HISTORY OF GENETIC DISEASE

The molecular genetics of Huntington disease — a history

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Abstract | The Huntington disease gene was mapped to human chromosome 4p in 1983 and 10 years later the pathogenic mutation was identified as a CAG-repeat expansion. Our current understanding of the molecular pathogenesis of Huntington disease could never have been achieved without the recent progress in the field of molecular genetics. We are now equipped with powerful genetic models that continue to uncover new aspects of the pathogenesis of Huntington disease and will be instrumental for the development of therapeutic approaches for this disease.

Huntington disease is a late-onset neurodegenerative disorder that follows an autosomal-dominant pattern of inheritance. It affects individuals from childhood to old age and follows a course that lasts 15–20 years[1]. There are no sporadic forms of the disease and, in most cases, symptoms present in mid-life and include psychiatric disturbances, motor impairments and a cognitive decline. Since the late 1970s, the scientific community and lay organizations have worked together to ensure that Huntington disease is at the forefront of new developments. In 1983 the Huntington disease gene (*HD*) was the first to be mapped to a human chromosome without any prior indication of the gene location. Over the following 10 years, some of the most innovative laboratories joined efforts to apply emerging gene-mapping and genomics technologies, which led to the identification of the *HD* mutation as a CAG-repeat expansion in 1993. The molecular approaches that have been applied to unravel the genetic basis of Huntington disease have been consistently successful. We have gained insights into the cellular mechanisms in which the HD protein participates and the mechanisms through which pathogenic mutations in the *HD* gene exert their deleterious effects.

It is now a good time to review the history of these achievements as we face the next challenge, which involves the translation of basic research into effective treatments (TIMELINE). I begin with an overview of the early history of the disease and the description of its clinical symptoms. I then discuss the approaches and people that successfully led to the mapping and cloning of the *HD* gene during the 1980s and early 1990s. The identification and analysis of the *HD* mutation explained the genetic basis of Huntington disease and also allowed rapid and accurate predictive testing for this disease: sections of this article are devoted to both of these aspects and their ethical implications. Our understanding of the function of the HD protein and some of the insights that we have gained into the molecular pathogenesis of Huntington disease through the generation and analysis of animal models of the disease are then presented. I conclude by discussing the approaches that are being used to develop therapies. In the future, the ability to predict the individuals who will develop Huntington disease must be turned to an advantage through the development of treatments that can substantially delay the onset of symptoms.

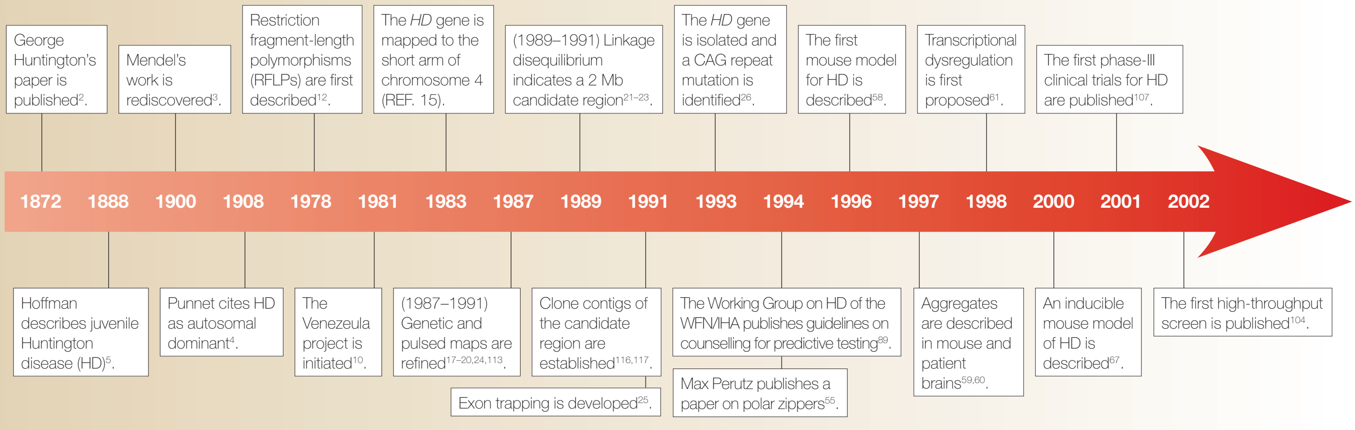
Genetics and symptoms

Although George Huntington was not the first to describe Huntington disease, his 1872 paper was so comprehensive that it was widely acclaimed from the outset and soon gained him international recognition[2]. His father and grandfather were physicians, practising in a rural community in New England, and as a child Huntington often accompanied them on their professional rounds. The collective experience of these 3 generations spanned 78 years and gave him a unique perspective on this hereditary disease. He delivered his paper 'On chorea' before the Meigs and Mason Academy of Medicine at Middleport, Ohio, on 15 February 1872 at the age of 22 (REF. 3) (FIG. 1). In this paper he described all the clinical features of the adult-onset form of the disease that we recognize today (which is also known as Huntington's chorea) and he clearly outlined its autosomal-dominant pattern of inheritance. The mechanism underlying his observation was not appreciated until after the rediscovery of Mendel's work[4] in 1900, when it was recognized that Huntington disease probably followed a Mendelian dominant pattern of inheritance[5].

