

New genes for old diseases: the molecular basis of myotonic dystrophy and Huntington's disease



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In medicine, as in many other fields, the science of genetics has shown its power most strikingly by its ability to throw new light on old and apparently insoluble problems. The two genetic disorders, myotonic dystrophy (dystrophia myotonica) and Huntington's disease, have formed the cornerstone of my work for almost 25 years. I have studied them from all angles, clinical and genetic, have written books on both [1,2], but only recently, with the isolation of the genes for each disorder and the recognition of the remarkable mutational mechanism involved, have many of the puzzling features that I have documented over the years been resolved.

The phrase 'new genes' indicates that in both these inherited diseases the genes have recently been isolated (in 1992 and 1993), while previous biochemical and other studies had given no clue to their nature or function [1,2]. Even more remarkably, both diseases are examples of a completely new type of mutation: unstable or 'dynamic' mutations in an expanded triplet repeat of bases, now recognised as forming a distinct and growing family of disorders caused by trinucleotide repeat expansions.

By contrast, the term 'old diseases' reflects the fact that they have been recognised for many years, over a century in the case of George Huntington's classical description of the disease [3] in 1872 (with even earlier reports now known to be of the same disorder), and a long history also for myotonic dystrophy, first described by Steinert [4] in Germany and by Batten and Gibb [5] in Britain in 1909. Both disorders were also among the first to be recognised as following Mendelian dominant inheritance, proposed for Huntington's disease in 1908 by Punnett [6] and for myotonic dystrophy in 1918 by Fleischer [7].

The term 'old diseases' has taken on added significance since the molecular basis was discovered, for, as will be seen, the original mutations predisposing to the disorders may indeed be very old—possibly many thousands of years.

At the time I started to work on these two disorders, neither I nor anyone else had reason to suspect that

they might be related to each other in any way. As can be seen from Table 1, the clinical features are very different. Huntington's disease is a disorder of the central nervous system (CNS), while myotonic dystrophy, in addition to the muscular wasting, myotonia and other clinical characteristics, shows a remarkable degree of multisystem involvement. When looked at from the viewpoint of the clinical geneticist, however, a number of common features start to emerge, not simply the dominant pattern of inheritance but the variability in age at onset, the apparent rarity of new mutations and, most notably, the existence of unusual childhood forms of the two disorders and the occurrence of 'anticipation', these features present a special phenomenon (Table 2).

Anticipation

Both myotonic dystrophy and Huntington's disease have traditionally been considered as disorders of adult life, and it was many years before it was recognised that they might occur in early childhood. Juvenile Huntington's disease was first fully recognised in the 1920s [8], though a likely case in a family had been noted as long ago as 1888 [9]; the distinctive congenital form of myotonic dystrophy was not documented until 1960 [10]. These childhood forms played a major role in shaping my own research in this field, notably congenital myotonic dystrophy, whose clinical and genetic features I studied extensively both

Table 1. Clinical features

Myotonic dystrophy	Huntington's disease
Progressive muscle weakness and wasting; myotonia	Progressive CNS degeneration
Multisystem disorder	No other systems primarily involved
Smooth and cardiac muscle involvement	Particular involvement of caudate nucleus and cerebral cortex
Endocrine disturbance, cataract and CNS involvement all frequent	Premature neuronal cell death the main feature

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Table 2. Classical genetic studies

Myotonic dystrophy	Huntington's disease
Autosomal dominant	Autosomal dominant
Exceptionally variable in clinical picture and age at onset	Very variable age at onset
New mutations apparently very rare	New mutations apparently very rare
Atypical congenital form	Atypical juvenile form
Anticipation (marked)	Anticipation (moderate)

in America [11] and in Britain [12,13] in the 1970s. Not only do the clinical features of this condition differ markedly from the classical adult form, but it is almost invariably transmitted by an affected mother, in contrast to what would be expected from autosomal dominant inheritance. During the course of my early research on myotonic dystrophy, I recognised the parallel with Huntington's disease (Table 3), where the rare childhood form also showed marked clinical differences from most adult onset cases, and where a striking parent-of-origin effect is also seen—but in this instance with most cases being paternally transmitted [14], the opposite of the maternal transmission of myotonic dystrophy. Thus in both disorders genetic studies were producing unusual, puzzling and remarkably comparable findings, despite the apparent dissimilarity of the conditions. This situation was heightened by the recognition that both disorders appeared to demonstrate 'anticipation', a finding central to the later molecular explanation of the genetic features.

'Anticipation' can be defined as the occurrence of a disorder with earlier age at onset (and usually greater severity) in successive generations [15]. Arising out of the rather confused concept of 'degeneration', especially in relation to mental illness, anticipation was

Table 3. Childhood forms of myotonic dystrophy and Huntington's disease

Congenital myotonic dystrophy	Juvenile Huntington's disease
Severe—often fatal around birth	Not from birth, but can occur as early as 5 years
Clinical picture different from adult form—hypotonia, mental retardation, little myotonia	Clinical picture differs from adult form—rigidity, general neurodegeneration
Occurs in same families as classical cases	Occurs in same families as classical cases
Almost always transmitted by affected mother	Usually paternally transmitted

first documented in a precise and accurate form by Fleischer [7] in 1918, who observed that apparently unrelated patients with myotonic dystrophy could be linked in previous generations through individuals who had cataracts in later life but who had no muscle disease. Since cataract was already a known clinical feature of myotonic dystrophy, Fleischer suggested perceptively (and we now know correctly) that cataract in these patients was a precursor for the development of the full disorder in subsequent generations, and that the disorder worsened and occurred with earlier onset with each transmission.

