Studies confirm region of chromosome 9 linked to risk for amyotrophic lateral sclerosis

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Genetic variations on chromosome 9 have been identified that might have a role in the development of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. Findings in two separate Articles published Online First in The *Lancet Neurology* add to the evidence that a region of chromosome 9 is linked to a higher risk of ALS across multiple populations.

About 5-10% of ALS (also known as motor neuron disease or Lou Gehrig's disease) is hereditary. A few genes have been linked to ALS, but these explain only a small proportion of familial cases. The cause of the more common sporadic ALS remains largely unknown. Several recent genome-wide association studies (GWAS) have identified a number of possible susceptibility genes, but replication of these associations has not been successful in independent studies. In 2006, linkage between familial ALS and chromosome 9 was first identified in Scandinavian families. However, subsequent research has not revealed a disease-causing gene variant.

In the first Article, Bryan Traynor from the National Institutes of Health, USA, and international colleagues did a GWAS to identify genetic risk factors for ALS in the Finnish population.

318 167 DNA variations known as single nucleotide polymorphisms (SNPs) were analysed in the genome of each of the 405 patients with

ALS (93 familial and 312 sporadic) and 497 controls.

The researchers found two genetic variations that contribute to risk of ALS. One was identified in the SOD1 gene, which has previously been associated with risk of ALS, on chromosome 21q (rs13048019), and the other was on chromosome 9p (rs3849942). One or other of these variations was found in more than 70% of patients with a family history of ALS, thus explaining a substantial proportion of familial ALS in Finland.

Additionally, the investigators defined a group of 42 SNPs (a 42-SNP haplotype) on chromosome 9p (shared by 44% of patients with familial ALS and 19% with sporadic ALS) that was linked to a significantly increased risk of ALS in the Finnish population. The shared haplotype also suggests a possible founder effect for the chromosome 9p locus in Finland.

The authors conclude: "The chromosome 9p21 locus is a major cause of familial ALS in the Finnish population".

Chromosome 9 locus was also found to be associated with ALS in a second Article. Ammar Al-Chalabi from King's College London, UK, led an international team in a two-stage GWAS to try and identify genetic variations responsible for increased risk of ALS. The researchers began by examining DNA samples from 599 patients with sporadic ALS and 4144 controls from the UK. They analysed SNPs to test previously reported genetic associations for ALS risk. Two specific genetic markers (rs3849942 and rs2814707) showed an association with sporadic ALS, both located on chromosome 9p.

To search for new genetic signals that would otherwise be difficult to detect, the researchers also did a joint analysis (the largest GWAS of ALS to date), combining the UK samples with an additional 4312

patients with ALS and 8425 controls from seven other countries.

Chromosome 9p21.2 was the only significantly associated locus identified; this locus has also been previously linked with frontotemporal dementia. Importantly, none of the SNPs in the ITPR2, FGGY, DPP6, and UNC13A genes previously reported to be associated with ALS achieved significance. The authors say that the lack of replication of previously associated SNPs suggests that these might have been false-positive or population-specific results.

The authors conclude: "We have found strong evidence of a genetic association of two single SNPs on chromosome 9 with sporadic ALS, in line with findings from previous independent GWAS of ALS."

In a Comment, Guy Rouleau and colleagues from the University of Montreal in Canada say: "Although the results presented here must be interpreted with caution, both studies identified a linkage disequilibrium block in the chromosome 9p21 locus, suggesting that a variant in this genomic interval might have a role in ALS and possibly frontotemporal dementia. However, because patients with familial chromosome 9p-linked ALS—frontotemporal dementia do not share a common haplotype, multiple variations, and thus multiple founders, are probably involved."

More information:

-- www.thelancet.com/journals/lan … (10)70184-8/abstract
-- www.thelancet.com/journals/lan … (10)70197-6/abstract

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