HOW TO DO IT

Draw a pedigree during the neurological consultation

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INTRODUCTION

Inherited genetic disorders account for about 5% of all medical consultations. The importance of a genetic contribution to a widening spectrum of disorders is becoming evident in neurology, indeed in all facets of medicine. Genetic factors may contribute to the development of disease, influence its course and severity, prognosis and response to therapy. Therefore, as our knowledge of the human genome expands, efforts are being made to identify genetic predispositions and influences to improve identification of risk, target pharmacotherapy, design gene therapy, and to provide more accurate assessment of prognosis. Recognition of risk should facilitate timely screening and early or presymptomatic treatment when available; and even in the absence of accepted treatment strategies this may still encourage appropriate lifestyle measures to reduce risk.

Better assessment of genetic risk is therefore an essential part of modern clinical assessment in all patients. A comprehensive family history is the first step and this is collected by the construction of a pedigree. This article is intended as a basic guide for the neurologist investigating and documenting pedigrees in a non-specialist clinic.

BEFORE STARTING

When collecting a family history, patients and their families must be told why the information is important. Many individuals have reservations about disclosing details of family members unless a valid reason is made clear to them. Communicating the benefits of such information is the first step in obtaining an accurate family history.

Recall of diagnoses in families can be inaccurate. Even if patients are forthcoming in disclosure, it must be remembered that they might be biased towards recognizing any illness in their family similar to their own whilst failing to recognize dissimilar illness that could still be significant. Also, perceptions of disease vary and it is not uncommon for generic terms such

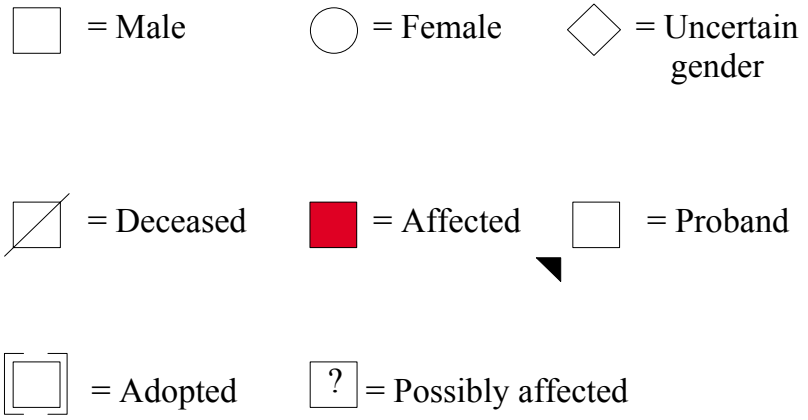

Figure 1 Standard symbols commonly used in pedigrees.

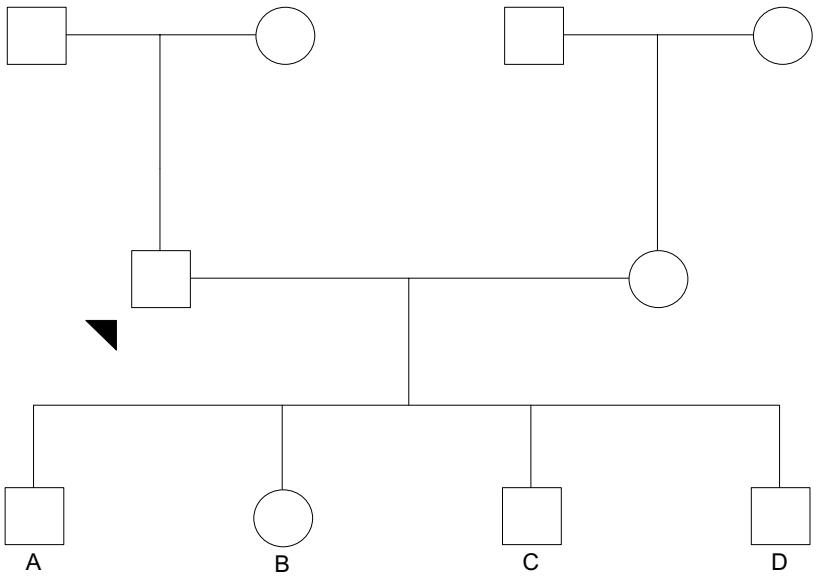

Figure 2 Proband (arrow) and wife with four children, eldest A on the left and the youngest D on the right.

