

Chapter

1

The human genome project – what it really means and where next

Sonia Gandhi and Nicholas W. Wood

Introduction

Many things in medicine and life are over-hyped and aspects of genetics and its impact are no exception. One can consider the excitement about gene therapy of a few years ago and more recently about stem cells where the public's expectations are raised so high and so quickly that nothing can survive this scrutiny. This is not the fault of the individual researchers who almost uniformly offer caution and, if anything, under-report the potential, but such is the desperation for progress in the treatment of a range of diseases that any such progress is seized upon and amplified by the press.

However, there is an area where we believe the full impact of the achievement is only just being touched on – the sequencing of the human genome. This was a huge endeavor undertaken by an international consortium and, by any measure, was a dramatic success. The United Nations Educational, Scientific, and Cultural Organization (UNESCO) universal declaration on the human genome and human rights states, “The human genome underlines the fundamental unity of all the members of the human family, as well as recognition of their inherent dignity and diversity. In a symbolic sense it is the heritage of humanity.”

The 3.08 billion base pairs (bp) of *Homo sapiens* DNA have now been sequenced and this ranks with the highest achievements of humans to date. This molecule has been reproducing itself for millions of years, and as it has mutated and under the influence of natural selection, it has resulted in the development of the myriad species on earth. To understand the significance of these mutations or variations is to start to address, at a molecular level, what makes us human and differentiates us from other species. Many more genomes have been or are being sequenced; this enables a very rapid interrogation of comparative data, what is similar and what is different between us and them. This has produced a number of really quite

surprising results and we are only starting to scratch the surface of this work:

- The human genome contains somewhere between 22 000 and 25 000 genes; this is far fewer than was estimated even 10 years ago. It is also surprisingly close in number to many other vertebrates and is only about twice the number needed to produce a fruit-fly.
- Human genes show a much higher degree of alternative splicing than those of other species, so each gene can potentially make different proteins. Interestingly, it has recently been shown that sometimes these alternate transcripts can have opposing functions. There is much more work to be done here.
- Functional domains of proteins (and their DNA correlates) are frequently found in lower species. In fact, the presence of conserved sequence (DNA or amino acid) is a strong indicator of an important, even if unknown, function. This follows the idea: why would it have been so conserved across millennia of divergence if it were not important?
- More than 90% of the domains that can be identified in human proteins are also found in the fruit-fly. This indicates that the core building blocks of vertebrate biology did not need the creation of a huge number of new domains. Biology just found a new way of improving upon these core resources.
- Comparison with distant species is useful for assessing the effects and presence of evolution, but to start to better understand the function of individual genes, it will be necessary to compare closely related species – ideally, a species whose physiology, anatomy, and broad behavioral characteristics are as similar to ours as possible.
- We will also need such comparative studies not only to determine the exonic-intronic structure but also to delineate gene control mechanisms.

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One of the major challenges, therefore, is how best to investigate and evaluate all these data. The field of bioinformatics is still in its infancy but one thing is certain, we are not going to be short on data. It will be the detailed and insightful organization and interrogation of the data that has the potential to deliver huge progress in the understanding of biology. The study of disease is only (albeit important) one aspect of this work. One can consider the study of the genetic aspects of disease as a way of prioritizing those variations of human DNA that should be studied in these initial stages.

Perhaps the simplest way to view disease genetics is a comparison of what we think of as simple (usually single) gene diseases and all those other traits among which are common diseases as well as the range of normal biological functions (height, intelligence, etc.). This book is concerned predominantly with the former. Of the 25 000 genes, approximately half are expressed in the nervous system (although this is a guess as one of the many other things we have to discover is the expression profiles of all the genes – both cell type and temporal). If one is to assume that mutations occur randomly, it confirms what we see in practice, namely that the nervous system has the lion's share of simple Mendelian disease. These Mendelian diseases are caused by generally rare mutation events. The changes that these mutations have produced are severe enough to produce dysfunction of the protein product, either by decreased productivity or by some novel toxic property. These mutations produce a high degree of disease risk; that is, they are the major or often the only cause of the disease. Once present on a chromosome, they carry with them a predictable recurrence risk dependent on the mode of inheritance and penetrance of the mutation.