These observations were widely accepted (though not explained) for several decades, until the analysis by Penrose [16] in 1948 suggested that anticipation in myotonic dystrophy did not represent a biological phenomenon, but could be explained by the natural variability of the disorder, by biases of observation and by the effects of the opposite allele. Penrose was strongly influenced by the difficulty in imagining any mechanism by which a gene could change in successive generations, as well as by the unscientific way in which anticipation had originally been proposed for mental illness and mental handicap.

Following Penrose's paper [16], the concept of anticipation virtually vanished from the literature for 30 years, but the underlying facts relating to myotonic dystrophy were more obstinate and eventually demanded reassessment. My own observations on the congenital form, with a possible maternal effect [11–13], showed that myotonic dystrophy could indeed worsen if transmitted by a woman. Thorough studies by Höweler *et al.* [17] in Holland, of families that had been observed continually for decades, showed that progressively earlier onset was a fact even when the biases had been eliminated. Finally, an interesting parallel could be seen for anticipation in another disorder, fragile X mental retardation, where the possibility of a two-step mechanism of mutation had already been raised by Sherman *et al.* [18]. In 1989 I suggested that something comparable might be occurring in myotonic dystrophy [19]. On a wider front it was becoming clear that anticipation was also apparent in Huntington's disease [20], though only in the male line of transmission, and that this was likely to underly the puzzling paternal transmission of the juvenile form already mentioned. Thus by 1990 it was clear that anticipation was real (Table 4). The only problem was that no obvious biological mechanism was known, either from man or from other species, that could explain it. This explanation had to await the development of the techniques of molecular genetics and the isolation of the genes involved.

Isolating the genes

For the first decade of my research on myotonic dystrophy and Huntington's disease, the genes involved were abstract concepts, not tangible entities

Table 4. Anticipation in myotonic dystrophy and Huntington's disease

Myotonic dystrophy	Huntington's disease
1918 first proposed (Fleischer)	Not suspected in early genetic studies
1948 explained by 'bias' (Penrose)	1969 paternal transmission of juvenile HD
1989 again suspected as 'real' from pedigree studies (Höweler)	1988 anticipation shown in male line only
1991 unstable DNA in fragile X suggested a biological mechanism	

that could be studied directly. Patterns of transmission and variation within families and populations could tell us much about the nature of the inheritance, but we were totally ignorant of the characteristics of these genes, or the nature of the proteins they produced. There were not even any substantial clues from biochemical research as to the type of protein that might be expected. Thus the possibility of 'positional cloning', the isolation of a gene through molecular techniques based solely on its position on the chromosome, proved to be of special importance for both myotonic dystrophy and Huntington's disease.

The full story of the isolation of these two genes has been told elsewhere [21,22], but I consider myself exceptionally fortunate to have been part of the Cardiff team that was, along with international collaborators, responsible for the successful identification of both genes and to have been able to be involved from beginning to end. It seems unjust to summarise ten years of intensive—and at times frustrating—work in a single table (Table 5), but now that the genes themselves are isolated, the path along the way is of less direct relevance to clinicians. It is worth noting,

Table 5. Positional cloning of the genes for myotonic dystrophy and Huntington's disease

Myotonic dystrophy	Huntington's disease
No clues from biochemistry	No clues from biochemistry
9-year search from first chromosomal location	10-year search from first chromosomal location
Single locus on chromosome 19	Single locus on chromosome 4
All 'candidate genes' misleading	Confusion over exact location from 'recombinants'
Gene and mutation identified 1992	Gene and mutation identified 1993

however, that the extensive gene mapping around these two chromosome regions, chromosome 19 in myotonic dystrophy and chromosome 4 in Huntington's disease, has resulted in a major general contribution to the human genome project, with a series of genes being discovered that has proved to be completely different from the ones being looked for, even though physically nearby. For example, one gene originally analysed in relation to Huntington's disease turned out to be that for a fibroblast growth factor and to be responsible for the bone disorder achondroplasia [23].

The process of moving from gene mapping based on family studies to actually identifying and isolating the genes proved extremely difficult for both diseases. One valuable clue, a particular contribution of our Cardiff group [24,25], was the recognition of the precise location by finding strong 'allelic association' or 'linkage disequilibrium' between specific marker alleles and the disease. In both disorders this helped greatly to pinpoint the region of chromosome to be analysed, while for myotonic dystrophy it provided strong evidence that the actual gene had been discovered when we found a particular marker constantly associated with the disorder [26].

Unstable mutations

How would we recognise the disease gene when we actually found it? Without a specific change characteristic of affected patients, there could be no proof that the gene found was really the right one. It was at this point that the significance of anticipation, and of looking across to research on other diseases, became greatest. In mid-1991 an unstable DNA sequence on the X chromosome was found to be responsible for the disorder fragile X mental retardation [27]; the explanation for anticipation in this disease provided an immediate parallel for myotonic dystrophy and Huntington's disease and gave a focus for the type of change to be looked for in the genes suspected of underlying these disorders. Within a year, an unstable DNA sequence had been identified in relation to myotonic dystrophy [26–29], and a year later (1993) the same proved true for Huntington's disease [30].

After I had worked for almost 20 years on both disorders in parallel, it seemed an extraordinary coincidence for both to show the same underlying mutational mechanism. As a clinical geneticist, I was even more surprised to realise that the instability and expansion of trinucleotide repeats was not simply new as an explanation for human disease, but was unknown in the whole of nature—no comparable situation was known for any species, such as the mouse or *Drosophila*, used in experimental genetic studies. Studies in the fundamental properties of this class of mutation are now providing insights into how genetic mutations can arise and spread.

Clinical features and molecular defect

As a clinician, I was struck by the way in which so many of the puzzling features of the disorders immediately started to fall into place. Foremost, of course, was anticipation, since we now had, for the first time, a clear biological explanation for what had been observed so long ago in myotonic dystrophy. Figure 1 shows this at the level of the individual family, with the expanded repeat sequence in the gene increasing progressively in each generation and corresponding to the earlier onset and greater severity. Nor is this finding confined to individual families. As can be seen from Figure 2, the overall earlier onset seen in offspring, as compared with the parental generation, is closely paralleled by the molecular status of these individuals, the younger generation mostly, but not all, showing larger repeats and an earlier age at onset.

The instability of the mutations also explains to a large degree why the disorders are so variable within a single kindred, unlike most genetic conditions where clinical characteristics and severity largely 'breed true'. Figure 3 shows the range of mutation expansion seen in a single Huntington's disease kindred. This variation is in total contrast to the usual situation for conditions such as haemophilia or cystic fibrosis, where an

identical mutation would be expected in all affected members of the same family. Table 6 summarises some of the main features of genetic instability seen in the two disorders.

We can now begin to assess the unusual childhood forms of both myotonic dystrophy and Huntington's disease in the light of our new knowledge and see how many of the puzzling features can be explained.

First, it is clear for both disorders that there is a broad correlation between size of trinucleotide repeat expansion and age at onset, and that for both disorders it is the childhood cases that show the largest expansions [31,32] (Fig 4). This can also be seen for myotonic dystrophy if patients are grouped into those with minimal disease (usually cataract alone), those with classical adult disease, and those with the severe congenital form [33] (Fig 5). Although the differences between the groups are marked, there is a considerable overlap, making caution necessary in using this information prognostically. In Huntington's disease the scatter is even greater, only the extremes of the molecular distribution showing any degree of constancy in relation to age of onset or severity. It is clear that other factors have an important influence on clinical expression of the genes.

Can we explain why in myotonic dystrophy the

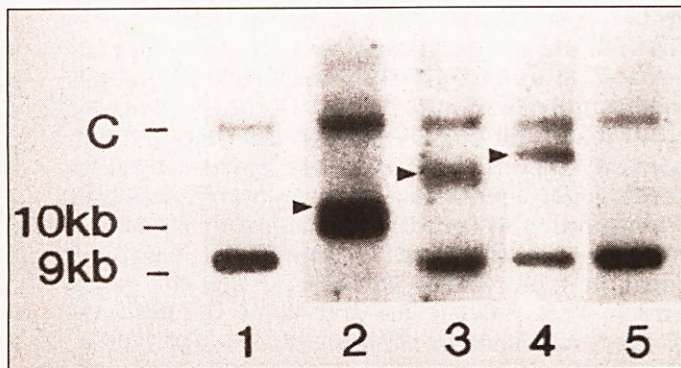


Fig 1. Anticipation in myotonic dystrophy. A three generation family with myotonic dystrophy, showing increased severity and earlier age at onset with successive generations. There is a corresponding increase in the expansion of the repeat sequence (arrowed) at the myotonic dystrophy locus. Columns 2, 3, 4 correspond to representatives of generations 1, 2, 3. Photograph published with family's permission