as 'stroke' to be used to describe a large variety of pathologies. For example, in a study assessing the validity of family history obtained at the bedside in 163 patients with subarachnoid haemorrhage (compared with review of hospital records of 1259 first degree and 3038 second degree relatives), the sensitivity of an accurate family history for first-degree relatives was 0.75 (95% CI 0.35–0.97) with a positive predictive value of 0.55. For combined first and second-degree relatives the sensitivity was less at 0.58 (95% CI 0.28–0.85) with a positive predictive value of 0.64 (Greebe *et al*. 1997). Therefore, description of the actual event or illness should be sought and, wherever possible, other family members interviewed to verify and obtain further information.

PRINCIPLES OF DRAWING A PEDIGREE

The date when the history was obtained and the pedigree drawn must be documented, and the name of the informant and person drawing the pedigree. Always use a blank sheet of paper (preferably horizontal rather than vertical). Remember to leave plenty of space between each individual because this allows further information to be added as and when it becomes available. Start with a single individual, usually the proband (the first person in the family coming to medical attention, identified by an arrow in the tree). Males are denoted by squares, females by circles and persons of unknown gender by diamond shaped symbols (Fig. 1). Each individual has a vertical individual line above him or her. A horizontal sibship line connects the vertical individual lines of siblings, with the eldest sibling to the left and the youngest to the right (Fig. 2). A vertical parental line connects the horizontal sibship line to the parents who are added above. Draw the horizontal relationship line between the parents. Then draw each parent's sibship line and their own vertical parental lines.

The tree is usually constructed around the proband or informant because this is where most information is initially available. The aim is first to draw a trunk with maximal data, and then to trace the roots (parents and grandparents). Branches of the family are added later (uncles, aunts and their children, cousins). Partners are added as applicable. Divorces and separation must be clarified (Fig. 3). Remember that although maternity is invariably a fact, paternity is often presumed. Always enquire about adoption, both into and out of the pedigree (Fig. 4). Stillbirths, spontaneous abortions and pregnancies must be noted (Fig. 4), and monozygotic and dizygotic twins (Fig. 5). Enquire about individuals presumed to be unaffected; in late onset disorders, unaffected members may become affected later. Also distinguish between unaffected individuals and individuals where scant information is available. Finally, review of the distribution of disease in the tree will identify possible patterns of inheritance in the family.

Individual data

Each individual is identified by his or her first name and surname. In the case of females,

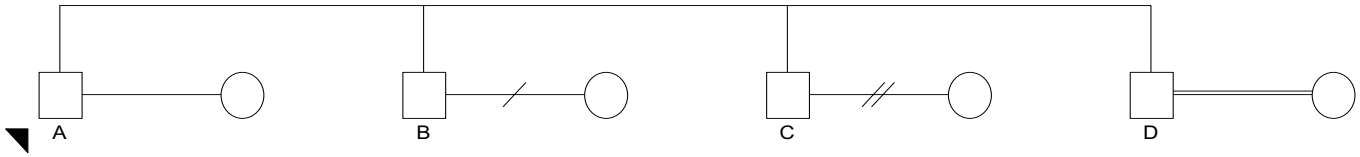

Figure 3 Marital relationships: Four brothers, A: married, B: separated (single slash), C: divorced (double slash) and D: consanguineous.

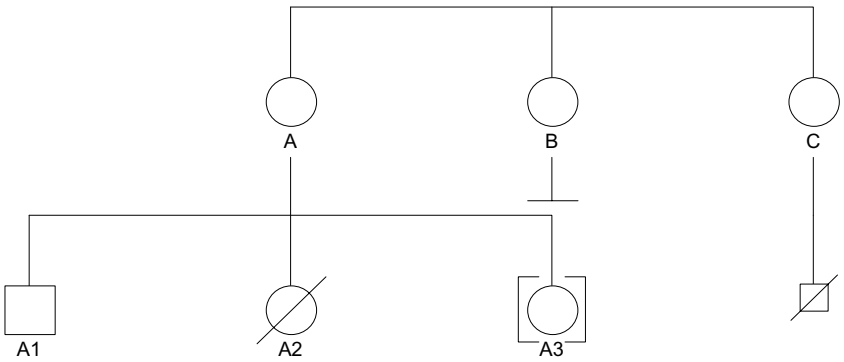

Figure 4 Three sisters A, B and C. A has a son A1, deceased daughter A2 and an adopted daughter A3 (adoption denoted by surrounding brackets). Sister B has no offspring. Sister C had one child who was stillborn (denoted by miniature symbol).

