GENETIC ADVANCES IN AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEMENTIA

A Hexanucleotide Repeat Expansion in C9ORF72 is the Cause of Chromosome 9p21-Linked ALS-FTD

CONTENTS

THE GENE

Chromosome 9p21 locus = chromosome 9, short arm, region 21

- Contains a six-nucleotide (hexanucleotide) repeat expansion: GGGGCC
- This repeat expansion is present in the **intron** of the gene C9orf72
- This gene codes for the C9orf72 protein, which is found in the CNS (function unknown)
- Present in everyone, but pathological in high numbers of hexanucleotide repeats

The discovery of mutations in this gene provides:

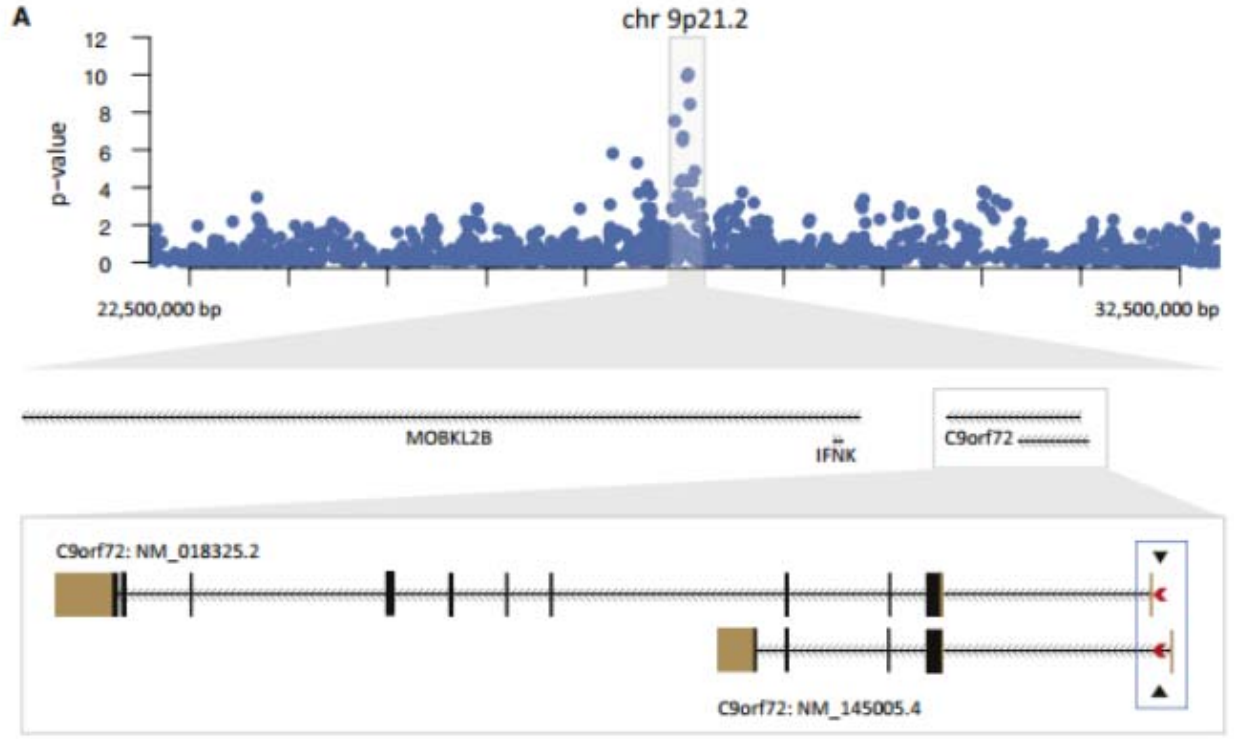
- A link between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)
- A genetic cause for many cases of familial and sporadic ALS
  - Repeat is present in 1/3 of familial ALS cases of outbred European descent and so is the most common cause of ALS identified, as of yet

SEQUENCING METHOD

Next-generation sequencing identified mutation

- Allows for sequencing of millions of small DNA fragments at the same time, unlike previous methods that could only sequence one fragment
- Vast amounts of computer data produced (difficult to translate this data into clinical information)
- The authors sequenced chromosome 9p21
  - DNA from affected member of familial line of ALS and DNA from an unrelated normal control
  - DNA from affected and unaffected family members
- Identified a mutation on the **intron** of C9orf72, which displays a drawback of exome sequencing

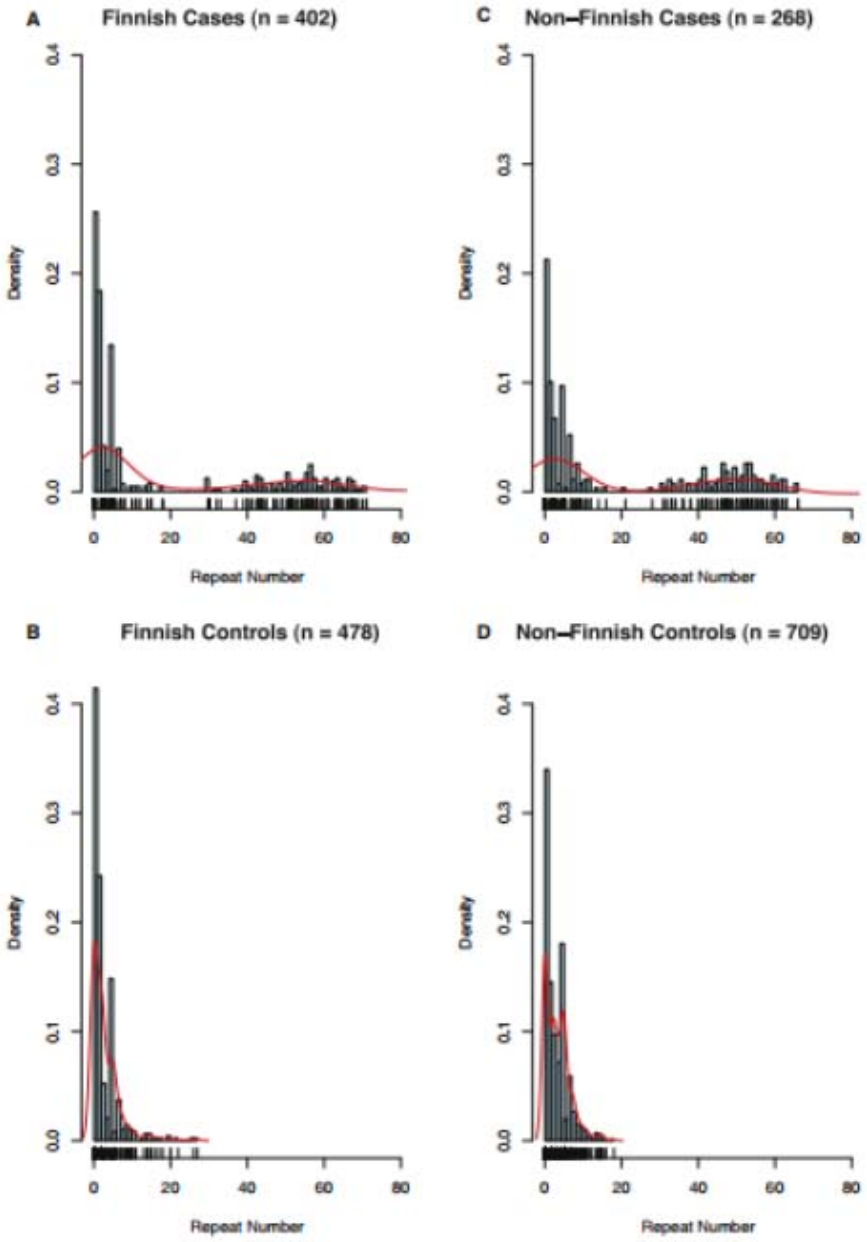
MAP OF CHROMOSOME 9P21



OVERVIEW

Finnish population

- Repeat expansion causes 46% of familial ALS and 21.1% of sporadic ALS
- 87% of familial ALS in Finland can now be explained by two genetic mutations (C9orf72 and D90A SOD1)
- Repeat highly associated with FTD (of note, 36.4% of Finish FTD cases had a personal or family history of ALS)
- Repeat expansion was not present in control individuals
- C9orf72 RNA found in CNS tissues – highest level found in cerebellum
- FISH analysis showed mutation is large in size – usually associated with pathology



