

# Mapping of ancestral segments commonly inherited among Irish sporadic ALS patients.

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## Introduction

- ALS is a fatal, progressive neurological disease characterised by the loss of motor neurons.
- 10% of ALS develops through mendelian inheritance while 90% occurs sporadically.
- Sporadic ALS (SALS) is thought to have a genetic component but to date this is poorly understood.
- One method to map the potential locations of recessive and poorly penetrant mutations is by mapping shared regions of homozygosity (ROHs) among ALS patients.

## Loss of Heterozygosity

- Genome-wide analyses of SNPs in humans have led to the appreciation that there are many regions of commonly inherited genetic material.
- These are termed regions of homozygosity (ROHs)
- When extended these regions suggest that an individual's parents share a common ancestor.
- Therefore identifying these commonly inherited regions in ALS patients will potentially map the location of recessive mutations.
- ROHs are extensive in the Irish as there are relatively fewer generations to our founding ancestors.

## Aim

- To identify regions of the genome shared by Irish ALS patients which are not found in controls.

## Methods

- 221 Irish patients and 211 Irish controls were included. See Table 1.
- Over 500,000 SNPs were genotyped using Illumina HumanHap genome-wide chips
- PLINK was used to identify regions of homozygosity (ROHs)
- ROHs were considered recurrent when they were observed in more than two participants and ALS-specific when they did not overlap with ROHs seen in controls

Table 1 – Characteristics of the study population.

Study Populations	Total	Male/female (%)	Mean age at onset (±SD)	Spinal onset (%)	Bulbar onset (%)
Patients with sporadic ALS	221	54/46	61	72	28
Controls	211	53/47	58		

## Results

- The number and average length of ROHs did not differ between cases and controls. See Table 2.
- The number of recurrent ALS-specific ROHs was greater than the number of recurrent control-specific ROHs (p = 0.001)
- Recurrent, ALS-specific ROHs were identified in 16 genes spanning the genome.** See Table 3.

Table 3 - Recurrent, ALS specific regions of homozygosity in the Irish population.

Chr	ALS (n)	Control (n)	Gene ID	GeneName	Putative role in ALS
15	7	0	AKAP-13	A-kinase anchor protein 13	Signal transduction and scaffolding
7	7	0	KCND-2	Potassium voltage-gated channel shal-related	KCND-2 rapidly inactivating outward K channel
7	7	0	TSPAN-12	trans-membrane-4 superfamily-1	TSPAN-12 involved cell development, signal transducer
14	7	0	GPHN	Gephyrin	Neuronal assembly protein anchoring inhibitory neurotransmitters
13	6	0	DACH1	Dachshund homolog 1	Determines cell fate in the eye and nervous system of Drosophila
2	6	0	FLJ42562	Hypothetical protein	~
7	6	0	Intergenic	~	~
2	5	0	DPP10	Dipeptidylpeptidase 10	Binds voltage-gated K channels altering expression and biophysical properties
14	5	0	PPP2R5E	Epsilon isoform of regulatory subunit B56	Various
14	5	0	WDR89	WD repeat domain 89	Various
14	5	0	SGPP1	Sphingosine-1 phosphatase	Various
14	5	0	SYNE2	Spectrin-repeat containing nuclear envelope 2	SYNE2 implicated in Emery-Dreyfus muscular dystrophy
3	5	0	IMPG2	Inter-photoreceptor matrix proteoglycan 2	Various
3	5	0	SEN7	Sentrin protease 7	Various
11	5	0	GRM5	Glutamate receptor, metabotropic 5	Evolutionarily conserved glutamate receptor
8	5	0	SGCZ	Sarcoglycan zeta	Component of dystrophin-associated glycoprotein complex for cell integrity
2	5	0	FLJ16124	Hypothetical protein	~
11	5	0	Intergenic	~	~

Table 2 – Number & Average length of ROHs in cases and controls.

Per individual	ALS (n=203)		CONTROL (n=204)		Comparison n p value
	Mean (Std dev)	Median (range)	Mean (Std dev)	Median (range)	
Number of LOH regions	39.1 (±5.9)	39 (23-57)	39.6 (±5.9)	39.5 (24-56)	0.41*
Total span of LOH across the genome	35.8 Mb (±6.9)	35.3 Mb (19.8-53.4)	36.2 Mb (±6.2)	35.6 Mb (21.9-53.6)	0.51**
Mean length of each ROH	915 Kb (±112)	893 Kb (671-1477)	916 Kb (±94)	904 Kb (698-1265)	0.49**

## Discussion

- We mapped 16 genes showing evidence of shared ancestry in at least five Irish ALS patients
- Several of these loci are biologically plausible candidates for ALS pathogenesis, including:  
two potassium channel receptors,  
a glutamate receptor,  
and several genes involved in neuronal integrity and signalling
- This is the first study to map ALS genes by ROH methods
- The next step will be to sequence these genes in those harbouring shared ancestral segments to identify variably penetrant recessive mutations