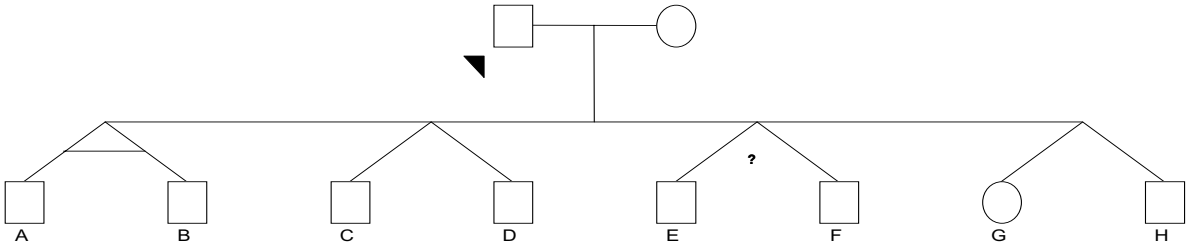

Figure 5 Twins. A and B are monozygotic twins, C and D are dizygotic twins, E and F are same sex twins but zygosity is uncertain, G and H have to be dizygotic twins (different sexes).

maiden names must be noted. Dates of birth are extremely helpful but if not available the year of birth is sufficient. Date of or age at death should be accompanied by the mode of death. Place of residence and death should be noted if known as this further helps in information gathering. Major life events such as illnesses, accidents, hospital admissions, development and progression of disability must be recorded. Psychiatric disturbances and cognitive difficulties are relevant to many inherited neurological disorders and should not be overlooked.

PATTERNS OF INHERITANCE

Inheritance may be simple (single gene) or complex (polygenic). For the purposes of this guide only single gene (Mendelian) and mitochondrial patterns of inheritance are considered.

Autosomal dominant inheritance (Fig. 6)

A dominant trait implies that the disease phenotype is caused by the presence of a single abnormal allele, i.e. it is present in a heterozygote. Transmission of the trait takes place from generation to generation without skipping a generation, i.e. some members of every generation are affected unless penetrance is incomplete (certain individuals with a mutation do not for some reason develop the disease at all) or a person with the trait may have died before the disease could become manifest. Each affected individ-

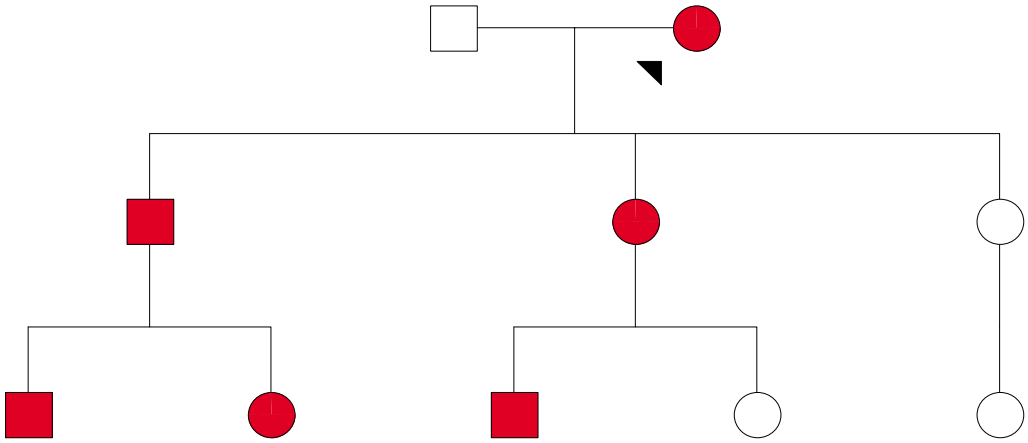

Figure 6 Pedigree displaying autosomal dominant inheritance. The proband (arrow) has three children including an affected son, one affected daughter and one unaffected daughter. The affected son has two children, male and female (both affected). The affected daughter has an affected son and an unaffected daughter.

