> The analysis uncovered 233 genetic variants that were associated with increased susceptibility to MS

grouped into 13 'communities' on the basis of interactions among their protein products. Gene expression and epigenomic analyses revealed enriched expression of these genes in a range of peripheral immune cells, including T cells, B cells, natural killer cells, monocytes and dendritic cells, and also in microglia — the resident immune cells of the CNS.

"We have a robust foundation to begin to map the sequence of molecular events that ultimately lead to a diagnosis of MS, after environmental influences and life experiences perturb the immune system in ways that enhance the effects of MS susceptibility variants," concludes De Jager. "We can use this information to develop powerful prognostic tools that will enable us to identify high-risk individuals who would benefit from primary prevention therapies."

Heather Wood

ORIGINAL ARTICLE International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science* **365**, eaav7188 (2019)

> The next step will be to establish how long before conversion to AD this increase in synchronization can be detected

continued to have MCI. In patients who developed AD, synchronization decreased between the first and second MEG recordings, whereas it increased in patients with continuing MCI.

Pusil and colleagues referred to this pattern of change as the 'X' model and suggested that progression from MCI to AD could be heralded by an initial increase in synchronization followed by a decrease in synchronization by the time AD is diagnosed. The next step will be to establish how long before conversion to AD this increase in synchronization can be detected.

"We will continue tracking of the remaining patients with MCI to provide information about the timing of the model, when the hypersynchronization happens and when network breakdown begins," explains Pusil. "This will enhance the utility of the model, providing useful information for designing pharmacological interventions."

Sarah Lemprière

ORIGINAL ARTICLE Pusil, S. et al. Hypersynchronization in mild cognitive impairment: the 'X' model. *Brain* https://doi.org/10.1093/brain/awz320 (2019)

GENE THERAPY

Oligonucleotide designed for ultimate personalized treatment

A custom-designed antisense oligonucleotide has been used to treat a unique form of Batten disease in a single patient in a study recently published in the *New England Journal of Medicine*. The study sets a precedent for rapid development of individually tailored treatment on the basis of genetic sequencing.

The study was led by Timothy Yu at Boston Children's Hospital in the USA, who first encountered the patient — a 6-year-old girl — through social media. She had been diagnosed with Batten disease, an autosomal recessive disorder; her symptoms included loss of vision, falls, dysarthria, dysphagia, seizures and cerebral and cerebellar atrophy.

Genetic testing had revealed one mutation in the *MFSD8* gene, which is associated with Batten disease. However, a second mutation, which is expected when a recessive disorder has manifested, had not been found. Building on his background in whole-exome and genome sequencing and analysis, Yu and his colleagues set out to reach a molecular diagnosis.

"I had a long-standing interest in difficult-to-find mutations as a cause of 'hidden heritability', and I had always been curious about 'half-diagnosed cases' — those 10% of clinically diagnosed cases with what should be a recessive disease, but for which one mutation is missing," explains Yu.

Whole-genome sequencing revealed a deep intronic mutation that had previously gone undetected. Yu's team showed that this mutation altered the splicing of *MFSD8* and reduced expression of the normal gene product. The underlying biology of this mutation was similar to that of the causal mutation in spinal muscular atrophy, a mutation that has been targeted successfully with the oligonucleotide nusinersen. On this basis, Yu and his team worked on the principles of nusinersen to develop a custom-designed oligonucleotide.

"We thought that if we could make a short synthetic stretch of RNA, just like nusinersen, utilizing the same chemical backbone and modifications, we ought to be able to find one that could block usage of our patient's aberrant splice site and restore the full-length gene," says Yu.

> it is possible to design, test and manufacture a drug customized to a patient's genomic sequence

The team designed multiple oligonucleotides to target the *MFSD8* splice variant and singled out the one that most effectively increased normal gene expression in fibroblasts from the patient. The oligonucleotide — which they called milasen — was developed for clinical administration, and permission was obtained from the FDA for its clinical investigation under an Expanded Access Investigational New Drug application.

Treatment of the patient with milasen led to stabilization of her scores on neurological and neuropsychiatric assessments — performance in these tests had previously been deteriorating. In addition, objective measures demonstrated that the number of seizures decreased.

"The major finding here was that it is possible to design, test and manufacture a drug customized to a patient's genomic sequence, and to do it all in a timeframe to be potentially useful for that patient. The speed with which these technologies can be brought to bear has the potential to change the paradigm — especially considering all of the devastating diseases for which even a proof-of-concept treatment has never been attempted," points out Yu. "This type of work also proves the value of a molecular diagnosis. This case is obviously an extreme example, but it certainly drives home the point that it is critical to understand exactly what your mutations are, given the potential treatment ramifications."

Ian Fyfe

ORIGINAL ARTICLE Kim, J. et al. Patient-customized oligonucleotide therapy for a rare genetic disease. *N. Engl. J. Med.* **381**, 1644–1652 (2019)