The diseases discussed in this book are virtually all of this type, although in some cases (e.g. Parkinson's disease and Alzheimer's disease) there are familial forms caused by such mutations as well as a much greater proportion that are sporadic and where the genetic load is unknown.

Mapping the human genome Impact of progress in sequencing

In 1980, to sequence a single 100 bp stretch in one attempt was considered a major success. Now, the large genome sequencing facilities can produce a

whole human genome sequence in approximately one day. The cost of sequencing has fallen dramatically and continues to do so. Basically, the cost has halved every 22 months since 1990, and there is a stated aim to try and sequence the whole genome for \$1000. This is looking increasingly achievable and it is likely that it will be a part of the medical assessment of the patient. We are entering an era where data will not be in short supply, but assigning meaning is the next great challenge.

Genetic variation and human disease

The assignment of a mutation in a gene causing a human disease is the first step in this process. In the initial phases of disease gene discovery, the defect was usually identified by the nature of its function. For example, a known enzyme deficiency was presumed and then proven to be because of a genetic defect in the gene encoding that enzyme. This only accounted for a very small proportion of disease gene discovery and most of the progress over the past 15 years has been a result of positional cloning (described in more detail in Chapter 2). As a result of this process, the gene is identified but its function is often obscure. However, the very fact that a mutation is shown to cause a phenotype quite quickly leads to testable hypotheses as to the gene's function. What is frequently forgotten, not least by the scientists themselves, is that the gene may have many functions, and labeling it as the Huntington's disease gene or the Parkinson's disease gene is just the tag line that has helped identification, and it is highly likely that its normal function is more complex than at first imagined. These major disease-causing genetic mutations are rare and yet variation throughout the genome is very common. Currently, the belief is that much of this variation is neutral and of no major genomic importance; however, such is the scale of the variation that even functionality of a tiny percentage leaves a large number of variants worthy of study. Human disease is believed by many (including these authors) to be a powerful and valuable tool for unlocking these functions. If one can identify variation that is shown to increase the risk of a disease, for example epilepsy, one can build a much more comprehensive picture of the genetic and molecular events that control seizures. Moreover, this knowledge would shed light on the normal physiology of nerve cells, how seizures start, and why they are self-limiting.

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The simplest method (at least in theory) to access this, is to discover all human variants and assay them in one's case-control series of interest. However, still very few human genomes have been sequenced in their entirety and it will be some years before an attempt of this sort is feasible. Even if this were not a sufficient barrier, there is the major issue of genetic heterogeneity. One of the major lessons from Mendelian disease is that different mutations in the same gene may cause different phenotypes (allelic heterogeneity), and that mutations in different genes can cause the same phenotype (genetic heterogeneity). These facts are borne out in nearly all the subsequent disease-based chapters. Therefore, it seems fairly safe to say that genetic variation of this more subtle variety is going to be even more difficult to identify. This will require the use of large sample sizes (probably 1000s) and, more importantly, clever phenotype definition and application. It may be that relatively little progress is made using the current clinicopathological phenotypes, and now there is much attention toward defining other phenotypes such as intermediate or endophenotypes. The basic principle here is that a component of the disease (e.g. some cognitive measure in schizophrenia) is genetically simpler, more heritable, and ultimately tractable and, therefore, will be easier to identify.

Pharmacogenetics

One human disease area for which there is rising hope of early success is the field of pharmacogenetics. The principle is that the trait (drug responsiveness or side-effect profile) is molecularly and genetically simpler. Additionally, the candidate gene list is more modest and chiefly comprises the metabolizer, transporter, or target of the drug. There is also the hope that were we to discover the variants that determine one's likelihood of responding and not developing side-effects, this would have a tremendous benefit to drug trial design and would likely impact on healthcare sooner than the discovery of disease-associated causal variants of otherwise unknown function. This field is moving rapidly, and it is highly likely that genetic testing before prescribing will become routine within a few years. Finally, if one considers a field such as epilepsy, most of the known drug targets for anti-epileptic drugs (e.g. ion channels, transporters, etc.) have also been shown to be mutated in some, usually rare forms of familial epilepsies. It is, therefore,

reasonable to expect, if one turns this around, to say that the finding of new genetic variants responsible for epilepsy provides new drug targets.

