Sporadic and familial

Clinically the sporadic and familial forms of MND are indistinguishable.

- familial MND accounts for about 5-10% of all MND cases
- MND is sporadic in about 90-95% of cases, developing for no apparent reason (MND Australia 2014).

Turner and others 2013

Two decades after the discovery that 20% of familial amyotrophic lateral sclerosis (ALS) cases were linked to mutations in the superoxide dismutase-1 (SOD1) gene, a substantial proportion of the remainder of cases of familial ALS have now been traced to an expansion of the intronic hexanucleotide repeat sequence in C9orf72.

Ravits and others 2013

Five to 10% of ALS is genetically transmitted mainly by way of dominant gene mutations and these numbers increase to as high as 15–20% when known genes are tested in patients who were thought to have sporadic disease. Approximately 60–70% of FALS pedigrees have genes that have now been identified, the main ones being SOD1, TARDBP, FUS, C9ORF72, OPTN, VCP, UBQLN, and PFN1 (reviewed in (65)). Clinical phenotype heterogeneity of FALS is as characteristic and as vast as SALS, and no clinical features easily distinguish one from another. Remarkably, this clinical phenotype heterogeneity is even seen in the same mutation in the same gene in the same kinship, implying phenotype is likely determined by factors other than the molecular cascade it triggers. However, some trends exist. Mutations in SOD1 and FUS tend to cause predominantly LMN syndromes. Mutations in TARDBP tend to begin in the upper extremity and to progress slower than average (66). Mutations in SOD1, TARDBP and FUS cause mostly motor syndromes and only rarely associated FTD. Mutations in FUS cause a juvenile as well as adult motor neuron disease syndrome. Mutations in C9ORF72 are as likely to cause FTD as ALS, often with psychosis. The ‘A4V mutation in SOD1 ALS is rapid while the ‘D90A’ mutation, unusual in that it is recessive, slow and indolent.

Orrell 2010

Several genes are linked to classical ALS, in particular SOD1 (copper/zinc superoxide dismutase), TARDBP (TAR DNA-binding protein 43) and FUS (fused in sarcoma/translated in liposarcoma), together with genes linked to other motor neuron disorders.

There is the consideration whether, for example, ALS/MND associated with SOD1 mutations is a specific disorder, which may respond to specific treatment.

In clinical practice, it is assumed that all ALS/MND patients will respond similarly to potential treatment, but it is important that in future, patients with specific genetic mutations are identified and analysed as subgroups. It may be that some gene-directed therapies will be targeted on specific genetic conditions.

Benatar and others 2009

Approximately 5% to 7% of ALS/MND patients report a family history of a similarly affected relative. Superoxide dismutase-1 gene mutations are the cause in about 20% of familial cases. In those with non-familial (sporadic) ALS/MND the cause is unknown.

There was no statistical evidence for a different response to treatment in patients with familial ALS/MND compared to those

with sporadic ALS/MND.

Future RCTs should document whether patients with familial ALS/MND are included and the presence or absence of a mutation in the superoxide dismutase-1 gene amongst those with familial ALS/MND.

Chio and others 2009

Most studies have not found any differences in outcome between patients with sporadic and those with familial. However, it is now generally accepted that different mutations of Cu/Zn superoxide dismutase (SOD1) have different effects on the age of onset of symptoms and on the rate of progression of the disease.

For example, A4V mutation is associated with an extremely rapid decline, with a mean survival of 12 months, whereas E21G, G37R, D90A G93C, and I113T mutations determine a more benign course, with a median survival >80 months). In most instances, clinically mild mutations are characterized by a prevalent lower motor neuron disease, with few or no pyramidal signs. Furthermore, some mutations, such as I113T, are characterized by large intrafamilial variations both in age of onset and in clinical phenotype, indicating the presence of modifying factors that may either be genetic or environmental in nature. A systematic analysis of the different phenotypes of SOD1 mutations is still lacking.