Genetic testing in neurology

Victoria Harrison

Andrea H Nemeth

Abstract

Genetic testing is now an integral part of most areas of medicine, but especially neurological services. This article seeks to provide clinicians with an overview of the complex mechanisms and ethical dilemmas that can arise in the care of families with a confirmed or suspected genetic condition. As genetics moves more into the mainstream, it is increasingly important for non-geneticists to have an awareness of how to approach these patients, the potential pitfalls and when to seek specialist advice.

Here we explain patterns of inheritance and their complexities including mitochondrial disorders, and mosaicism. We also explain different types of genetic testing including presymptomatic, diagnostic and carrier testing. We provide an overview of the ethical framework of genetic testing including confidentiality and consent, genetic testing in children and genetic testing in at-risk relatives. We also describe core technologies for genetic testing including cytogenetic and molecular genetic analysis. Close liaison with clinical genetics services and medical genetics laboratories is recommended in order to stay up to date with the type, availability and appropriateness of any genetic test.

Keywords carrier testing; confidentiality; consent; diagnostic testing; genetic testing; neurogenetics; neurology; presymptomatic testing

Introduction

Genetic testing is now an integral part of most neurological services. In this article we seek to provide a brief overview of the important issues that must be addressed when genetic testing is considered. A glossary of terms and key take-home messages can be found in Boxes 1 and 2.

Family history and inheritance

An accurate family history and a detailed family tree allow the clinician to consider the likely mode of inheritance. **Reduced penetrance**, **variable expressivity**, **anticipation** and the occurrence of ***de novo*** **mutations** may complicate assessments.[1]

Victoria Harrison ***MB ChB MRCP*** *is a Specialist Registrar in Clinical Genetics at the Churchill Hospital, Oxford University Hospitals NHS Trust, UK. Conflicts of interest: none declared.*

Andrea H Nemeth ***BSc MBBS DPhil (Oxon) FRCP*** *is a Senior Clinical Research Fellow at the Nuffield Department of Clinical Neuroscience, University of Oxford and Consultant in Clinical (Neuro) Genetics at the Churchill Hospital, Oxford University Hospitals NHS Trust, UK. Conflicts of interest: none declared.*

Glossary of terms

Anticipation An increase in the severity and/or a reduction in the age of onset of a condition in subsequent generations. Often associated with trinucleotide repeat disorders when gene instability can lead to an expansion in the number of repeats

Chromosomal translocation Rearrangement between non-homologous chromosomes (e.g. 14 and 21). They can be balanced, resulting in no apparent loss of genetic material or unbalanced resulting in loss of genes

De novo **mutation** A new mutation that has occurred for the first time in an individual, rather than being inherited from a parent

Germline/gonadal mosaicism Mosaicism confined to those cells involved in reproduction

Karyotype The appearance of chromosomes under a light microscope

Proband Individual in a family presenting for medical attention

Reduced penetrance A proportion of people with the specified genotype do not develop the associated phenotype

Somatic mosaicism Mosaicism affecting the diploid cells

Trinucleotide repeat disorder A repetitive sequence of three base pairs that is associated with disease once the number of repeats reaches a certain threshold

Uniparental disomy (UPD) Two copies of a chromosomal region originating from one parent, with no copies from the other parent. A phenotype is due to the presence of imprinted genes, or by the unmasking of a recessive condition

Variable expressivity The range of clinical features seen between individuals with the same mutation

Whole exome sequencing (WES) Only the coding regions of DNA (exons) are sequenced using next-generation sequencing technology

Whole genome sequencing (WGS) The entire genome (~3.5 billion base pairs of DNA) is sequenced using next-generation sequencing technology

Box 1

Single gene disorders

Autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL) inheritance patterns are summarized in Figure 1.

