

Gene Signatures Predict Interferon Response for MS Patients

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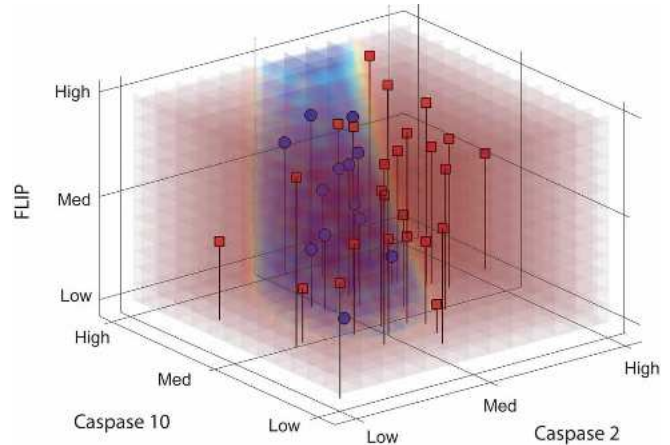
Multiple sclerosis (MS) can be an unpredictable disease. It develops when the body's immune system attacks healthy nerve cells and disrupts normal nerve signaling. Patients experience a wide range of symptoms—including tingling, paralysis, pain, fatigue, and blurred vision—that can appear independently or in combination, sporadically or persistently. Although symptoms appear in no particular order, flare-ups are common in the majority of patients.

MS flare-ups are commonly treated with beta-interferon. Adverse effects are not uncommon, and, more importantly, a sizable proportion of patients show a reduced response, or no response at all. Given the variability of the disease and treatment response, being able to predict how a particular patient is likely to respond to interferon would help doctors decide how close to monitor the patient or even whether to consider alternative treatments. In a new study, Sergio Baranzini et al. describe a computational model that can predict a patient's therapeutic response to interferon based on their gene expression profiles.

Immune cells typically secrete interferons to fend off viruses and other pathogens. Interferons stem viral infection by inhibiting cell division in neighboring cells—thus preventing the virus from reproducing—and triggering pathways that kill the infected cells. It's thought that interferon therapy may relieve symptoms associated with MS by correcting imbalances in the immune system that lead to disease. Interferon therapy produces changes in the gene expression profile of targeted cells—that is, it inhibits or activates certain genes—which in turn alters the cells' activity.

Blood samples were taken from 52 patients with relapsing-remitting MS (marked by acute flare-ups followed by partial or full recovery), and their RNA was isolated from a class of immune cells called peripheral blood mononuclear cells. After patients started interferon therapy, blood was taken at specific time points over the course of two years. Baranzini et al. measured the expression level of 70 genes—including a number involved in interferon interactions and immune regulation—at each time point.

The authors used statistical analyses to search for gene expression profiles that were associated with patients' therapeutic outcomes. They looked for patterns in analyses of single genes, gene pairs, and gene triplets, and found their model's predictive accuracy increased with gene number. They also looked for genes that showed different expression patterns over the two years based on patient response, time passed, and



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Expression levels of three genes in beta-interferon responders (red) and non-responders (blue)

patient response over time. These analyses identified genes that increased activity independently of clinical response (interferon can activate genes that have no effect on disease), as well as genes that were associated with a good or poor response. Some of these genes were also the best predictors of patient response before therapy was started.

This approach can predict the probability of a good or poor clinical response with up to 86% accuracy. Baranzini et al. offer hypotheses to explain how the observed gene activity might produce the differential responses to therapy—for example, a poor response may stem from downstream signaling events rather than from problems with drug metabolism. But the authors caution that the mechanisms connecting these genetic signatures to specific outcomes—and the mechanisms that produce a positive interferon response—have yet to be established. For now, these patterns should be thought of as markers. Still, these results suggest that doctors could one day tailor MS patients' treatments to their molecular profile, and perhaps take some of the uncertainty out of this capricious disease.