BioBank

One of the major difficulties with association study design of the sort needed to find disease susceptibility genes is the danger of biases in controls or the cases, which lead to false-positive association (discussed in more detail in Chapter 2). One way around this is to access incident cases. The United Kingdom has established a BioBank of 500 000 individuals who will provide lifestyles, environmental factors, and a DNA sample. As these individuals succumb to disease, the frequencies of DNA variations between those in the cohort who have a certain disease trait and those who do not will provide a great potential for disentangling putative gene–environment interactions. This resource has only just begun to be collected and it will be many years before its full benefits are felt.

An important initial step in creating the capacity for exploiting such a resource has come from the large case-control consortia, which recently have started to report on large-scale, systematic, genome-wide association studies in common diseases.

Other tools to help improve understanding

The encyclopaedia of DNA elements project

The ENCODE project was begun in 2003 and is endeavoring to identify the functional elements in the genome. The human genome sequence is basically a list of ingredients; we have virtually no idea how this recipe is acted upon to produce a functioning human (or any other life form, for that matter). A key element of this process is the regulatory control of switching genes on or off, and what determines the expression level and splicing variation. This project seeks to characterize enhancers, promoters, protein binding sites, and other regulatory elements. It is starting with a selected 1%, and it is hoped that what is learnt from this initial study will have lessons for the rest of the genome.

The knockout mouse project

When a disease-associated gene is found, one of the first questions is: what does it do? The usual answer is

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that we do not know. We gain some insights into the question by asking what it looks like, especially if it encodes domains that look very like something else about which we do know something, such as a kinase domain. However, these musings only take us so far; of major importance is what it does in a living system; better still, if it is closely related to us; for example, a mammal. Inevitably, the laboratory concerned or, more usually, one sets up experiments that manipulate the gene, knocking out or in, or doing so only when conditions are appropriate (conditional knockouts). Now there is an international project to provide publicly available knockouts of every mouse gene. It is sometimes the case that knocking out a gene, which is needed early in development, produces embryonic lethality in the homozygous state. Therefore, a system of conditional knockouts is also being generated – dependent on external triggers, the mouse gene can be knocked out at any stage, so one can let the mouse develop and then switch the gene off, as required. These resources will be hugely valuable to genomic science and understanding disease-causing mutations.

Comparative genomics

Advanced draft or complete sequences are now available for five mammals – human, mouse, rat, chimpanzee, and dog. Many other vertebrates are close behind these. The ability to compare the basic coded differences between the species is now within sight and the potential gains, as detailed above, are enormous.

Summary

The future for genetic medicine is bright. Soon we will know much more about human genetic variation, genomic control, and even how we got to the top of the evolutionary tree (at least for the time being). For those interested in the nervous system and neurobiology, the impact this field will make will be huge. It will become unimaginable to future generations that we could hope to understand the nervous system without discovering and studying the building blocks; however, that is for the future. This book attempts to synthesize what we know now and a little of how we got here. It is divided into the major disease areas and, as can be seen from scanning the contents page, the impacts have already been felt in virtually all branches of neurology. Fortunately, genetics is simple and if one can get past the jargon, one is left with a couple of rules

(formulated by Mendel) and a huge improvement in our technical ability to investigate the processes.

Neurogenetics is still in its infancy but it is now part of the core curriculum of most residency training schemes. This book hopes to provide both the neurologist in training as well as some of the neurologists who trained before these developments with the core discoveries and excitement of the field. Of course, it is a rapidly moving field and there will be some genes that will be discovered between finishing the writing and the book appearing on the shelves. However, we hope that these new discoveries can be tagged on to the basics discussed here.