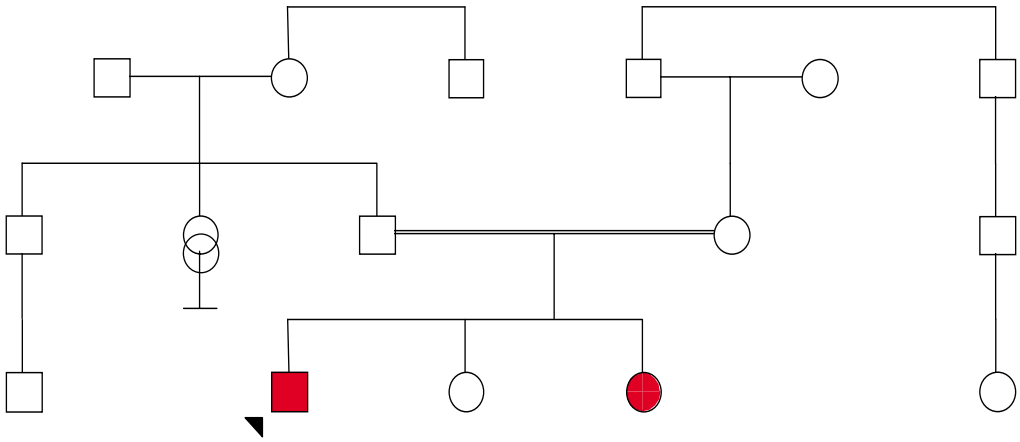

Figure 7 An example of autosomal recessive inheritance. Note absence of clinical illness in parents (consanguineous marriage), uncles and aunts and cousins.

ual has an affected parent (except in the case of *de novo* mutations) and each child of an affected individual has a 50% chance of inheriting either the altered or normal allele.

Autosomal recessive inheritance (Fig. 7)

In recessive inheritance the disease phenotype is observed only in the homozygous state (both alleles abnormal). Pedigrees display affected members within a single generation (often siblings) with unaffected parents (often consanguineous) and unaffected offspring. Recessive disorders are more frequent in geographically isolated communities (mountainous regions, islands) and isolated religious communities (e.g. Amish). In recessive traits, all children of two affected parents (homozygotes) will be homozygotes and affected. On mating of two unaffected heterozygotes, 25% of their offspring will be homozygous normal (normal alleles), 50% heterozygous unaffected (one allele abnormal) and 25% homozygous affected (both alleles abnormal).

X – linked inheritance (Fig. 8)

Such traits are either dominant or recessive. Recessive traits are expressed only in males whereas dominant traits are expressed in both females and males. It is to be noted that because males have only one X chromosome, they are considered hemizygous and not heterozygous for X-linked genes.

