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Patient and family fact sheet:

Neurological conditions
Neurological Conditions

GP's role

- Discuss familial risks of common neurological conditions.
- Refer to neurological services for **diagnostic** genetic testing for Huntington disease and early onset familial Alzheimer disease.
- Refer to neurological/Genetics Services for **predictive** and **pre-symptomatic** genetic testing for Huntington disease and early onset familial Alzheimer disease.
- Refer family to relevant support group (see *Contacts, support and testing*).

Overview of neurological and neuromuscular conditions

- Most common adult-onset neurological conditions are multifactorial in cause.
- A minority of adult-onset neurological conditions are inherited and due primarily to a mutation in a single gene (eg Huntington disease).
- Some genetic variations (polymorphisms) may be associated with a higher risk of developing certain neurological conditions.
- Testing for polymorphisms is currently only on a research basis and neither recommended nor available for routine use (eg ApoE4 in Alzheimer disease predisposition).

Table 1. Examples of inherited adult onset neurological and neuromuscular conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genetic testing information</th>
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</thead>
<tbody>
<tr>
<td>Creutzfeldt-Jakob disease and other prion diseases</td>
<td>a</td>
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<tr>
<td>Early-onset Parkinson disease</td>
<td></td>
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<tr>
<td>Familial Alzheimer disease</td>
<td>a*</td>
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<tr>
<td>Familial epilepsy</td>
<td>a</td>
</tr>
<tr>
<td>Familial motor neurone disease</td>
<td>a</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>b*</td>
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<tr>
<td>Hereditary peripheral neuropathies (Charcot-Marie-Tooth disease)</td>
<td>a*</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis</td>
<td>a</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>b</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>a</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
<td>a*</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>b*</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>b*</td>
</tr>
<tr>
<td>Spinocerebellar ataxias</td>
<td>a*</td>
</tr>
</tbody>
</table>

a Genetic testing may be available for some familial forms of this condition.
b Genetic testing is available for this condition.
* These conditions may present earlier in life.
Indications for referral

- Take a family history, noting family members believed to have the neurological condition or suggestive neurological symptoms. Where possible, the family history should cover three generations and include grandparents, uncles, aunts and cousins.
- Refer individuals or family members to Genetics Services or specialist neurogenetic services where there are:
  > Proven (clinically or by genetic testing) personal or family history of an inherited neurological or neuromuscular condition
  > Personal features consistent with an inherited neurological or neuromuscular condition
  > A suspicious family history:
    - Two or more family members affected with apparently the same condition
    - A significantly earlier age of onset than average
    - Unusual aggregation of neurological diagnoses

1 Not all States have a neurogenetics service or clinic. Contact Genetics Services to discuss the most appropriate clinic to refer to (see Contacts, support and testing).

Management of symptomatic individuals

- Diagnostic genetic testing for some conditions may be performed to confirm a clinical suspicion and/or to identify the causative mutation, enabling at-risk individuals to have predictive genetic testing (see Contacts, support and testing).
- Genetic testing can be complex and is often best arranged by a clinical geneticist or clinicians in a neurogenetics clinic after detailed neurological assessment.
- Depending on the condition, referral of the individual to a neurogenetics clinic or Genetics Services before or after genetic testing for information, counselling and/or case management is important to ensure people have access to the best range of supports to meet their needs and also so that the family implications of the diagnosis can be considered.
- Contact Genetics Services for details of the most appropriate clinic for referral.
- Consider referral to a support group for the condition, as it may be a useful and supportive contact for the person (see Contacts, support and testing).

Management of asymptomatic at-risk individuals

- Predictive testing may be available through Genetics Services or specialist neurogenetics clinic.
- In some cases a family-specific mutation has to be identified in an affected family member before predictive testing can be offered.
- Consider referral to a support group for the condition they are at risk for, as it may be a useful and supportive contact for the person (see Contacts, support and testing).
Huntington disease

Clinical features
- Huntington disease (HD) is an inherited condition that gives rise to progressive, selective, neuronal cell death.
- Symptoms can be classified into three basic groups:
  - **Physical** – involuntary, jerky movements or ‘chorea’, abnormal gait, bradykinesia, hyperflexia, abnormal eye movements, dysarthria and dysphasia
  - **Cognitive** – impairment including disturbances in verbal fluency, cognitive speed, the retrieval of memories, ability to persist at a task or change cognitive sets, therefore causing difficulties with judgment, planning, problem solving and eventually dementia
  - **Emotional** – including personality changes such as impulsiveness, perseveration, disinhibition, depression, mood swings and aggression
- These symptoms usually commence between the ages of 30 and 50 years, and become progressively worse over time.
- However, onset can occur in children and people in their later years.
- Not all people will experience all the symptoms, nor will the symptoms appear in any particular order.
- An individual with HD lives on average for 15 to 20 years after developing the first symptoms.

Genetics
- HD follows an autosomal dominant pattern of inheritance. Each child of an individual with HD has a 50% risk of inheriting the mutated gene.
- HD is caused by a mutation in the gene called huntingtin.
- The mutation is the result of an increase in size (expansion) of a certain part of the gene where a tri-nucleotide sequence, CAG, is repeated over and over again (known as a triplet repeat). See Contacts, support and testing.
- The huntingtin gene normally contains the triplet CAG repeated up to 26 times.
- In people with HD, or those who will develop HD during their lifetime (if they live long enough), the CAG triplet is repeated 40 times or more in one copy of their huntingtin gene.
- Where an individual has the CAG triplet in one copy of their huntingtin gene repeated between 27 and 39 times (intermediate range), careful interpretation is required when assessing the meaning of this result for the individual and their family.
- It is not possible to predict at what age symptoms will appear based on the number of repeats in the mutated huntingtin gene. However, on average the larger the gene expansion the earlier the age of onset.

The size of the gene expansion is unstable down generations. Expansions of any size have the potential to increase from one individual to their child, with larger expansions associated with paternal transmission.

- Predictive genetic testing does not require identification of the mutation in an affected family member.

Prevalence
HD has a population frequency of approximately 1 in 10,000.
Investigations

- Genetic testing is available for the diagnosis of a symptomatic individual or for predictive testing of an asymptomatic at-risk individual.

Symptomatic individuals

- Refer symptomatic patients to a neurologist or neurogenetics service for neurological assessment and genetic testing to confirm diagnosis.

Asymptomatic at-risk individuals

- Refer to Genetics Services for discussion and counselling around predictive genetic testing.

Management of symptomatic individuals

- There is currently no cure for HD.
- Symptomatic treatment is available for some of the features of HD, such as chorea and depression.
- Discuss informing other family members of the diagnosis with the individual (see Genetics in practice).
- Suggest/encourage contact with the Australian Huntington Disease Association in their State/Territory (see Contacts, support and testing) for information, support, counselling, advocacy and ongoing monitoring of the patient’s/family’s support and service needs.

Management of asymptomatic at-risk individuals

- Explore and document the family history of HD, including age of onset of affected family members.
- If the individual wishes to explore their risk further, discuss direct referral to Genetics Services or neurogenetics service, or contact with a support group for information and counselling.
- An appointment with Genetics Services or a neurogenetics service will involve:
  - Detailed assessment of risk and discussion of availability of genetic testing
  - Support during decision making regarding testing
  - Pre- and post-test counselling
- Up to 80% of people at risk of HD choose not to have genetic testing prior to onset of symptoms (predictive testing) as they feel that knowledge of their genetic status would not be helpful and may increase anxiety.
- If the individual does not wish to discuss genetic testing with the predictive testing service, they may still benefit from ongoing support and contact with an HD support group.
Alzheimer disease

- The great majority of people with Alzheimer disease will have developed the condition for unknown reasons but not due to inheriting a familial form of the disease.
- Alzheimer disease:
  - Can be familial or sporadic and, in either instance, can have early (<60 years) or late onset
  - Is the most common cause of dementia in people older than 40 years
  - Is a pathological diagnosis based on the presence of amyloid plaques and neurofibrillary tangles and cannot be diagnosed with certainty by clinical assessment
- The risk of developing the condition increases with age, like other forms of dementia.

Non-familial late-onset Alzheimer disease

- There is no discernible increase in risk for the individual if the family history comprises:
  - No relatives with Alzheimer disease, or
  - Grandparent only with Alzheimer disease, or
  - Parent with Alzheimer disease diagnosed before the age of 65 years, and the patient is asymptomatic and currently several years older than 65
- For individuals with a family history of Alzheimer disease, the risk of Alzheimer disease depends on the degree of relationship and number of relatives affected. In most cases, the individual is more likely not to develop Alzheimer disease.
- The risk of late-onset Alzheimer disease among 1st relatives of individuals with probable or definite Alzheimer disease by age 85 years is approximately a 2.5 fold increase over that of the general population.

Familial Alzheimer disease

There are two forms:
- Early-onset familial Alzheimer disease (EoFAD)
- Late-onset familial Alzheimer disease (LoFAD)

Early-onset familial Alzheimer disease (EoFAD)

- **Clinical features**
  - Typically occurs in middle age (less than 60 years) but is otherwise indistinguishable from sporadic early-onset Alzheimer disease.

- **Criteria for EoFAD:**
  - A family with two or more affected people with onset age <65 years in more than one generation of a family, with clinically suggestive symptoms or pathologically proven Alzheimer disease in at least one individual.
  - An individual or family member with a disease-causing genetic mutation in one of the genes causing early-onset familial Alzheimer disease.
Genetics
- Represents 1% of all cases of Alzheimer disease.
- Follows a pattern of autosomal dominant inheritance.
- The vast majority of individuals affected are sporadic cases where there is no family history of the condition.
- Mutations in the gene presenilin-1 (PS-1) are implicated in over 50% of families with EoFAD.
- Other genes that are known to cause EoFAD are amyloid precursor protein (APP) and presenilin-2 (PS-2).

Late-onset familial Alzheimer disease (LoFAD)

Clinical features
- Typically has an onset >65 years and is indistinguishable from non-familial late-onset Alzheimer disease.

Genetics
- No single causative genes have been recognised for LoFAD.
- A susceptibility gene, ApoE, which has three forms (alleles) - ApoE2, ApoE3 and ApoE4 - has been identified for Alzheimer disease.
  > An individual’s risk of developing late-onset Alzheimer disease is related to the combination of ApoE alleles they carry
  > Those individuals with one or two copies of the ApoE4 allele are at increased risk of developing Alzheimer disease
  > However, 50% of all people with late-onset Alzheimer disease do not have a copy of ApoE4. It is possible to have this form of the gene and not develop dementia despite living to old age

Prevalence
- The prevalence of dementia in individuals over the age of 85 years is estimated to be 25 to 45%.
- Approximately 10% of all persons over the age of 70 years have significant memory loss and more than half of these individuals have Alzheimer disease.
- About 25% of all Alzheimer disease is familial.
- About 1 to 6% of all Alzheimer disease is early-onset (<60 years) and about 60% of EoFAD.
- LoFAD is responsible for up to 10% of late-onset cases.

Investigations
- Predictive genetic testing is available for at-risk relatives of individuals identified with EoFAD due to mutations in PS-1, APP and PS-2.
  > However, the testing is only available when a specific mutation has been identified in an affected family member
- Testing for ApoE status for Alzheimer disease has been the subject of debate. To date, local collaborative groups and international bodies have recommended that ApoE not be used for diagnostic or predictive testing for Alzheimer disease.

Management
- Refer to neurogenetics or Genetics Services for the following:
  > Any individual with a personal or family history consistent with early-onset familial Alzheimer disease (see ‘Criteria for EoFAD’).
  > Any individual with two or more affected family members with late-onset Alzheimer disease over one generation within the same parental line.
  > While ApoE testing for Alzheimer disease risk is not recommended, individuals requesting ApoE testing for Alzheimer disease risk may benefit from referral to a neurogenetics clinic for further discussion.
Neurological conditions

Motor neurone disease

**Clinical features**
- Motor neurone disease is also known as amyotrophic lateral sclerosis (ALS) or Lou Gehrig disease.
- It is a rapidly advancing condition characterised by progressive muscle weakness due to the death of motor neurons in the brain, brain stem and spinal cord.
- This affects movement of the limbs, speech, swallowing and respiration.