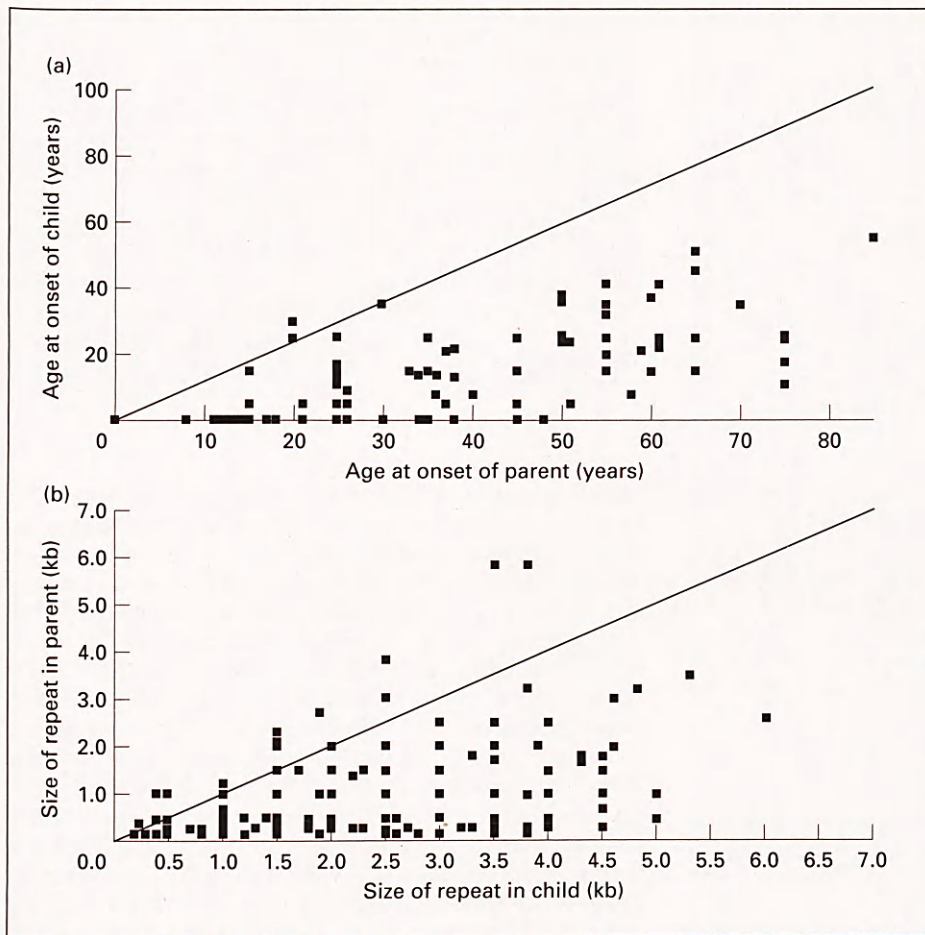


Fig 2. Anticipation at the clinical and molecular levels. Comparison of parental and childhood generations in myotonic dystrophy showing close correspondence of anticipation in the same series of families for (a) age at onset, with onset predominantly at earlier age in offspring, (b) increased size of mutational expansion in offspring

severe congenital cases are almost all maternally transmitted, while in Huntington's disease the opposite occurs (Table 7)? The paradox can be readily explained if we take into consideration the size of the expansions. In congenital myotonic dystrophy these are very large indeed—up to several thousand repeats; pooled data between centres show that in paternal transmission there seems to be a size limit and that beyond this limit the repeat number is more likely to decrease than increase [34]. Perhaps sperm carrying very large expansions are less viable. No such limit exists for female transmissions, thus explaining the maternal transmission of the most severe cases.

In Huntington's disease, on the other hand, even the most severe juvenile cases have quite small expansions (rarely over 100 repeats). Analysis of sperm samples from male Huntington's disease patients shows a more variable and generally larger repeat number than that found in blood samples from the same individual [35], suggesting that in this range spermatogenesis is more likely to produce large expansions, and thus juvenile disease, than is transmission from an affected mother. For myotonic dystrophy, patients with around 100 repeats will mostly be mildly affected, and it is of interest that such mild cases are

also most often of paternal origin—thus there is no real difference between the disorders, provided one is comparing similar size ranges of the mutation.

Origin of the mutations

It has long been recognised for both Huntington's disease and myotonic dystrophy that truly isolated cases likely to represent new mutations are very unusual. If care is taken, almost all cases can be shown to be derived from an affected parent (often minimally affected) or can be linked through ancestors to other branches of the family who have the disorder.

Our new concept of unstable or dynamic mutation, with the associated anticipation, now explains why these linking ancestors are so mildly affected or even entirely healthy. Where they are available for testing, these ancestors commonly show a molecular repeat number that is at the borderline between normal and abnormal ranges [36,37]; some of them may develop symptoms if they live long enough, but others will remain unaffected, only being recognised if they have passed on an expanded sequence to their descendants. Such individuals may provide links between families extending back many generations. Thus the many