Box 1 Decoding the jargon

- Allele – we all have two sets of chromosomes and hence two copies of a gene. If these vary (which they often do), these different forms are called alleles.
- BAC (bacterial artificial chromosome) – a useful packing tool used to engineer and handle quite large pieces of DNA.
- Cloning – a process of generating as many copies of a given piece of DNA as required. It has been the bedrock of the major developments.
- cDNA (complementary DNA) – a copy of a transcribed gene as it uses mRNA as its template. DNA is more stable and therefore easier to handle.
- Conservation – genes or fragments of genes can be compared across species; those present in more than one organism are said to be conserved. Generally, the greater the conservation (i.e. the more species in which any given gene is basically the same), the more fundamental and important this DNA structure is.
- EST (expressed sequence tag) – short segments of DNA corresponding to a piece of cDNA and, therefore, representing a tag for a gene as opposed to a non-transcribed part of the DNA.
- Genome – a complete description of the DNA sequence of an organism.
- Genotype – usually means the combination of two alleles that an individual carries at any given gene locus.
- Haplotype – a combination of alleles found tightly associated with one another. It forms the basis of much of the current hunt for genes underlying common forms of disease (see Chapter 2).
- Introns and exons – genes are not coded in solid blocks of sequence; the coding segments are called exons and the stretches (intervening

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Box 1 (cont.)

segments) are introns. The function of introns is unknown, but it is emerging that there is some conservation in some stretches implying an as yet unknown function (see conservation). This biunitary arrangement allows for the selection of parts or all of the coding components of the gene (i.e. alternative splicing).

- mRNA – this is the message created from the DNA template. The RNA copies across the whole gene (introns and exons), and then molecular machinery (the spliceosome) cuts out the intronic segments, leaving the messenger RNA to move out to the ribosome to undergo translation.
- Mutation – a change in the DNA sequence to a reference state (usually some ancestral sequence). Although used most frequently to imply a pathological state, this is most often not the case (see polymorphism).
- Phenotype – the physical characteristics of a cell or organism. From a medical point of view, it is used as the description of a disease state.
- Polymorphism – a mutation that is above a certain frequency in the population (usually >1%). Generally used to denote a variation that is not implicated in disease causation, but even this will change as more functional characteristics are applied to these polymorphisms (see Chapter 2).
- Proteome – the complete set of proteins encoded by the genome.
- Recombination – along with mutation, this is the engine behind diversity and evolution. It is also the point of gender as it allows crossing-over of DNA from one ancestral chromosome to the other. It is used by geneticists to help map disease genes.

- SNP (single nucleotide polymorphism) – hugely common polymorphisms (about one every 1000 bp). These are receiving a lot of attention to inform on our evolutionary past and help map the risk of common diseases (see Chapter 2).
- Splicing – the process of intron removal and also of excluding certain exons at certain times (alternate splicing).
- Transcription – the process of copying from the DNA code into RNA.
- Transcriptome – the complete set of mRNAs transcribed from a gene.
- Translation – the process of building a specific sequence of DNA based upon the mRNA message. This is performed by ribosomes.

Useful websites

OMIM: <http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>

GeneClinics and Gene Tests: <http://www.geneclinics.org/>

UKGTN: <http://www.ukgtn.nhs.uk/gtn/>

Rare diseases: <http://www.orpha.net/consor/cgi-bin/home.php?Lng=GB>

GENDIA (Genetic diagnostics): <http://www.gendia.net/index.html>

Web pages with useful documents related to genetic counseling and testing:

<http://www.hdfoundation.org/resources/testing.php>

<http://www.genome.gov/19516567>

<http://www.eurogentest.org/>

<http://www.gig.org.uk/index.html>

Chapter

2

Genetic counseling and genetic testing for neurogenetic disorders

David Craufurd and Peter S. Harper

Introduction

Advances in genetics have probably had more practical applications in the field of the inherited neurological disorders than in any other area of medicine. It is thus essential that all clinicians involved with these conditions, whether as a specialist in the field or as part of more general neurological practice, are fully informed about what the applications of genetics can offer patients and their families. Being fully informed does not mean that they need to be directly involved in all these applications, although increasingly, some areas are forming part of regular clinical practice; even more important is to know one's own limitations and what can be offered by other services, including clinical and laboratory genetics for inherited disorders.