**Genetics**
- Inherited motor neurone disease shows:
  - Familial aggregation
  - An earlier age of onset than average (40s or younger)
  - Clinical features essentially the same as the sporadic form
- Approximately 10% of cases of motor neurone disease are thought to be due to mutations in a single gene.
- About 20% of all inherited motor neurone disease is due to mutations in the SOD1 gene
  - In these cases, the inheritance pattern is autosomal dominant
  - However, some causative mutations in SOD1 are not fully penetrant so the person may remain asymptomatic despite having the mutation
- Other genes in which mutations can cause motor neurone disease include:
  - ALS2 which follows a pattern of autosomal recessive inheritance
  - ALS4 which follows a pattern of autosomal dominant inheritance and is associated with variations in the SETX gene

**Investigations**
- Diagnostic and predictive genetic testing if appropriate may be available through a neurogenetics service or Genetics Services.

**Management**
- Consider referral to a neurogenetics service or Genetics Services where:
  - More than one member of a family has motor neurone disease
  - A sporadic case has an early age of onset
**Parkinson disease**

- **Clinical features**
  - Individuals with onset before 20 years of age are considered to have juvenile-onset Parkinson disease.
  - Those with onset before 50 years of age are classified as having early-onset Parkinson disease.
  - Those with onset after age 50 years are considered to have late-onset Parkinson disease.

- **Genetics**
  - 70 to 90% of cases are sporadic.
  - The majority of cases with a family history do not have a clear inheritance pattern and could be the result of exposure to common environmental factors and/or a genetic predisposition, or simply a chance familial aggregation.
  - Some cases of juvenile/early-onset Parkinson disease have been shown to be due to mutations in the parkin gene which follow a pattern of autosomal recessive inheritance.
  - A very few cases of the condition have been shown to be due to mutations in the \( \alpha \)-synuclein gene and follow a pattern of autosomal dominant inheritance.

- **Prevalence**
  - Affects more than 1% of individuals 55 years of age and more than 3% of those over 75 years of age, but may also affect younger people.

- **Investigations**
  - Genetic testing for Parkinson disease is not currently available outside research protocols.

- **Management**
  - Referral to a neurogenetics service or Genetics Services may be considered for families with unusual features, such as familial aggregation and/or early-onset Parkinson disease.
Bibliography


National Organisation for Rare Disorders (NORD). http://www.rarediseases.org/

Neurological conditions

There are a number of neurological conditions which have a genetic basis. These include Huntington disease, myotonic dystrophy, Charcot-Marie-Tooth disease, Friedreich ataxia, muscular dystrophies and others.

These conditions tend to appear at varying times of life and get progressively worse, although there are exceptions.

All these conditions have a different genetic basis. If you or anybody in your family has one of these conditions, you should discuss seeing a genetic service with your doctor.

Most other neurological conditions – Alzheimer’s disease, Parkinson’s disease, stroke, motoneurone disease and others – are usually not based on a simple genetic alteration. But occasionally, genetics plays a part. You should talk to your doctor about the possibility of there being a genetic basis to these common conditions if:

- The condition comes on much younger than usual, or
- Two or more members of the family have the same condition.

In such cases, you would want to help your doctor understand your family history (see fact sheet on ‘Your family history’) and you may be referred to a genetics service for specialised advice.

Contacts and further information

- All states and the ACT have familial cancer services. Contact them through your local state or territory health department.
- Australasian Genetic Alliance at http://www.australasiangeneticalliance.org.au
- National Organization for Rare Disorders at http://www.rarediseases.org
- MyDr at http://www.mydr.com.au
- The Centre for Genetics Education at http://www.genetics.edu.au
- HealthInsite at http://www.healthinsite.com
- MedicineNet at http://www.medicinenet.com
- For other related fact sheets, you can contact the Gene Technology Information Service on free call Australia-wide 1800 631 276 or email gsis-australia@unimelb.edu.au or visit Biotechnology Australia’s website at http://www.biotechnology.gov.au