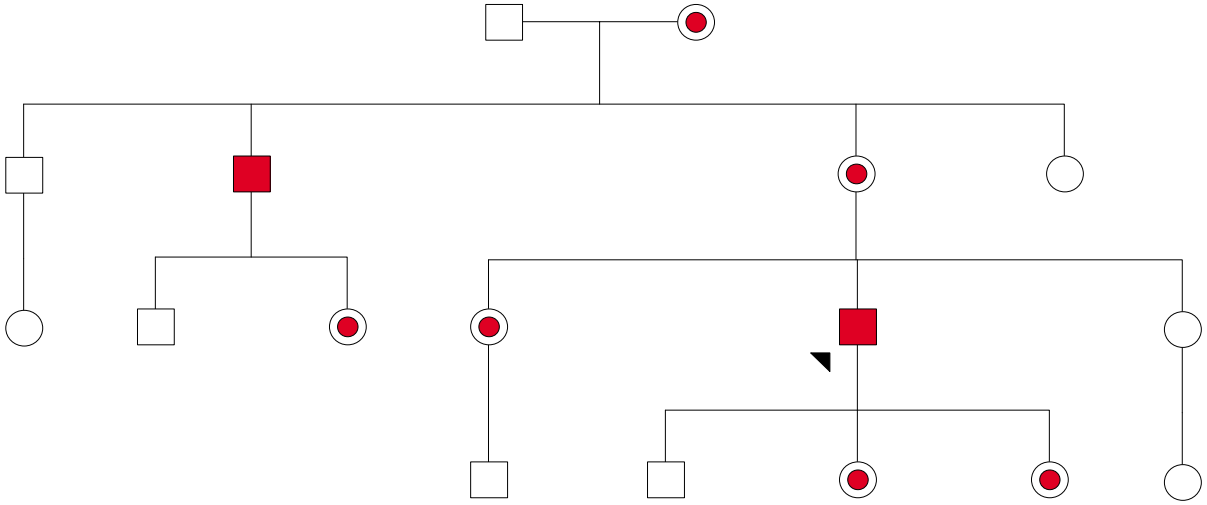

Figure 8 An example of X-linked recessive inheritance. There is no male-to-male transmission, all daughters of affected males are obligate carriers (red circle within white circle), 50 percent of male offspring of carrier mothers are affected and 50percent of daughters of carrier mothers are heterozygote carriers themselves.

In X-linked recessive traits (the majority), pedigrees demonstrate affected males with neither affected parents nor offspring. There is no male-to-male transmission. All daughters of affected males are obligate heterozygotes (carry the abnormal X allele from their father with a normal copy from their mother). These female heterozygotes serve as carriers and will transmit the trait to 50% of their sons (affected hemizygotes). The daughters of female heterozygote mothers have a 50% chance of being unaffected homozygotes (non-carriers) and a 50% chance of being unaffected heterozygotes (carriers).

In X-linked dominant traits (which are rare), all female offspring of affected males are affected. 50% of male offspring of an affected female heterozygote and 50% of female offspring of an affected female heterozygote will be affected. In contrast to autosomal dominant inheritance, there is no male-to-male transmission.

Occasionally random inactivation of X chromosomes in females during the late blastocyst stage of development may result in an effective hemizygous state (the Lyon hypothesis). Females heterozygous for X-linked traits have clones of cells, in which either the normal or abnormal allele is active (the other allele being inactive). If by chance in a female individual, the normal allele is inactivated more often than the abnormal allele, the female is effectively similar to an affected hemizygous male, with a larger proportion of her cells expressing the abnormal X chromosome (Fig. 9). This phenomenon may explain expression of X-linked

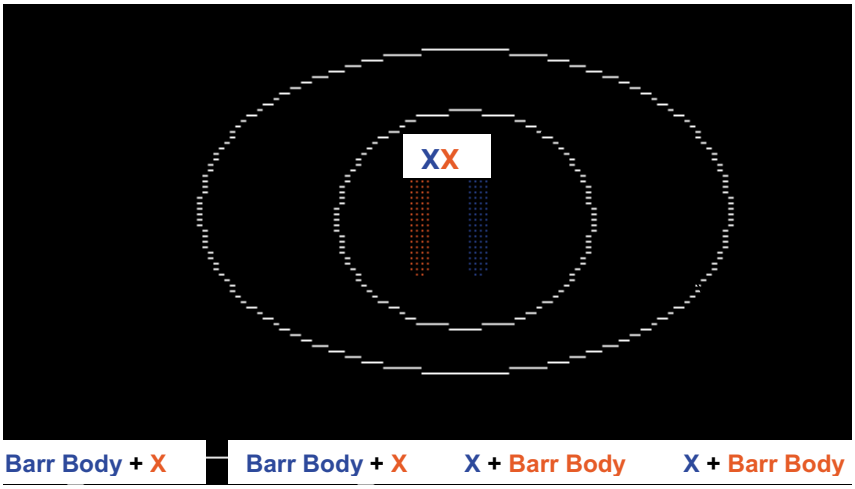

Figure 9 The Lyon Hypothesis – in the late blastocyst stage in females, either of the two X chromosomes is randomly inactivated in different cells, leading to clones of cells with one of the two X chromosomes intact and the other forming a Barr body. If a larger proportion of cells have an active abnormal X chromosome, then the female may manifest an X-linked recessive trait.