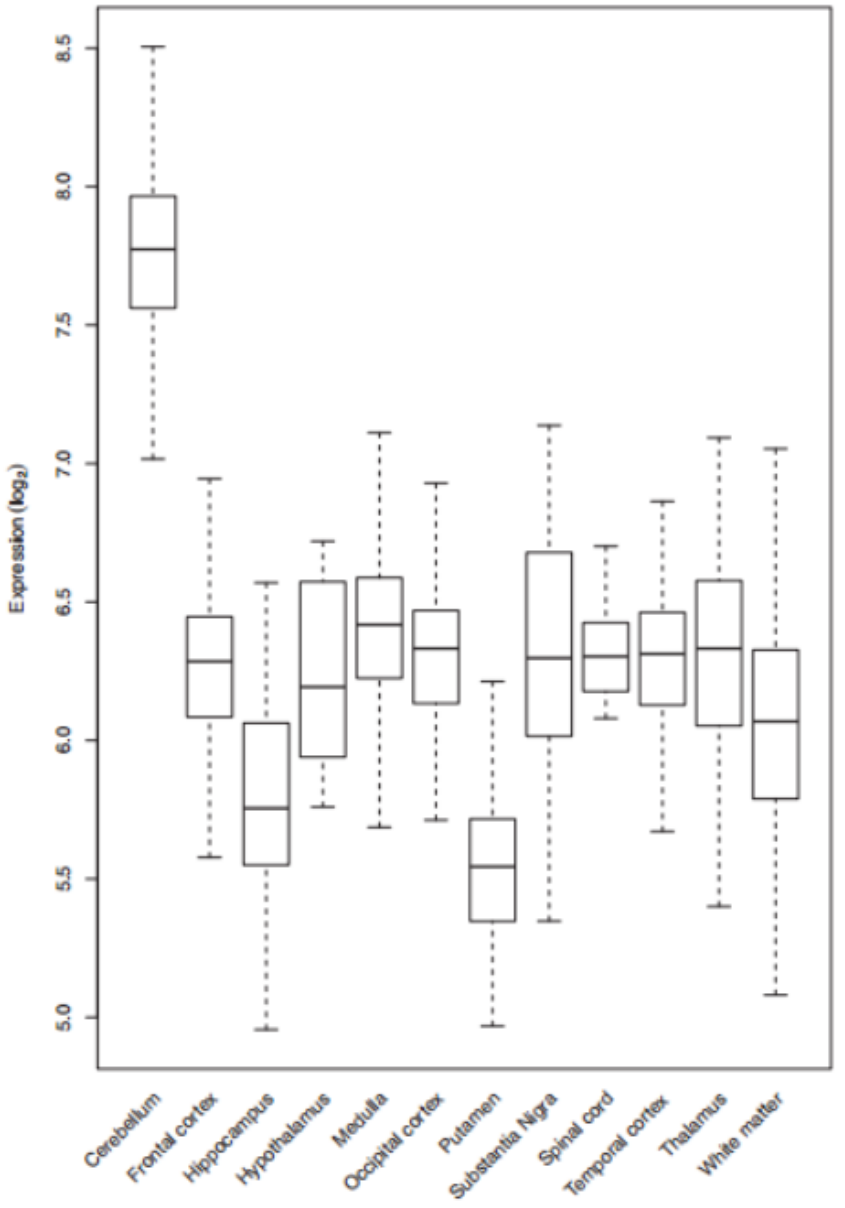
LOCATION OF C9ORF72 RNA FROM NEUROPATHOLOGY - EXPRESSION ARRAYS

RNA taken from tissue specimens of unaffected individuals

Various presentation of disease may be explained by expression of RNA in different areas of brain and spinal cord

Provides evidence that the gene is expressed in CNS tissues

No definite increase in RNA levels found in normal and affected individuals



CONCLUSION

Repeat expansion in C9ofr72 is a **monogenetic** cause of chromosome 9p21-linked ALS-FTD

Difficult to assess multifactorial diseases with many SNPs

Must consider penetrance

Does having the mutation always mean the pathology will develop?

Research into the genetics of disease is advancing hugely

New techniques are faster and allow for more DNA fragments to be sequenced

More mutations out there waiting to be discovered

QUESTIONS?