

# Next Generation Gene Hunting in Amyotrophic Lateral Sclerosis

<https://www.neurodegenerationresearch.eu/survey/title-of-pinext-generation-gene-hunting-in-amyotrophic-lateral-sclerosis/>

## Title of project or programme

Title of PI Next Generation Gene Hunting in Amyotrophic Lateral Sclerosis

## Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
-------	---------	---------	-------------	---------

Dr	Christopher	Shaw	King's College London	UK
----	-------------	------	-----------------------	----

## Address of institution of lead PI

Institution King's College London

Street Address Institute of Psychiatry, De Crespigny Park

City London

Postcode SE5 8A

## Country

- United Kingdom

## Source of funding information

Medical Research Council

## Total sum awarded (Euro)

1889221.58

## Start date of award

01-11-2009

## Total duration of award in months

48

## The project/programme is most relevant to

- Motor neurone diseases

## Keywords

### Research abstract in English

Amyotrophic lateral sclerosis (ALS, also known as motor neurone disease) causes progressive paralysis and takes the lives of 1,200 people in the UK every year. There are no effective treatments and little is known about its causes. Most ALS is sporadic but in 10% it is clearly familial (FALS), due to a single gene mutation inherited in an autosomal dominant fashion. Clinically and pathologically,

familial and sporadic ALS are indistinguishable and many cases of sporadic ALS may be caused by gene defects with low penetrance. Most genetic neurodegenerative disorders are due to mutations that cause a change in the amino acid sequence. Four genes known to cause ALS account for only 25% of familial and 7% of sporadic ALS. We aim to identify the remaining FALS genes in order to offer comprehensive counselling and gene testing to at-risk families and concerned individuals with apparently sporadic disease. This will dramatically improve our understanding of disease pathogenesis and significantly advance drug discovery.

Here we propose an unprecedented gene hunting effort using revolutionary techniques including DNA capture, deep resequencing and high-density SNP genotyping. Using an initial cohort of cultured lymphoblast lines from 100 FALS cases we will extract high quality DNA, RNA and protein. Using the Nimblegen 2.1m array we will capture ~180,000 exons (comprising ~70% of the human genome) for sequencing on the Solexa GAII. We will also perform high density SNP genotyping on the Illumina Quad650 arrays looking for ancient common founder mutations. Lastly we will target genes implicated in pathways implicated in ALS pathogenesis not represented in the Nimblegen arrays.

Our five criteria for prioritising variants are those that (i) change the amino acid sequence, (ii) segregate with disease within kindreds, (iii) affect multiple families, (iv) have multiple mutations in multiple families and (v) have a low mutation frequency in multiple control populations. Variants that meet these criteria will be confirmed by Sanger sequencing and compared to the controls in SNP databases. Genes with confirmed mutations will be screened in a second cohort of local familial (200) and sporadic cases (2,000). We will notify our FALS Network partners of the most promising genes (frequency 1%) and request screening in their FALS and SALS cohorts to determine their global frequency and ethnic variation. Having identified mutations with a high likelihood of pathogenicity we will test for toxicity in cell lines, primary neurons and simple animal models (embryonic chicken and zebrafish).

### **Lay summary**

#### **In which category does this research fall?**

- Basic research