The complex and extensive field that has evolved (and is still evolving), known as neurogenetics, contains not only a very wide range of different types of disorder, but also workers with very different backgrounds and skills, a factor that greatly influences how genetic advances are applied.

Among neurologists, some will have a strong research and academic orientation, while others will have a more service oriented approach. There is a major difference in most countries between pediatric and adult neurology, while among neurologists specializing in the latter, there is often a strong distinction between those involved primarily in neuromuscular diseases and those whose focus is on central nervous system (CNS) disorders. The types of neurogenetic disorder seen will vary greatly according to these groups (see Table 2.1).

Among clinical geneticists, likewise, there is considerable variety. Some will have a strong research and clinical interest in specific areas of inherited neurological disease and, especially in the United Kingdom, may be integrally involved in long-term management, often jointly with relevant neurologists. Others may be more laboratory oriented.

Table 2.1. Principal groups of neurogenetic disorders

<i>Childhood</i>	
	Neurodevelopmental defects
	Progressive childhood neurodegenerations
	Non-progressive neurometabolic disorders
	Neuromuscular disorders
	More common childhood neurological disorders with a complex genetic basis
<i>Mainly adult</i>	
	Progressive late-onset central nervous system degenerations
	Progressive neuromuscular disorders
	More common adult disorders with a complex genetic basis

It follows from this diversity of both disorders and professionals that it is neither possible nor wise to lay down strict rules for how and by whom genetic services should be applied in practice, but some useful guidelines are possible, and we hope that some of the key points will emerge from this chapter.

Patterns of inheritance

Most professionals involved with neurogenetic disorders will have at least a simple knowledge of genetics and transmission within families, but it is worth pointing out here how this influences the various practical applications now possible for families. Some of the pitfalls are also important to note. For those requiring more detail, there are several simple books available.

A remarkably high number of serious neurological disorders follow single-gene Mendelian inheritance, in both childhood and adult life; it is in this group where genetic risks are often high and where

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applications are possible. Therefore, it is vital that clinicians are aware of and alert for Mendelian conditions among the much larger numbers of disorders showing a more complex inheritance that they see.

Autosomal recessive inheritance

This type of inheritance underlies numerous childhood neurogenetic disorders, many developmental in origin, others more progressive and with a defined metabolic or biochemical basis. Increasingly, these two groups are merging and the concept of inborn errors of development is becoming established alongside inborn errors of metabolism, as the molecular pathways of development are becoming clearer.

At a practical level, the only high genetic risk in families where an autosomal recessive disorder has occurred is for siblings (one in four); because almost all are extremely rare outside unusual populations, the chance of a homozygous affected individual occurring among offspring, offspring of healthy siblings, or cousins is extremely rare. Heterozygous carriers of such genes are almost invariably entirely healthy, an important factor in genetic counseling as increasing numbers found to be heterozygous after a genetic test are worried by their status and convinced that they have or will develop a mild form of the disorder in question. In fact, it should rarely be necessary to undertake carrier testing unless there are particular circumstances; if it is done, it is essential to emphasize the lack of clinical (and usually genetic) significance of being a carrier.

Consanguinity, frequent in many populations across the world, may raise special issues when a recessively inherited genetic disorder is diagnosed in the family. Here it is important that any genetic risk can be balanced against the social benefits involved; an accurate estimate of risk, based on the degree of relationship of partners to the affected individual, is essential in allowing individuals to make informed decisions.

Autosomal dominant inheritance

Such inheritance is seen in a series of important, progressive neuromuscular and CNS disorders of later life, and may present particular challenges owing to late onset, variability, and the existence of extended family at significant risk. For all these reasons, the clinical geneticist is likely to be involved in genetic applications to a much greater extent than is the case

Table 2.2. Genetic counseling issues in Huntington's disease and other late-onset autosomal dominant disorders

Stigma of disorder – family and wider attitudes
Variability – in severity and age at onset
Uncertainty – arising from variability
Numerous relatives often at risk – issues of extended family
Serious implications for unaffected heterozygotes
Possibility of unusual genetic mechanisms (see Table 2.3)

for many childhood autosomal recessive disorders, where the pediatrician or pediatric neurologist often will have the principal role. Despite the deceptively simple inheritance pattern – a 50% risk for offspring of an affected patient and no significant risk for offspring of an unaffected relative – the practical situation is often complex and full of pitfalls. A paradigm of the problems is provided by Huntington's disease (HD), a disorder with which we, the authors, have been extensively involved over many years.