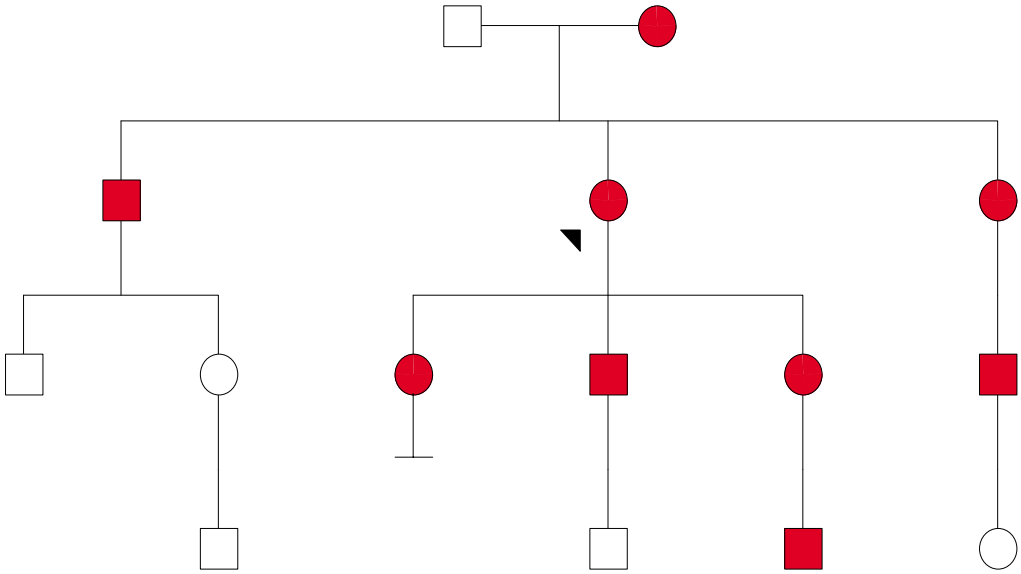

Figure 10 Mitochondrial inheritance. Females transmit the trait to all offspring (males and females). Males do not transmit the trait.

recessive traits in females. Females with Turner syndrome (45, X) may also express X-linked recessive traits.

Mitochondrial inheritance (Fig. 10)

Mitochondrial DNA is maternally inherited. Pedigrees display a typical pattern in which all offspring of affected females are affected. Affected males do not transmit the trait to their offspring. Because certain areas and systems of the body, such as cardiac muscle and the central nervous system, have a high content of mitochondria, mitochondrial disease usually manifests as neurological and myopathic syndromes. For a useful synopsis of mitochondrial disorders we suggest referral to an earlier article in *Practical Neurology* (Chinnery 2003).

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FURTHER READING

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PRACTICE POINTS

- Start on a blank sheet of paper and leave plenty of space.
- Remember that maternity is a fact but paternity is always presumed.
- Distinguish between unaffected individuals and individuals with scanty clinical information.
- When taking a family history there is a bias towards recognizing similar illness in relatives, and a failure to recognize dissimilar but significant illness.
- Always clarify generic terms such as 'stroke'.
- Attempt to verify information by asking multiple sources.

APPENDIX

Basic genetic nomenclature

- Alleles – these are the alternative forms of a gene at a particular locus. There may be several normal and abnormal alleles of a gene.
- Autosome – a chromosome that is not a sex chromosome (human males and females have 22 pairs of autosomes).
- Autosomal dominant traits – disorders transmitted on autosomes and expressed in the heterozygous state.
- Autosomal recessive traits – disorders transmitted on autosomes and expressed only in the homozygous state.
- Expressivity – this refers to the nature or severity of expression of an abnormal allele in an individual.
- Gene – the inherited factor that interacts with the environment to influence or determine a trait, in other words the phenotype.
- Genotype – this describes the genetic constitution of an individual.
- Heterozygote – individuals in whom alleles at a locus are different are called heterozygous. If one allele is abnormal the individual is called a carrier.
- Homozygote – individuals in whom both alleles at a locus are identical are said to be homozygous.
- Locus – the specific location of a gene on a chromosome.
- Penetrance – this refers to the presence or absence of clinical manifestations due to an abnormal allele. It is an all or none phenomenon. In a particular genetic disorder, the number of individuals expressing the disease divided by the total number of individuals with the abnormal allele estimates penetrance.
- Phenocopy – this refers to a copy of a phenotype, either by another genetic disorder or by an environmental insult.
- Phenotype – this refers to the expression of a gene following interaction with the environment.
- X-linked traits – disorders transmitted on the X chromosome.

A guide to neurological genetic disorders and their modes of inheritance. For a definitive guide see Online Mendelian Inheritance in Man (OMIM).