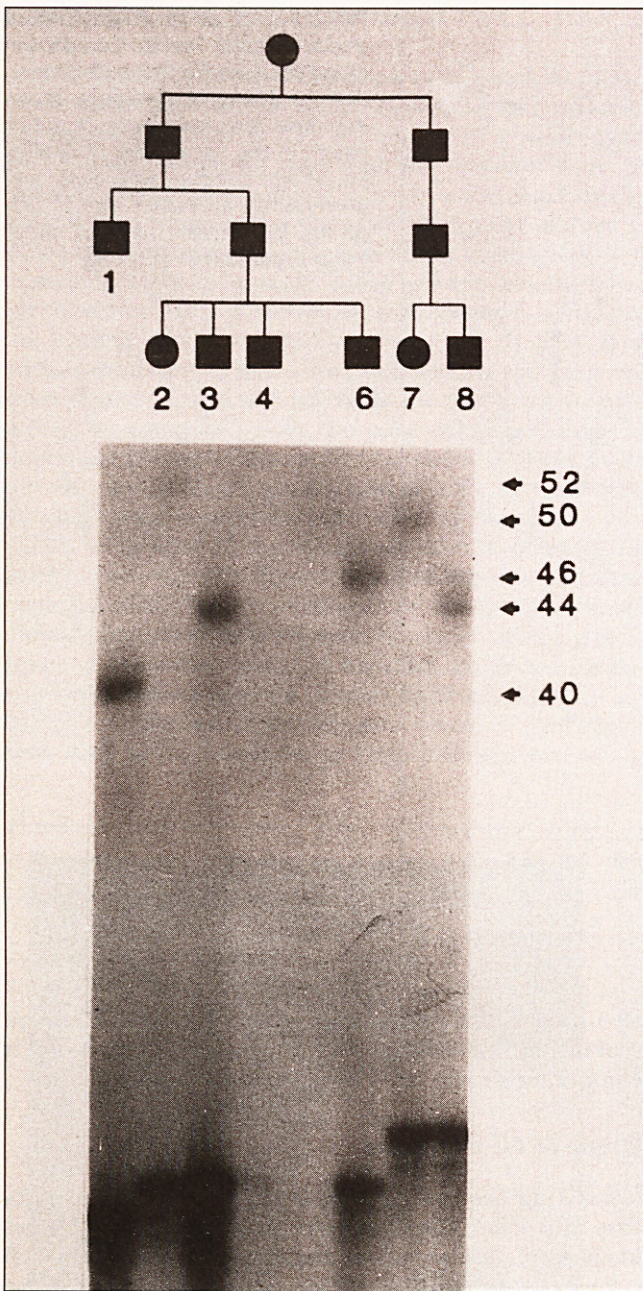


Fig 3. Unstable DNA sequence in Huntington's disease. Molecular analysis for the HD mutation in a single kindred, showing the variable degree of expansion in different family members [47]

Myotonic dystrophy	Huntington's disease
Normal range less than 30 repeats	Normal range less than 35 repeats
Disease range extreme (50–2,000 + repeats)	Disease range moderate—mostly 40–60 repeats
Somatic variation marked	Little somatic variation seen
Germ-line and somatic expansions may differ considerably	Expansion in spermatogenesis (possibly little in oogenesis)

many occasions. However, if one analyses DNA markers around the gene to give a composite pattern or haplotype, one finds that this also seems to be unique for myotonic dystrophy over most of Europe and beyond [24], suggesting that most cases may have a common origin. Study of the normal range of repeats at the myotonic dystrophy locus shows considerable variation between ethnic groups, with the polymorphism also clearly present in non-human primates [39]. Thus the original change that eventually led to most cases of myotonic dystrophy may have occurred many thousands of years ago, with a gradual increase over many generations until the number of repeats reached a point where the altered gene became significantly unstable and started to produce clinical problems.

One observation that may prove to be related to the origin of the myotonic dystrophy mutation is that the disorder is exceptionally rare in Africa south of the Sahara [40], whereas over most European and Asiatic populations, including Japan, it is relatively common. It is thus possible that the principal original mutation occurred after the African races had diverged from others, but before any separation of Asiatic and Caucasian races. An alternative suggestion is that there could be a 'predisposing haplotype', absent or rare in Africans, from which the myotonic dystrophy mutation might have arisen more than once. Whatever the outcome, it can be seen how important the study of these disease mutations is becoming as part of the analysis of our general evolutionary history.

Gene function

What do we know about the nature of the genes themselves, their function, and the proteins they produce (Table 8)?

One of the striking developments of molecular biology has been the increasing feasibility of sequencing large stretches of DNA. Once the genes and mutations for myotonic dystrophy and Huntington's disease had been identified, sequence data could be generated and predictions made from computer-

families in Northern Quebec with myotonic dystrophy [38], where the frequency of the disease approaches 1 in 400, can almost all be traced back to a single individual born in France in the 16th century.

The origin of the mutations may go back much further than this. Almost all patients with myotonic dystrophy who have been studied around the world have shown the same unstable type of mutation, but it could be argued that this had arisen separately on