Leaving aside the issues of predictive testing, which will be discussed later in the chapter, HD shows, in clear-cut form, many of the problems that are present, although to a lesser degree, in other neurogenetic disorders; Table 2.2 summarizes some of these. Stigma associated with the disorder remains a very real factor, despite the development of active support groups; the combination of psychiatric and physical problems creates a special burden for families and may make people reluctant to seek advice or help. Variability in age at onset (and in clinical features) has the consequence of uncertainty, which many people at risk find very hard to live with and which has major personal consequences for relationships and life decisions generally. This is one of the main reasons for people seeking predictive testing.

Extended families

Such families may indeed be extended and extensive, creating real issues as to how far a professional should go in contacting those at risk who may be unaware of it. The skills and facilities needed to handle these often difficult family situations are very different from those required for the clinically affected individual, and it is largely for such reasons that the clinical geneticist takes the main role in such cases. Indeed,

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Table 2.3. Unusual genetic mechanisms in dominantly inherited neurogenetic disease that may affect genetic risks and genetic counseling

Mechanism	Examples
Gonadal mosaicism	Tuberous sclerosis, Charcot–Marie–Tooth disease
Anticipation from genetic instability	Myotonic dystrophy, Huntington’s disease, spinocerebellar ataxias
Parent-of-origin effects	Juvenile Huntington’s disease, congenital myotonic dystrophy
Genetic imprinting	Angelman syndrome

it is a general finding that many clinicians are not fully aware of the fact that most individuals requesting and requiring genetic services are not patients at all but are healthy individuals. Most neurologists (like other clinicians) wish to spend their time with those actually affected with a particular disorder, rather than with healthy family members, so it is here (as discussed in relation to general principles of genetic counseling) that establishing the appropriate balance and relationships between neurologist and clinical geneticist is important.

Implications for gene carriers

For gene carriers, the implications are completely different in dominant from recessive inheritance, a point obvious to professionals but often less so to families. Thus, a healthy carrier for the mutation almost inevitably will develop the condition at some future point, in contrast to carriers for autosomal recessive disorders, who will remain healthy. Not all dominant disorders are similar to HD in this respect, however. For myotonic dystrophy, the detection of a mutation in a healthy adult may well mean a milder (possibly minimal) disorder in later life in comparison to those showing early onset disease.

Unusual genetic mechanisms

Unusual genetic mechanisms are a particular pitfall for autosomal dominant disorders and some of these are summarized in Table 2.3. Inherited neurological disorders have proved to involve a remarkable number of these and their elucidation has led to major discoveries in our understanding of genetic mechanisms and pathogenesis, having implications for medicine more widely. At the practical level of

genetic counseling, these may considerably modify risks given to those seeking advice. Thus, gonadal mosaicism means that the recurrence risk for the siblings of an apparently isolated case is not zero but about 1%–3% according to the disorder, on account of the possibility of a parent carrying the mutation in the germline even though appearing to be entirely normal clinically. Such affected sibships with normal parents may mimic recessive inheritance (as in Charcot–Marie–Tooth disease). Anticipation resulting from genetic instability, seen notably in myotonic dystrophy but also in other trinucleotide repeat disorders, means that not only may the severity be greater and onset earlier for offspring, but that parent-of-origin effects may be seen, as in the greater likelihood of juvenile HD with paternal transmission, and the predominant paternal origin of kindreds from healthy individuals with an intermediate allele. Genetic imprinting, owing to differences in gene activation during male and female transmission, may also underlie parent-of-origin effects.

