Finding new genes causing motor neuron diseases

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Statement of authenticity

No part of the work described in this thesis has been submitted in fulfilment of the requirement for any other academic degree or qualification. Except where duly acknowledged, all experimental work was performed by the author.

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Abstract

Neurodegenerative disorders are a diverse group of disorders that affect specific subsets of neurons. Motor neuron diseases, neurodegenerative disorders of motor neurons, are seen commonly as sporadic cases and less frequently as familial disease forms. The familial forms show genetic and phenotypic heterogeneity. Clinically motor neuron diseases may be seen as rapidly progressive disorders like amyotrophic lateral sclerosis, ALS or slowly progressive disorders like hereditary motor neuropathies, HMN.

The only proven causes for motor neuron diseases are gene mutations that lead to motor neuron degeneration in familial disease forms. Only some of these genes have been identified and have contributed greatly to our understanding of the neurobiology of familial and sporadic disease forms. Identification of additional disease causing genes would help enhance our knowledge of the pathophysiological mechanisms underlying all forms of motor neuron disorders, which would lead to early diagnoses, effective prophylaxis and efficient therapies for these disorders.

This study aimed to find gene mutations that cause rapid and slowly progressive familial motor neuron disorders in Australian families and to determine their relevance to sporadic forms of motor neuron disease.

The familial forms of ALS show reduced disease penetrance, that is, not all gene mutation carriers manifest the disease. This study examines ALS penetrance in a group of Australian families. The most frequently observed mutations in ALS families are

cytosolic superoxide dismutase/SOD1 gene mutations. In a collection of ALS families in our centre, families without the common SOD1 gene mutations were genotyped for other ALS genes and loci and studied using genetic linkage and haplotype analyses. Studies in a large Australian ALS family further confirmed genetic heterogeneity in non-SOD familial ALS, all known autosomal dominant ALS genes and chromosomal loci were excluded as cause of disease in this family. Such families can be studied further to identify additional disease genes and loci mapped in other ALS families. These families represent powerful resources for identification of additional ALS genes. Identifying the pathogenic genes in families with reduced disease penetrance may be more relevant to sporadic forms of disease.

dHMN is a chronic neurodegenerative disorder predominantly affecting motor neurons. In a large Australian dHMN family, all the known dHMN genes and chromosomal loci were excluded as cause of disease. A genome wide microsatellite screen was performed in this family and genetic linkage was established to a novel 12.98 Mb locus on chromosome 7q34.2-q36. Candidate genes in this large interval will be screened based on their function and expression profile. Identification of a new dHMN locus provides the basis for future identification of a novel gene involved in motor neuron degeneration.

Genes in dHMN have been shown to be pathogenic in ALS and Charcot Marie Tooth syndromes. The new locus for dHMN mapped in this project would lead to identification of a novel dHMN gene, which may elucidate the pathogenesis underlying a wide range of neurodegenerative disorders.

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Publications

Papers

Identification of a new locus for distal hereditary motor neuropathy on chromosome 7q34.2-q36. Submitted for publication to Neurology.

Genetic causes of ALS: review article. Submitted to the International journal of Neuroscience.

Haplotype studies in small ALS families support genetic heterogeneity in familial ALS. (in preparation)

Disease penetrance in familial ALS varies from high tolow merging with sporadic disease. (in preparation).

Abstracts

Finding new genes causing diseases of motor neurones. Presented at the Genome Conference, Lorne, Victoria, Australia, February 2004.

Localising new genes causing Amyotrophic Lateral Sclerosis. Presented at the Genome Conference, Lorne, Victoria, Australia, February 2004.

Searching for a chromosomal locus for distal hereditary motor neuropathy in an Australian family. Presented at the University of Sydney, Fourth research conference 2004: "From Cell to Society 4" at Leura, NSW, November 2004.

Finding new genes causing amyotrophic lateral sclerosis. Presented at the 15th International ALS/MND symposium, Philadelphia, December 2004.

Searching for a new locus associated with hereditary motor neuropathy. Presented at the University of Sydney, Neuroscience Showcase, August 2005.

Haplotype studies in small ALS families: usefulness in the search for new genes causing ALS. Presented at the 18th World Congress of Neurology, Sydney, November 2005 and the 16th international ALS/MND symposium Dublin, December 2005.

Search for a novel chromosomal locus causing distal hereditary motor neuropathy in an Australian family. Presented at the 18th World Congress of Neurology, Sydney, November 2005.

Haplotype studies are useful in small ALS families to search for new gene mutations. Presented at the 26th annual meeting of the Australian Neuroscience Society, Sydney, January 2006.

Novel chromosomal locus for a form of distal hereditary motor neuropathy. Presented at the annual meeting of Australian Neurologists, Canberra, May 2006. Awarded the James Lance Young Investigator award for best oral presentation.

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Abbreviations

AD	Autosomal dominant
AGRF	Australian Genome Research facility
ALS	amyotrophic lateral sclerosis
AOA2	Ataxia ocular apraxia -2
APEX nuclease	Apurinic/apyrimidic endonuclease
AR	Autosomal recessive
CMAP	Compound Muscle action potential
CMT	Charcot Marie Tooth syndrome
CNTF	Ciliary neurotrophic growth factor
CRGH	Concord Repatriation General Hospital
CSAHS	Central Sydney area health service
CSF	Cerebrospinal fluid
DCTN1	Dynactin 1
dHMN	Distal hereditary motor neuropathy
DNA	Deoxyribonucleic acid
dNTPs	deoxynucleotide triphosphates
EAAT2	Excitatory amino acid transporter 2
EBV	Ebstein Barr virus
EDTA	Ethylene diamino tetra acetic acid
EMG	Electromyography
FALS	Familial ALS
FDA	Federal drug authority
FTD	Fronto-temporal dementia
GC content	Guanine and cytosine content
HLA	Human leucocyte antigens
HMN	Hereditary motor neuropathy (ies)
HSP	Heat shock protein
LL	Lower limbs
LOD	Linkage of odds
MEP	Magentic evoked potentials
MND	Motor neuron disease
NAIP	Neuronal apoptosis inhibitory protein
NF	Neurofilament
NIPPV	Non-invasive intermittent positive pressure ventilation
OMIM	Online Mendelian inheritance in man
PAGE	Polyacrilamide gel electrophoresis
PCR	Polymerase chain reaction
PD	Parkinson's disease
PON	Paroxonase
RFLP	Restriction fragment length polymorphisms
RNA	Ribonucleic acid
SALS	Sporadic ALS
SMA	Spinal muscular atrophy
SNAP	Sensory Nerve action potential
SOD1	Superoxide dismutase 1
SPG	Spastic paraplegia

TE	Tris EDTA
tRNA	Transfer RNA
UBI	Ubiquinated inclusions
UCSC	University of California at Santacruz (Human Genome browser)
UL	Upper limbs
VAPB	Vesicle associated membrane protein B and C
VEGF	Vascular endothelial growth factor