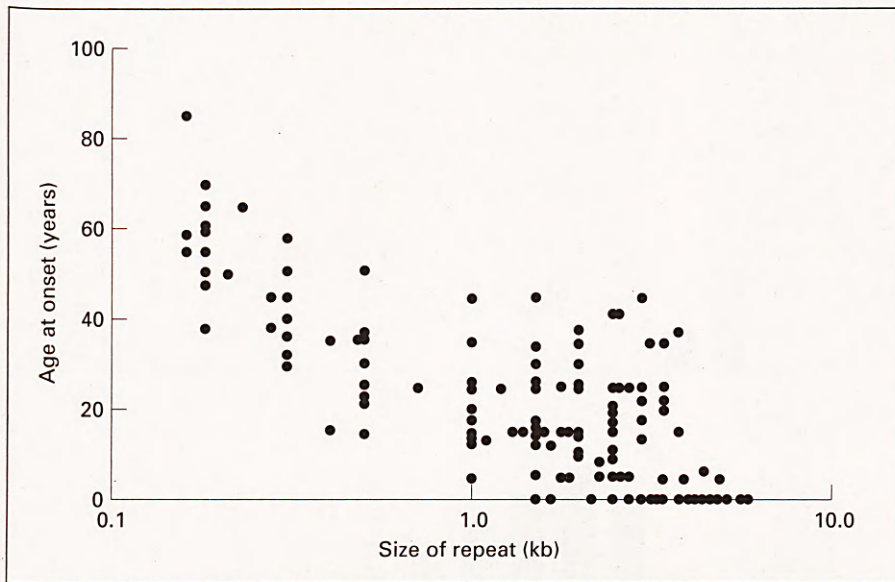


Fig 4. Correlation of phenotype and genotype in myotonic dystrophy: age at onset and mutation expansion

stored sequence databases regarding the structural and functional properties to be expected from the amino-acid sequence of the proteins. In the case of myotonic dystrophy this prediction strongly suggested that the protein would be a member of the serine-threonine protein kinase family [41-43]. This suggestion is now being confirmed by identifying the protein biochemically and by functional studies. This fits well with what we know about the physiological basis of myotonia; a series of non-progressive myotonic disorders has been shown to result from defects of the sodium and chloride ion channels in muscle, and it can be speculated that the myotonic dystrophy protein kinase may modify the activity of these ion channels, as well as being important for the integrity of the muscle membrane.

For Huntington's disease, by contrast, the sequence prediction offered no suggestions of possible function [30], nor was there any homology with sequences

previously described. (This at least was of some relief to the teams involved, since it would have been an anticlimax to ten years of search if it had turned out that the gene was already known in some other species!) Current research shows that the protein produced is widely distributed in brain tissue and elsewhere, but it will be some time before we are clear as to its function.

Trinucleotide repeat expansions in general

The insights gained from identifying the genes and unstable mutations for myotonic dystrophy, Huntington's disease and also fragile X syndrome, have led to the recognition that we are dealing with a general mechanism of mutation and with a growing family of genetic disorders showing a number of common properties, as well as significant differences.

Table 9 shows the chronological sequence of this

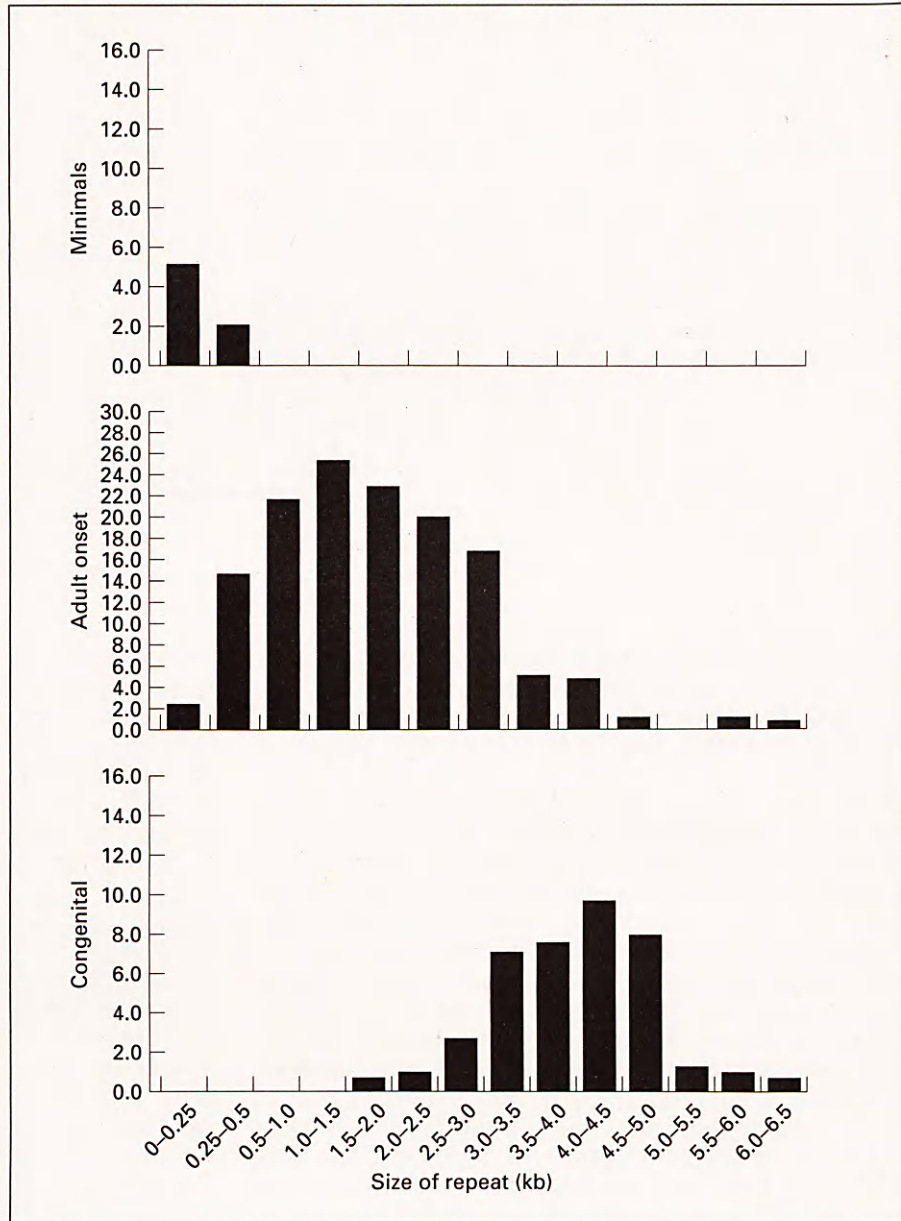
Table 7. Childhood forms of disease: the molecular basis

Congenital myotonic dystrophy	Juvenile Huntington's disease
Largest expansions, may exceed 2,000 repeats (but overlap non-congenital range)	Largest expansions (but rarely over 100 repeats)
Parental expansions also larger than average	Usually occur when parent already has substantial expansion
Size limit of expansion through male meiosis, so female transmission of congenital cases	Male transmission explained by increased mean repeat size in sperm compared with other tissues

Table 8. Properties of the normal genes

Myotonic dystrophy	Huntington's disease
Moderate size—15 exons	Large gene—67 exons
Sequence predicts protein to be a serine-threonine protein kinase	No clues from sequence as to function of protein
Predominant expression in muscle	Expressed in all cell types
Probably important in controlling activity of ion channels	Protein localised in cytoplasm, not nucleus
Expanded trinucleotide repeat (CTG) in in 3' untranslated region of gene	Expanded trinucleotide repeat (CAG) in 5' translated region of gene

Fig 5. Correlation of phenotype and genotype in myotonic dystrophy: main clinical groups and mutation expansion



growth; other members have joined the group since this lecture was delivered, notably (and unexpectedly) the recessively inherited Friedreich's ataxia [44]. Perhaps of greater relevance, however, is the recognition that the conditions can also be grouped functionally in a way that can allow us to understand important similarities and differences. In the right-hand side of Table 9, myotonic dystrophy, fragile X syndrome and Friedreich's ataxia are grouped together but separate from Huntington's disease and other disorders now known to show trinucleotide repeat expansions. These first two conditions show the most striking anticipation and range of clinical variation, reflecting the extent of the expansions and the consequent genetic instability, which is itself strongly size dependent. These diseases

also show the greatest somatic variation between tissues (data not yet available for Friedreich's ataxia). Huntington's disease and the other neurological degenerations, by contrast, show a more modest range of expansion, little somatic variation and, as already mentioned, a lesser degree of anticipation mainly in the male line. It is also striking that all the members of this second group show CNS degeneration, with differences in cell types affected, but with molecular defects so similar in their ranges of expansion that figure legends reporting these could be transposed between the disorders without it being noticed. How can we explain the real differences between the two groups?

The most logical answer, and the simplest (Table 10), seems to be that in the first group (myotonic

Table 9. Trinucleotide repeat expansions: the wider grouping

Chronological sequence	Functional grouping
	Group 1 (Sequence untranslated)
1991	
Spino-bulbar muscular atrophy (SBMA)	Fragile X syndrome (types A and E)
1992	Myotonic dystrophy Friedreich's ataxia
Fragile X syndrome (type A) Myotonic dystrophy	
	Group 2 (Sequence translated)
1993	
Huntington's disease	SBMA
Spino-cerebellar ataxia (SCA1)	Huntington's disease
Fragile X syndrome (type E)	SCA1
1994	DRPLA
DRPLA (dentato-rubro-pallido-Luysian atrophy)	Machado Joseph (SCA3) SCA2
Machado-Joseph ataxia (SCA3)	
1996	
Spinocerebellar ataxia (SCA2) Friedreich's ataxia	

dystrophy, fragile X and, very recently, Friedreich's ataxia) the trinucleotide repeat showing expansion is not located in the coding sequence of the gene and thus does not actually appear in the protein product. Precisely how the expansion produces disease pathology is still uncertain, but in simple terms some interference with the normal gene function can be envisaged, the degree of which is directly related to the size of the expanded repeat. Small expansions cause little or no clinical pathology, and the repeat has to expand to a massive degree before the most severe consequences are seen.

In the second group, by contrast, the repeat sequence is, in all cases, placed in the coding region near the 5' end of the gene. It can thus be expected to appear in the protein product and has been proved to do so in Huntington's disease and also in Kennedy's disease (spinobulbar muscular atrophy), the first disease in which a trinucleotide repeat mutation was identified but whose significance was only recognised later. A further point of considerable significance is that in all members of this second group the repeat trinucleotide is CAG, coding for glutamine, unlike the first group, where the repeat trinucleotide is CTG in the case of myotonic dystrophy and CGG in fragile X.