An important cause of variability in dominantly inherited disorders, in particular tumors, is the necessity for a somatic mutation, often a result of chromosomal loss, to occur on the opposite chromosome in order for a dominantly inherited condition to express itself. This two-hit hypothesis is seen in such tumor syndromes as von Hippel–Lindau disease and in other (mainly non-neurological) cancers determined by tumor suppressor genes. As a result, while the transmission pattern for susceptibility is dominant, there may be considerable variability according to whether or where the necessary second somatic event takes place.

In summary, genetic counseling for autosomal dominant disorders may be straightforward, but frequently is not, as the space devoted to the topic in this chapter has tried to indicate.

X-linked inheritance

Although the number of neurogenetic disorders inherited on the X chromosome is relatively limited, they produce practical issues out of all proportion to their frequency, with potential difficulties not seen in autosomal inheritance. Table 2.4 lists some of the more frequent and important conditions in this group.

The first point to be noted is that X-linked disorders usually cannot be classified strictly as recessive or

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Table 2.4. Important neurogenetic disorders following X-linked inheritance

<i>Neurodevelopmental</i>	
Hydrocephalus (specific type)	
Incontinentia pigmenti (lethal in males)	
Pelizaeus Merzbacher disease	
<i>Metabolic</i>	
Adrenoleukodystrophy	
Lesch–Nyhan syndrome (hypoxanthine–guanine phosphoribosyltransferase deficiency)	
Menkes syndrome	
Mucopolysaccharidosis type 2 (Hunter syndrome)	
<i>Neuromuscular</i>	
Charcot–Marie–Tooth disease (one type)	
Muscular dystrophy (Duchenne and Becker types)	
Muscular dystrophy (Emery–Dreifuss type)	
Myotubular myopathy (one type)	
<i>Central nervous system</i>	
Kallmann syndrome	
Spinobulbar muscular atrophy (Kennedy's disease)	

dominant. Heterozygous females commonly show some degree of clinical involvement, and the frequency and extent of this varies greatly according to the disorder. Thus, for some disorders (e.g. type 2 mucopolysaccharidosis and Lesch–Nyhan disease) significant clinical involvement in heterozygotes is exceptional, while in others (e.g. adrenoleukodystrophy and X-linked Charcot–Marie–Tooth disease) it is relatively frequent. A manifesting female may present with an apparently different phenotype and, in the absence of an affected male in the family, be misdiagnosed (e.g. Duchenne muscular dystrophy, adrenoleukodystrophy). In some disorders (e.g. X-linked hyperammonemia), clinical problems may occur only under conditions of metabolic stress.

In the past, this clinical variability of heterozygotes, reflecting variation in X-chromosome inactivation, was also seen in tests of carrier detection, making it impossible to reassure women at risk completely, on the basis of a normal result (e.g. creatine kinase in Duchenne dystrophy). This problem has

largely been removed by DNA-based tests, where the heterozygous state can be seen unambiguously.

A surprising number of clinicians are still confused by the basic pattern of X-linked transmission for the offspring of affected males (e.g. Becker muscular dystrophy, X-linked Charcot–Marie–Tooth disease). Because a man cannot transmit his only X chromosome to a son, all such sons (and their descendants) have no genetic risk; however, as all his daughters will receive his X chromosome, they will all (not 50%!) be heterozygous carriers. This is one of the few genetic situations (barring issues of paternity) where one comes close to certainty.

Mitochondrial inheritance

A small but important group of neurogenetic disorders are determined not by nuclear genes but by genes forming part of the mitochondrial genome. Included in this group are progressive disorders of childhood and adult life, which may affect either the CNS, muscle, or both, as well as other systems. From the viewpoint of genetic counseling, the key factor is whether the germline is involved. Some disorders (e.g. most cases of myoclonic epilepsy with ragged red fibers [MERRF] and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke [MELAS]) are associated often with large somatic deletions of mitochondrial DNA and are usually sporadic. Others (notably Leber's hereditary optic neuropathy) are the result of germline mitochondrial point mutations and may be maternally inherited; there is virtually no risk of transmission through the male line – a helpful point for genetic counseling.

For female transmissions, this situation is made more complicated by the frequent occurrence of heteroplasmy, the presence of both a normal and abnormal mitochondrial cell line, which gives a variable risk for offspring of affected women. Unfortunately, molecular testing is often unable to give greater precision, as the degree of heteroplasmy varies from tissue to tissue, and can only be an approximate guide to the likelihood of clinical problems occurring.

General principles of genetic counseling

No attempt is made here to cover the psychological or even the more generic counseling aspects of genetic counseling, although these are of great importance and need to be considered by all those intending to be involved. It is important, however, to consider

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Table 2.5. General aims of genetic counseling

Information on genetic risks
Information on wider aspects of the disorder
Clarification of genetic and diagnostic uncertainties
Information on further genetic options (including genetic testing)
Information on possibilities for management, therapy, prenatal diagnosis
Supportive but nondirective framework for all the above

some of the main general factors, and the first of these is: what are the aims of genetic counseling? Table 2.5 summarizes some of these, and also some of the aspects that are not (at least in our opinion) valid aims, but which may be considered as such (and have been, in the distant past), at times with disastrous consequences.

The main reason why people request genetic counseling is to obtain accurate information on the risks of a possibly genetic disease occurring in themselves, their children, existing or future, or in other relatives. Alongside this numerical risk, accurate information is needed on the disease itself, its range of severity, age at onset, and system involvement, as well as present and likely future possibilities for therapy. Such information is often more important, although also often less certain, than the actual risk of recurrence, and assessing it may require considerable clinical as well as genetic expertise.

Particularly for those where the genetic risk is high and the disorder serious, genetic testing may be required, as covered more fully later in the chapter. Such testing may be a necessary part of making a specific genetic diagnosis in an affected individual; it may be needed for establishing or excluding the heterozygous carrier state; it may be used for predictive (presymptomatic) testing, or prenatal or (at a very early stage) preimplantation genetic diagnosis.

All these important options need to be considered in the light of the more general aspects of genetic counseling. The interpretation of and need for genetic tests may depend critically on the risk situation of the individual and on his/her wishes; indiscriminate use of tests on those not at significant risk or not wishing for them is not good clinical practice. In this respect, it should be noted that people often may request testing when what they really wish for (and need) is

a more general provision of information, which may (or may not) involve an actual laboratory test. Unfortunately, often it is easier to fill in a form and send a sample to the laboratory than to undertake the more time-consuming course of exploring what a person's wishes and worries actually are.

An essential component of genetic counseling is a nondirective approach, allowing the individual (or couple) to make their own informed decision, rather than being told what is best for them. This approach differs considerably from most in diagnostic or therapeutic medicine, where patients generally will wish to be guided regarding the best course. As clinicians ourselves, involved in both genetic counseling and management of particular disorders, we have found it a considerable challenge at times to separate the different roles. It is important, however, not to confuse nondirectiveness with lack of support – providing a supportive framework is essential if people are to be able to reach often difficult and traumatic decisions, as with presymptomatic or prenatal testing – while continuing support, regardless of what decision has been made, is equally important.

An essential component of genetic counseling is adequate time, and this actually is the most difficult and most expensive factor to preserve in most health-care systems. It is simply not possible to deal with the complex issues, genetic and personal, that arise in genetic counseling without having adequate time, generally one hour for a new consultation. If one does not have this time available, it is better not even to try to be involved in genetic counseling, as it is likely to do more harm than good. A hurried consultation may leave people confused, with vital questions unanswered and the real issues never surfacing. Most patients and their families remain remarkably considerate of doctors and, when faced with an obviously busy or hurried clinician, often will decide not to raise questions that they know are going to be difficult to answer.

It goes without saying that anyone involved with genetic counseling needs to be a good communicator. We all consider ourselves to be able at this (although an objective opinion from others is likely to be a better guide!). Important elements include a sympathetic as well as knowledgeable approach; enjoying relating to people and their problems; willingness to listen, not just to talk; an ability to use simple language and to avoid technical details; and projecting a feeling of supportiveness. Even those who are good