Baranzini SE, Mousavi P, Rio J, Caillier SJ, Stillman A, et al. (2004) Transcription-based prediction of response to IFN β using supervised computational methods. DOI: 10.1371/journal.pbio.0030002

Dispersal or Drift? More to Plant Biodiversity Than Meets the Eye

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Over 250 million years ago (mya), all the continents of Earth formed a single land mass called Pangaea. Some 50 million years later, this supercontinent began to split in two, forming Laurasia—now North America, Asia, and Europe—and Gondwana—present-day Antarctica, Australia, South America, Africa, and India. After another 50 million years, Gondwana, too, broke up. At the end of the Cretaceous period, New Zealand split off (about 80 mya), then South America and Australia

separated from Antarctica (about 35 mya). Fairy-tale quality aside, the story of continental drift fits comfortably with the geological and fossil record and feeds our understanding of current distributions of plant biodiversity.

Although we know how and when Pangaea broke apart, the distribution of fossils of the same species on many different continents, separated by vast ocean waters, challenges us to explain how they got there. Plant life on New Zealand,

for example, shares striking similarities to that on other Southern Hemisphere land masses, but scientists have yet to agree on how this came to pass. In particular, one genus, *Nothofagus*—the southern beech tree, a plant whose 80-million-year-old fossil history goes back to the days of Gondwana—has polarized views on the nature of Southern Hemisphere biogeography.

One theory suggests that geographic barriers (New Zealand and Australia are

separated by the Tasman Sea) would have prevented species expansion after the break-up of the continents, so similar contemporary species must have already existed in both places before New Zealand broke away from Gondwana. In this scenario, called vicariance, ancestors of existing lineages drifted with the repositioned land masses. Another hypothesis, born of existing distributions and fossil data, suggests that long-range oceanic dispersal is more likely. But since *Nothofagus* seeds are not considered ocean-worthy vessels, many believe vicariance is the only possible explanation.

Peter Lockhart and colleagues argue that a clear picture of the divergence dates of various southern beech species could help clarify the relative contributions of vicariance versus dispersal. But they would need significant lengths of DNA sequences to reliably characterize the evolutionary history of each species.

Consequently, Lockhart and colleagues analyzed a 7.2-kilobase fragment of the chloroplast genome (which typically ranges from 110,000 bp to 160,000 bp) for 11 species of three *Nothofagus* subgenera—*Lophozonia*, *Fuscospora*, and *Nothofagus*—from South America, Australia, and New Zealand. Reconstructing the trees' evolutionary relationships (phylogeny) based on analyses of their chloroplast sequences, the authors discovered a nuanced evolutionary history that supports vicariance for some species and dispersal for others.

Assuming that beech was present throughout Gondwana (which fossil data support), the sequence of the



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***Nothofagus*, the southern beech, on the slopes of Mt. Ruapehu in New Zealand (Photo: Peter Lockhart)**

Gondwana breakup should be reflected in the beech's phylogeny. New Zealand beeches should be more distantly related to both Australian and South American species, because of the greater period of separation—65 million years compared to 30 million years. Yet Australian and New Zealand beeches are more closely related to each other than to South American species, which reflects more recent relationships. Given that fossils of all beech subgenera extend back to the New Zealand Cretaceous period, the dating of splits and the nature of the relationships indicate extinction of beech lineages within current subgenera in New

Zealand, and possibly in Australia and South America.

Lockhart and colleagues' analyses suggest that the relationships of the Australian and New Zealand *Lophozonia* and *Fuscospora* species are too recent to have roots in Gondwana, indicating a role for transoceanic dispersal. The evolutionary relationship between the Australasian and South American *Fuscospora* lineages, however, is consistent with vicariance. These divergence results, the authors conclude, indicate that current distributions of *Nothofagus* cannot be explained solely by continental drift (followed by extinction of some species) and that contemporary New Zealand *Nothofagus* species are not direct descendants of the beeches thought to have reached the island after the split from Antarctica.

Taken together, the results highlight the need for caution in evaluating fossil evidence. The fossil record doesn't necessarily capture when a species first appeared, and a continuous fossil presence can mask extinctions and reinvasions. The authors conclude that their molecular data make the case for investigating possible mechanisms of long-range dispersal—especially the dispersal properties of *Nothofagus* seeds—and stresses the need to consider more complex hypotheses to explain something as dynamic and complex as the evolutionary history of biodiversity.

Knapp M, Stöckler K, Havell D, Delsuc F, Sebastiani F, et al. (2005) Relaxed molecular clock provides evidence for long-distance dispersal of *Nothofagus* (southern beech). DOI: 10.1371/journal.pbio.0030014