The classification of unstable trinucleotide repeat disorders into these two categories, untranslated and translated, has considerable clinical consequences and greatly influences how one thinks about the ways in which mutation and disease are related. In the translated group it seems likely that only a modest expansion

Table 10. Trinucleotide repeat expansions in untranslated and translated groups

Untranslated*	Translated
Myotonic dystrophy and fragile X	Huntington's disease and other CNS degenerations
Nature of repeat varies	All are CAG repeats
Phenotype varies	All are CNS degenerations
Expansion and instability often extreme; much somatic variation	Expansion and instability moderate; little somatic variation
Anticipation marked	Anticipation modest

*Details for Friedreich's ataxia not yet available

sion can be produced without lethal effect, since the structure and function of the protein will be directly affected by its altered sequence. Thus only a moderate degree of instability will occur, with relatively little somatic variation and only modest anticipation. In the untranslated group, by contrast, expansion of the repeat sequence can reach a massive degree, at which point marked anticipation and somatic variability due to the extreme instability will be seen.

Looking ahead

Are there many more trinucleotide repeat disorders still awaiting discovery? My personal view has been that myotonic dystrophy and fragile X could well be the only disorders in the untranslated group, since it would be surprising if clinicians and geneticists were to have overlooked in other disorders the spectacular degree of anticipation seen and recognised so long ago in myotonic dystrophy. The recent discovery of a large GAA expansion in the intron of the gene responsible for Friedreich's ataxia [44] means this requires reassessment. The group of translated CAG repeats, however, with Huntington's disease as the prototype, has already been joined by several other CNS degenerations, where a slight degree of anticipation had been documented, and others, such as familial spastic paraplegia, seem likely candidates. A personal speculation would be that any new diseases in the translated group will also be CNS degenerations, not disorders of other systems, while if any were to be found in the untranslated group, they might affect any organ.

Following through on this speculation (Table 11) implies that grouping these conditions as untranslated (myotonic dystrophy) and translated (Huntington's disease) is fundamental to research strategies for understanding the conditions and their pathogenesis. If an expanded repeat sequence does not appear in the protein, then it can only produce pathology by interfering with the normal function of the gene. Thus for myotonic dystrophy, the nature and normal role of

Table 11. Trinucleotide repeat expansions and pathogenesis of disease—some speculations

Untranslated group	Translated group
Pathology through interference with normal gene function	Pathology may directly involve repeat sequence — primary gene function may be little affected
Phenotype will reflect function of specific gene involved — widely different according to nature of gene	Phenotype related to neuronal effects of glutamine repeat in protein — similar despite differences in gene function
Understanding and future therapy for disease likely to be related to understanding of specific gene function	Understanding and therapy could prove related to modification of neuronal effects of the repeat as well as specific genes involved

the protein kinase (and of adjacent genes that may well also be affected by the expansion) [45] is critical and, once we understand its function in different tissues, will relate directly to our understanding of the disease. Thinking ahead to future therapy, this may well be related to factors that can restore or alter the normal gene function. Pharmacological agents could well be imagined as effective, at least in arresting progression of adult onset cases.

For Huntington's disease and others in the translated group, future directions might be quite different. It seems likely that the presence of an expanded glutamine repeat in the protein molecule may have direct effects on gene function [46], and that the effect might be to some extent comparable regardless of the specific function of the gene concerned. Until we know more about the exact nature of these genes and the proteins that they produce and interact with this is perhaps a rash speculation, but we already have some evidence from one member of this group, Kennedy's disease, where the mutation is in the androgen receptor [47]; other mutations that destroy the function of this gene have no neurological effects, while in Kennedy's disease itself the endocrine features are minimal. It might seem heretical to suggest that the pathogenesis of Huntington's disease will have nothing to do with the function of the Huntington's gene! Nor would I advocate this view, but it may well prove that the direct effects of the mutation are as relevant as the specific properties and function of the gene in which it is placed. Again this could be relevant to therapeutic approaches, which might turn out to be fruitfully related to those factors influencing the neuronal effects of glutamine repeats.

The new understanding being made possible by molecular analysis is truly revolutionising the way we look at these 'old diseases' and at the old problems that classical genetic and clinical studies had identified

but could not solve without the new techniques. It is salutary, though, to appreciate to what a large extent these new advances have rested upon the old foundations; without the recognition of anticipation, of the unexpected parent-of-origin effects, the clinical variability and the apparent lack of mutations, the new discoveries would have been considerably delayed.

Standing at the interface of clinical medicine and molecular genetics enables me to see more clearly the value of the different types of observation and experiment, and how important it is for those with clinical and scientific training to communicate and collaborate with one another. I have been especially privileged to see this happen for the two disorders, myotonic dystrophy and Huntington's disease, that have been my main interest for almost 25 years, and to be able to begin to look ahead to a time when we can consider using our new understanding to devise treatment for the many patients who remain afflicted by these serious, relatively frequent, and challenging genetic disorders.

Acknowledgements

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