Mitochondrial inheritance

Mitochondrial DNA (mtDNA) is inherited exclusively maternally and encodes proteins essential for adenosine triphosphate (ATP) production.[2–4] Family history may confirm maternal inheritance, but many cases are sporadic and a high index of suspicion is required. Mutations can affect all mitochondrial DNA (homoplasmy) or only a proportion of it (heteroplasmy). When heteroplasmy is present, a minimum amount of abnormal mtDNA must be present before there is dysfunction. This 'threshold effect' is tissue specific and contributes to the highly variable phenotypes.[3,4] Clinical features suggestive of an underlying mitochondrial disorder

Take-home messages

- Take a detailed family history and draw a family pedigree
- Confirm any known or suspected diagnoses in the family whenever possible
- Seek advice from clinical genetics and/or medical genetics laboratories in order to confirm what tests are available and appropriate
- Provide detailed information on any request card
- Be aware of the indication (e.g. diagnostic, presymptomatic or carrier test) for requesting a genetic test on your patient
- Ensure the patient has been counselled appropriately and knows the implications of any possible test results
- Discuss important issues, such as allowing relatives access to results, and document these as part of the consent-taking process
- Help the patient to communicate genetic information to relatives and/or arrange further cascade testing if appropriate
- Be aware of technological changes in genetic testing in a clinical and research setting
- Consider whether a referral to a specialist or clinical genetics service is required

Box 2

include myopathy, seizures, cardiomyopathy, liver/renal dysfunction, diabetes, deafness, eye abnormalities, and a raised plasma lactate.[2–4] Samples from tissue such as muscle are often useful for diagnosis.

Mosaicism

Mosaicism (Figure 2) describes two or more cell populations with different genotypes and can be **somatic** or **germline/gonadal**. Germline mosaicism may result in a higher recurrence risk than expected.[1] For example, the recurrence risk for mothers of boys with genetically confirmed Duchenne muscular dystrophy (DMD) but who themselves have a normal genetic test is approximately 5%.[5,6] This risk can be as high as 20% depending on the genetic information known.[6]

Genetic testing

Before having a genetic test patients should fully understand the possible implications for their own health as well as their family. Discussions may include advice on prognosis, reproductive risks and choices, insurance and driving. Referral to a specialist (e.g. neurologist, clinical geneticist) with knowledge and experience of the condition is often required. Patients lacking mental capacity should be tested only once it has been determined to be in their best interest, usually after consultation with the family and appropriate professionals.[7]

Diagnostic testing

The aim of diagnostic testing is to confirm or exclude a diagnosis, but it may also guide future management, predict prognosis and clarify the genetic risk to family members. Even when the genetic basis for a condition is known, a molecular test may not be available. Liaison with medical genetics laboratories is extremely helpful in determining which tests are available and appropriate.

Presymptomatic testing

A presymptomatic/predictive test (PST) is an indication of future risk rather than current clinical status. It is undertaken most commonly in someone at 50% risk of inheriting an adult-onset AD condition, such as Huntington's disease (HD), but it may occasionally be used for conditions with other modes of inheritance. PSTs should be carried out by a service with specialist expertise, usually a clinical genetics service, and often involves several appointments over a variable period of time.[7] Wherever possible, molecular confirmation of the diagnosis in the affected family member should be sought and in some cases is a necessary pre-requisite to testing.

A PST may not always involve a genetic test; for example an MRI brain scan may show typical white matter changes in a person at risk of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy).[8] The same care with counselling and consent should be taken when undertaking non-genetic investigations in at-risk individuals (see below).

Carrier testing

The term 'carrier' usually refers to a person with a heterozygous mutation, such as the parents of a person with an AR condition or the mother of one with an XL condition. Carrier testing is undertaken when there is a family history (cascade testing, as in spinal muscular atrophy) or when an individual is part of an at-risk population (e.g. Tay–Sachs disease in Jewish populations). Occasionally, one or both parents of a child with an AR condition are not carriers, due to non-paternity/maternity, uniparental disomy or a *de novo* mutation, altering the recurrence risk.

There may be important health and screening implications for carriers of some conditions, such as the risk of adrenomyeloneuropathy and adrenal insufficiency in female carriers of X-linked adrenoleukodystrophy.[9]

Insurance

There is a concordat and moratorium, agreed between the Association of British Insurers and the Department of Health, stating that results of presymptomatic genetic tests do not need to be disclosed by applicants for insurance.[10] The only current exception to this rule is when applying for life insurance over the value of £500,000 if the condition in question is HD.[10] This agreement has recently been extended until 2017.[11] Family history and the outcome of a diagnostic genetic test should be disclosed if requested and may be taken into account.

Ethical considerations

Consent and confidentiality

The Joint Committee on Medical Genetics has published new guidance on consent and confidentiality in clinical genetic practice, highlighting a number of issues that should be raised when informed consent is obtained,[7] which include: