



Introduction

Following diagnosis of a relative with motor neurone disease other family members may express understandable anxiety and ask: "Will I get it too?" This factsheet attempts to provide some answers to that question. You should also read and understand factsheets 1B and 3 in this series to gain full understanding of how and why MND can be inherited.

MND is an umbrella term that describes the symptoms of the disease processes rather than the cause of the disease. In the same way that a rash can be a symptom of an allergy to something you have been in contact with, have eaten or have washed your clothes in, MND can be the result of a number of different causes of motor-neurone deaths (also called "cellular pathologies".) These different pathologies suggest that there may be several different causes of the severe motor neurone loss and damage that is diagnosed as MND

The different forms of MND are sometimes grouped by clinicians according to where the first symptoms appear and whether the disease includes damage to upper motor neurones alone, lower motor neurones alone or involves both upper and lower motor neurones. What clinicians cannot include in their diagnosis is what, exactly, is the underlying cause of the death of these cells, since such an investigation would cause unacceptable damage to the person's nervous system.

The four commonest forms of MND are listed in the table below, along with the approximate percentage of MND patients affected by each form of the disease. Little is known about the genetics of the latter three forms (Bulbar Palsy, Progressive Muscular Atrophy [PMA] and Primary Lateral Sclerosis [PLS],) therefore the bulk of the known genetic information relates to the form of MND known as ALS (Amyotrophic Lateral Sclerosis.)

(See factsheet number 1 "What is MND?" for more information.)

Form of MND	% of Patients
ALS	65
Bulbar	25
PMA	7.5
PLS	~1

Ninety to ninety-five percent of MND cases are described by specialists as "sporadic MND." The term "sporadic" means that the disease has occurred in isolation and no other family member is known to have, or have had, MND before the current person was diagnosed. If there is no prior history of MND in the family the first known occurrence is most likely to be a sporadic form of the disease.

Familial ALS is suspected when ALS has affected at least two blood relatives of a family, more so when they are in different generations. About 5 to 10% of all ALS cases are "Familial" in origin and the family will probably already know of other blood relatives who have previously been diagnosed with the disease. Medical

MND Scotland is the working name of the Scottish Motor Neurone Disease Association, the only charity funding research and providing care and information for those affected by MND in Scotland.

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scientists consider “familial ALS,” often abbreviated to FALS, as a “rare” disease.

At the time of production of this factsheet (November 2008) there appears to be agreement among medical scientists that for all practical purposes FALS is clinically indistinguishable from the much more common sporadic ALS. In both familial and sporadic ALS the rate of progression of the disease varies from individual to individual.

Is There A Genetic Component In FALS?

The simple answer to this question is, “Yes, there is a genetic component to FALS that can be transmitted at the time of conception from parent to child.” However, understanding the inheritance of FALS isn’t as straightforward as in other inherited diseases.

ALS is considered to be a “life limiting” illness. As such, it is often the person’s last illness. However, many people who carry the ALS related genes die of some other cause long before their ALS susceptibility becomes evident. It is for this reason that ALS sometimes appears to “skip” generations. Typically people with inherited MND will show their first symptoms between 40 and 55 years of age. Yet it is recorded that a lady with familial MND did not show symptoms until she was 92 years of age, while another sufferer of familial ALS first showed symptoms when she was 13. 80 years of life between them. Diabetes, heart disease, a road accident or stroke could well have claimed the life of the former patient, but they didn’t. It is probable many people have died of other causes without ever suspecting they carried a gene for this disease.

The published studies of the genetics of familial ALS usually involve relatively small numbers of patients; therefore the addition of only one or two extra people to the study group can greatly influence the resultant statistics. For this reason alone there is doubt about the precise percentage of inherited cases and the range of 5 – 10% is generally accepted as reflecting both the highest and lowest percentages found in various studies.

In the year 2005 120 people who had been diagnosed with MND died in Scotland. Overall 55,747 died in Scotland that year. Dividing the first total into the second reveals that MND is involved in one in 465 deaths. About $\frac{2}{3}$ of the 120 MND patients would have had ALS and if we accept the higher figure of 10% of ALS cases being due to familial ALS, then about 8 of those who died in 2005 might have had familial ALS.

With only 8 cases per year (at most) in a population of just over 5 million people it is obvious that statistical studies of FALS will be difficult in Scotland as there are not enough patients to give good statistical results.

What Genes are Involved in ALS?

At the time of writing 24 genes are suspected to be involved in ALS. One of these genes, the so called “SOD1” gene (its full name is copper-zinc-superoxide dismutase 1) has been shown to be responsible for up to 30% of all familial cases of ALS. The other 70% or so of FALS cases might be due to any one of several other candidate genes. Of the 24 genes thought to be involved in ALS 16 are associated with familial (inheritable) conditions and 8 are associated with sporadic conditions.. However, this is not the whole picture. (See factsheet number

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3 “Introducing Genetics” for further information.)

Of the 16 genes associated with FALS, about 8 of them are associated with specific forms of the disease that run in particular families or populations. For example, the gene for ALS 8 was introduced to Brazil by a Portuguese emigrant in the early 19th century and affects only his descendants. The gene for ALS 2 is a recessive gene and only manifests its effects when a person has 2 defective copies of the gene - a situation most often associated with children produced by the intermarriage of cousins in certain North African people. Similar “particulars” relate to the other numbered forms of ALS. In consequence the conditions known as ALS 2, through to ALS 8 tend to be associated with identifiable groups or families. For the majority of people in Scotland the question is do they have sporadic ALS, or familial ALS, both of which are considered to be variants of ALS 1.