When describing the symptoms, George Huntington noted that the movement disorder is accompanied by personality changes (nervous excitement) and a cognitive decline (tendency to insanity). He also noticed that families that suffer from Huntington disease were characterized by an increased incidence of suicide, thereby he described many aspects of the adult disease.

George Huntington did not encounter the juvenile form of Huntington disease during his work. This form, which is defined as onset before the age of 21 years, was first described by J. Hoffman using data from a three-generation family. Hoffman identified 2 daughters with onset at 4 and 10 years who showed rigidity, hypokinesia and seizures[6]. This was the first observation showing that the juvenile form of the disease could manifest with clinical features

Timeline | **Benchmarks in Huntington disease research**



WFN/IHA, World Federation of Neurology and the International Huntington Association.

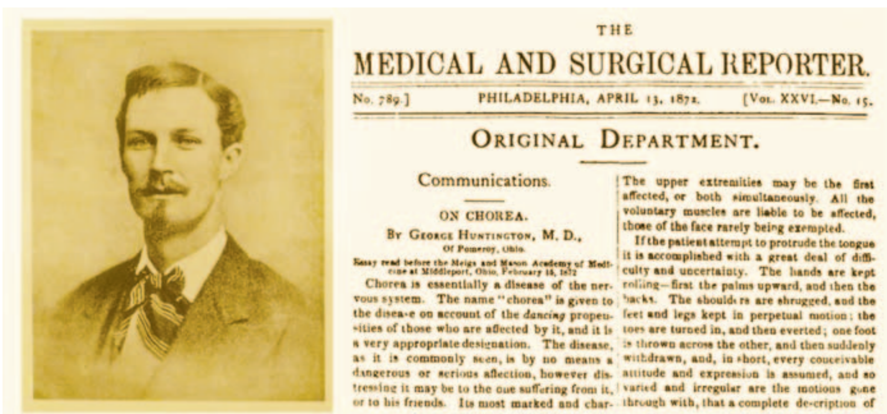
that were strikingly different from those seen in the adult-onset disorder[2]. In 1998 extensive analysis of the 'Huntington disease roster' US database revealed that the *HD* gene shows ANTICIPATION, but only on paternal inheritance[7], with the consequence that juvenile cases of Huntington disease inherit the disease from their father. Since the cloning of the *HD* gene, mutation analysis has begun to reveal the molecular basis of this gender bias[8,9], although the mechanism is not understood (see below).

Mapping the *HD* gene

In the late 1970s, David Housman suggested to Allan Tobin, who was the scientific director of the Hereditary Disease Foundation (HDF), that new developments in the field of molecular genetics might facilitate the mapping of human disease genes. Following this conversation, an HDF workshop (BOX 1) was organized to discuss different strategies for mapping the *HD* gene[10]. Mapping human genes and the generation of linkage maps were not new concepts, but there were few available genetic markers that could be applied to the human genome[11]. This situation changed in 1978 after the identification of RESTRICTION FRAGMENT-LENGTH POLYMORPHISMS (RFLPs) close to the β-globin gene[12], which revealed polymorphic variation in DNA sequence between individuals. Although the extent of this variation was unknown, it was soon proposed that RFLPs might occur sufficiently frequently within the genome to allow the generation of DNA-based linkage maps of human chromosomes and the mapping of disease genes[13]. David Housman and James Gusella initiated the first *HD* gene-mapping project using RFLPs at the beginning of the 1980s. Although the most successful strategy and the length of time required for the completion of this project were subjects for intense debate, it was apparent that large well-characterized families with Huntington disease were required. Fortunately, a large family with Huntington disease had already been found in Venezuela.

Nancy Wexler had made some exploratory visits to Venezuela in the late 1970s because of reports of a high incidence of Huntington disease in the communities of San Luis, Barranquitas and Laguneta, around the shores of Lake Maracaibo. She headed the first research expedition to Maracaibo in 1981 with the aim of identifying individuals that were homozygous for the *HD* gene[14], and of generating the resources necessary to implement the mapping project. Because it was unclear whether Huntington disease was a HETEROGENEOUS disease, it was advantageous to study a large family emanating from a single founder, thereby ensuring that all affected individuals carried the same mutation in the same gene. The team established detailed pedigrees and made a neurological and cognitive assessment of affected family members and at-risk relatives. They also took blood samples to send back to the Gusella laboratory for DNA isolation and the establishment of cell lines. Remarkably, and contrary to all expectations, using the Venezuela kindred and a large Ohio family, the Gusella laboratory found linkage to Huntington disease with the eighth polymorphic marker tested (G8), which mapped the gene to the short arm of chromosome 4 (REF. 15). This was the first genetic disease locus to be mapped to a chromosome without any prior knowledge of its chromosomal location.