Autosomal Dominant disorders

Neuro–cutaneous syndromes

- Von Hippel-Lindau 11q13, 3p26-p25
- Neurofibromatosis 1 17q11.2
- Neurofibromatosis 2 22q12
- Tuberous sclerosis 9q34, 16p13.3

Movement disorders

- Huntington's disease 4p16.3
- Hereditary spastic paraplegia 3, 4, 6, 8, 10, 12, 13, 17, 19, 24
- Spino-cerebellar ataxias SCA 1–10
- Dentato-Rubral-Pallido-Luysian atrophy 12p13.31
- Episodic ataxia 1/myokymia 12p13
- Episodic ataxia 2/nystagmus 19p
- Episodic ataxia 3 1p
- Episodic ataxia 4
- Oppenheim dystonia (DYT1) 9q34.1
- Dystonia (DYT 6) 8p21q22
- DYT7 18p
- Dopa-responsive dystonia (Segawa) (DYT5) 14q22.1

Epilepsy

- Benign Rolandic epilepsy
- Juvenile myoclonic epilepsy

Stroke

- CADASIL 19p13

Muscle

- Myotonic dystrophy 19q13.2
- Proximal myotonic myopathy (PROMM) 3q
- Myotonia congenita 7q35
- Familial motor neuron disease 21 (20%)

- Facioscapulohumeral dystrophy 4q35
- Limb-girdle muscular dystrophy 1 A, 1B, 1C
- Welander distal myopathy 2p13
- Griggs-Udd distal myopathy 2q31–33
- Hyperkalaemic periodic paralysis 17q23.1-q25.3
- Hypokalaemic periodic paralysis 1q31-q32

Peripheral nerve

- Charcot-Marie-Tooth CMT-1 A 17p12-p11.2 (PMP22)
- CMT-1B 1q21.1-q23.3
- CMT-2 A 1p36
- CMT-2B 3q13–22
- Hereditary Sensory Autonomic Neuropathy 9q22.1-q22.3
- Familial amyloid polyneuropathy 18q11.2-q12.1
- Acute intermittent porphyria 11q24.1-q24.2

Migraine

- Familial hemiplegic migraine 1 19p13
- Familial hemiplegic migraine 2 1q21–23

Autosomal Recessive disorders

Movement disorders

- Wilson's disease 13q14.3 – q21.1
- Ataxia-telangiectasia 11q22.3
- Friedreich's Ataxia 9q13
- Spastic paraplegia 5, 7, 11, 14, 15, 25
- Metachromatic leukodystrophy
- Hallevorden-Spatz disease 20p12.3-p13
- Neuroacanthocytosis 9q21
- Abetalipoproteinaemia 4q22-q24

Stroke

- CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy)

Muscle

- Spinal muscular atrophy (SMA) 1, 2, 3 5q11-q13
- Limb-girdle muscular dystrophy 2 A–G
- Miyoshi myopathy 2p13
- Nonaka myopathy 9p1-q1

Peripheral nerve

- Charcot-Marie-Tooth disease 2 CMT2
- CMT3
- CMT4
- Hereditary Sensory Autonomic Neuropathy types 2, 3 and 4
- Refsum's disease

Mitochondrial disorders

- Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS)
- Myoclonic Epilepsy associated with Ragged Red Fibres (MERRF)
- Leber hereditary optic neuropathy
- Neuropathy, Ataxia and Retinitis Pigmentosa (NARP)
- Mitochondrial NeuroGastroIntestinal Encephalomyopathy (MNGIE)
- Progressive external ophthalmoplegia
- Kearns–Sayre syndrome
- Leigh syndrome

X-linked disorders

- Adrenoleukodystrophy Xq28
- Incontinentia pigmentii Xq28, Xp11
- Pelizaeus-Merzbacher disease Xq22
- Kennedy disease Xq11–12
- Dystonia 3 DYT3 (Lubag) Xq13.1
- Duchenne muscular dystrophy Xp21
- Becker muscular dystrophy Xp21
- Emery-Dreifuss muscular dystrophy Xq28
- Spastic paraplegia 16 Xq11.2
- Lesch–Nyhan syndrome Xq26-q27.2
- Fabry's disease Xq22
- Mcleod's syndrome Xp21.2-p21.1
- Menkes disease Xq13.3