What Is The Possible Role Of Sod1 Genes In MND/ALS?

Free radicals are molecules, which are normally “mopped up” within cells by substances such as SOD1, which are known as “antioxidants”. Free radicals are damaging to DNA, protein and fat in cell membranes and are implicated in a wide range of diseases.

The healthy protein made by the SOD1 gene is used to eliminate free radicals of oxygen from the body. Researchers suggest that mutated SOD1 genes may impair removal from motor neurone cells of these free radicals. This failure could have serious effects due to the damage the free radicals might cause, but the mutated protein might be of greater

importance in the wider picture of the disease.

Proteins resulting from mutated genes are of similar or greater importance than free radicals as they might have biological effects their “normal” forms do not. This is known as a “gain of function.” Some studies suggest mutated SOD1 appears to have gained the function of being difficult to break down, causing it to build up and poison the cells in which it accumulates. While certain SOD1 mutations appear to function normally in the removal of oxygen free radicals, being as effective as normal SOD1, they still seem to be toxic to the cell that contains them. Meantime other SOD1 mutations are both unable to remove oxygen free radicals are equally toxic to the cell.

WHAT ARE THE ROLES OF OTHER “CANDIDATE GENES”?

Although every gene makes a protein; in many cases the proteins made by the candidate genes are not yet known, and in those cases where the protein product has been identified the protein’s role is still unknown.

However, looking at this question from the opposite side we know there are many processes which go wrong in MND, but we do not know what genes are responsible for controlling these processes. We can therefore guess that some of the candidate genes for which a function is unknown might be responsible for some of the malfunctions for which a gene is unknown.

Since genetic MND research is still in its very early stages we can also suppose there are genes and processes responsible for MND still to be discovered

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that will eventually pair up to explain the majority of MND cases.

Just as we need to take in food and oxygen and move them around the body to release energy, so a nerve cell also needs to take in food and oxygen for the same reasons. The food and oxygen used by the nerve cell have already been partially prepared by our own digestive system and put into the bloodstream by our lungs. And, as we use hormones and other chemicals to send signals around our bodies telling them when to do certain things, such as controlling sugar levels in blood or heal a wound, a healthy nerve cell also uses certain kinds of chemicals as signals for effective functioning, growth and repair.

In a neurone, damage to a gene that makes a signalling molecule, or damage to one that makes a particular kind of building block molecule, would mean that the repair is not possible in that cell and so the neurone might accumulate damage without ever being repaired.

In the brain a chemical called glutamate is used to transmit signals from cells known as astrocytes to the motor neurone cells, but once it has crossed out of the astrocyte the glutamate needs to be removed or it will quickly build up to a level which is toxic to motor neurones. It is thought that damage to other genes responsible for making the molecules that mop-up this glutamate might slow down its removal allowing it to build up and cause damage, effectively poisoning the cell.

Another possibility is that the energy system of the motor neurone is disrupted. One structure found in all cells is responsible for the very last stages of the digestive process when the basic molecules of sugar or fat are finally converted to energy the cell can use. This structure is known as the mitochondrion and makes the energy available by a series of chemical reactions known as the "cytochrome chain". It is known that several genes controlling different stages in the cytochrome chain can be affected in people with MND, we can therefore guess that some of the candidate genes for which a function is unknown might be responsible for some of the malfunctions for which a gene is unknown.

WHERE CAN I FIND OUT MORE ABOUT FALS?

For people who have concerns about FALS, confidential genetic counselling is available throughout Scotland from staff attached to one of the four regional genetic centres. Outreach clinics are often held at locations other than the main centres. Access to genetic counselling is normally by referral from your GP.

If you are concerned about the possibility of also having one of the genes responsible for MND your first port of call should be your GP. However, please note that the genes responsible for the majority of inherited MNDs are not yet identified, Those that are known still account for less than half of the inherited cases of MND.

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Regional Genetics Centres

(East) Scotland Human Genetic Laboratories

Human Genetics Unit, Level 6, Ninewells Hospital and Medical School, DUNDEE DD1 9SY Tel: 01382 632035 Fax: 01382 645731
Catchment areas: Dundee, Perth, N Fife, Angus, Perthshire

(North) Scotland Clinical Genetics Service

Department of Medical Genetics, Medical School, Foresterhill, ABERDEEN AB25 2ZD
Tel: 01224 552120 Fax: 01224 559390
Catchment areas: Grampian, Highland, Orkney & Shetland, Western Isles

(South East) Scotland Regional Genetics Centre

Department of Clinical Genetics, Western General Hospital, Crewe Road, EDINBURGH EH4 2XU Tel: 0131 651 1012 Fax: 0131 651 1013
Catchment areas: Lothian, Fife, Borders

(West) Scotland Regional Genetics Service

Institute of Medical Genetics, Yorkhill NHS Trust, GLASGOW G3 8SJ Tel: 0141 201 0365 Fax: 0141 201 0700
Catchment areas: Greater Glasgow, Argyll & Clyde, Ayrshire & Arran, Forth Valley, Lanarkshire, Dumfries & Galloway

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