).
2. Lupski, J. R. *et al. N. Engl. J. Med.* **362,** 1181–1191 (2010).
3. Roach, J. C. *et al. Science* advance online publication doi:10.1126/science.1186802 (2010).