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MOTOR NEURON DISEASE

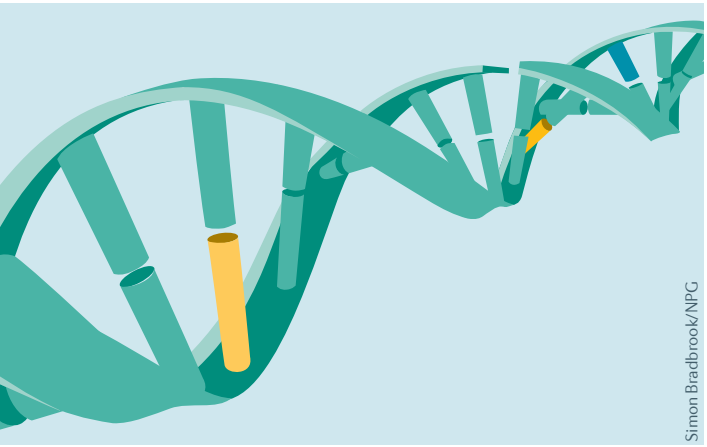
New insights into genetic risk factors for amyotrophic lateral sclerosis

> The studies … provide direct insight into the molecular pathways that are altered in ALS

Two novel studies shed light on the genetic background of amyotrophic lateral sclerosis (ALS). The studies, published in *Nature Genetics*, provide direct insight into the molecular pathways that are altered in ALS.

In the first study, Ammar Al-Chalabi, Jan Veldink and co-investigators set out to detect associations between ALS and millions of single nucleotide polymorphisms (SNPs) across the genome. Via international collaboration, the researchers obtained SNP data from >12,000 individuals with ALS and >23,000 controls.

To test the strength of the associations, the researchers used not only a traditional meta-analysis approach, but also a newer linear mixed modelling approach, which increases statistical power by correcting for undetected relatedness between individuals and for population-based differences in allele frequencies. To exclude false positives, they then replicated the associations in a second set of genomic samples from an independent cohort of 2,579 patients and 2,767 controls.



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After replication, three novel risk loci for ALS were confirmed: *SCFD1*, involved in vesicle transport; *MOBP*, the variants of which have been linked to supranuclear palsy; and *C21orf2*, which codes for a mitochondrial protein that is presumed to have a role in several cellular functions, such as DNA repair and maintenance of the cytoskeleton.

"We also found evidence that the genetic architecture of ALS is different from conditions such as Alzheimer disease or schizophrenia, in which multiple small-effect variants add up to create risk," says Al-Chalabi. In ALS, one or a few large-effect, relatively rare variants in each person seem to contribute most to the risk. As a result, personalized medicine, such as gene therapy or pharmacological treatments targeting the relevant pathway in an individual patient, could be feasible in future; however getting such therapies on the market is not necessarily straightforward, as any given target would likely be present in only a few people.

"It should also be noted that the three genes we identified in this study are risk factors, but not sufficient on their own to cause ALS," Al-Chalabi comments. "Testing an individual for these genes is, therefore, currently not useful."

In another study, Veldink, John Landers and co-workers used exome-wide rare variant burden analysis to determine the combined frequency of rare variants in all genes in a case–control cohort of >1,000 index patients with familial ALS (FALS) and >13,000 controls. "We decided to use 10 well-established ALS genes as a training set to identify the best combination of allele frequency cut-off, and then applied the optimized settings to our patient cohort," Landers explains.

NEK1 showed exome-wide significance for association with FALS. "By our estimates, ~3% of patients with ALS carry a risk variant in *NEK1*", says Landers. Loss-of-function *NEK1* mutations were the most common form of detected ALS-associated variations.

Interestingly, one of the genes identified in the study by Al-Chalabi and colleagues, *C21orf2*, interacts with *NEK1*. Like *C21orf2* — and several previously identified ALS-associated genes — *NEK1* is involved in cytoskeletal dynamics.

Both Al-Chalabi and Landers point out that functional characterization of the protein products of the new-found risk genes is an essential step towards targeting ALS-associated pathways. In the meantime, they also continue genetic studies of ALS, and emphasize the importance of international collaborations, such as Project MinE, which is partly funded by donations from the 2014 Ice Bucket Challenge campaign.

"Obtaining genetic samples and funding have been the limiting factors," says Al-Chalabi. "Worldwide collaboration has allowed us to increase sample numbers and use funds more efficiently."

Hemi Malkki

ORIGINAL ARTICLES van Reenen, W. *et al.* Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat. Genetics* http://dx.doi.org/10.1038/ng.3622 (2016) | Kenna, K. P. *et al. NEK1* variants confer susceptibility to amyotrophic lateral sclerosis. *Nat. Genetics* http://dx.doi.org/10.1038/ng.3626 (2016)