Nancy Wexler recruited a dedicated team for the Venezuela expeditions, who continued the research for the following 20 years[16], until the recent political situation made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ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

BY GEORGE HUNTINGTON, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of

Figure 1 | **George Huntington as a young man.** Reproduced from the 'Huntington number' of *Neurographs*[118]. This was the title page of George Huntington's 1872 paper in the *Medical and Surgical Reporter*.

it too dangerous to continue. The Venezuela kindreds now encompass 18,149 individuals spanning 10 generations, of whom 15,409 are living[16]. This is a unique longitudinal study of a non-medicated population that has mostly arisen from a single founder and that shows a wide range of clinical variability. These well-characterized kindreds will be an invaluable resource for the identification of genes that modify the onset and progression of Huntington disease.

Cloning the *HD* gene

Mapping the *HD* gene paved the way for isolating the gene, identifying the disease-causing mutation and uncovering the molecular pathogenesis of the disease. However, G8 turned out to be 4 cM (approximately 4 Mb) away from the *HD* gene[17,18]. The technology required for gene isolation did not exist in 1983. Few polymorphic DNA markers, which were restricted to BIALLELIC RFLPs, were available. The amount of DNA that could be contained in genomic DNA clones was limited, and the presence of repetitive sequences and/or sequences that were difficult to clone made it impossible to walk along a chromosome for more than 100–200 kb. Essentially, the entire field of gene cloning and genomics had still to be invented.

To facilitate the gene-cloning effort, the HDF invited laboratories developing expertise or resources to join forces in a formal collaboration, and organized regular workshops to facilitate the free exchange of materials and ideas between the group members. This collaboration was a novel approach in the field of human genetics, as in the mid 1980s the research projects that involved mapping and cloning of human disease genes tended to be highly competitive. The gene was eventually cloned in 1993 by the Huntington disease collaborative group, which was composed of six laboratories headed by Francis Collins, Jim Gusella, David Housman and John Wasmuth in the United States and Peter Harper and Hans Lehrach in the United Kingdom. Other groups led by Rick Myers, David Cox and Michael Hayden also contributed to the cloning efforts.

Although genetic linkage analysis placed the *HD* gene between G8 and the telomere[17], this type of analysis could not accurately define the precise position of the gene within this region. To further pinpoint the location of the gene, strategies were used to take advantage of recombination events that had occurred within this chromosomal region in individuals with Huntington disease. The aim of these approaches was to position the *HD* gene on one side or the other of the recombination events; however, such events were rare and the strategy crucially depended on an accurate diagnosis. By 1989 four such events had been identified: three of them placed the gene close to the 4p telomere, whereas the fourth one predicted a location closer to G8 (REF. 19). Cloning the 4p telomere defined the end of the chromosome and indicated that the highly repetitive 100 kb of DNA within the telomeric candidate region was an unlikely place for the gene[20]. To determine which polymorphisms were in LINKAGE DISEQUILIBRIUM (LD) with *HD*, studies were conducted to analyse the frequency with which specific alleles of the polymorphisms that were genetically linked to Huntington disease were inherited with the *HD* mutation. The LD analysis also indicated that the gene was most likely to reside in a 2-Mb region closer to G8 than to the telomere[21–24]. Following the cloning of the gene, it was revealed that the three individuals with putative recombination events pointing to the telomeric location did not have Huntington disease.

Various genetic and physical mapping and cloning strategies were combined to define and clone the *HD* candidate region (BOX 2). A novel EXON TRAPPING approach was used to extract exons from cosmids that contained genomic DNA from this 2-Mb region[25]. Trapped exons were used to screen cDNA libraries to isolate genes that were dubbed as 'interesting transcripts' (ITs) by the Gusella and MacDonald group. IT15 and IT16 together comprised most of a 10,366-bp transcript stemming from a large gene that came to be known as IT15. The gene contained a CAG-triplet repeat in exon 1 within the ORF that was polymorphic on normal chromosomes and expanded on *HD*-mutated chromosomes[26].

The causative mutation

Triplet-repeat mutations were unknown until 1991, when a CCG expansion in the 5′ UTR of the fragile X mental retardation 1 (*FMR1*) gene was found to cause FRAGILE X SYNDROME[27] (see also Online links box) and a CAG expansion in the ORF of the androgen receptor was found to cause SPINAL AND BULBAR MUSCULAR ATROPHY[28] (see also Online links box). In 1992 a CTG expansion in the 3′ UTR of the myotonic dystrophy protein kinase (*DMPK*) gene was found to cause MYOTONIC DYSTROPHY[29] (see also Online links box). Within weeks of the publication of the *HD* mutation the size of the CAG repeat was being determined in unaffected populations and those affected by Huntington disease in genetic clinics around the world, and genotype–phenotype correlations began to emerge[8,30,31]. Over the following 3 years the Huntington disease-associated alleles and unaffected CAG-repeat distributions were defined. The unaffected range is $(CAG)_{6–35}$ repeats. Alleles of $(CAG)_{40}$ and above are fully penetrant and cause Huntington

Box 1 | Extraordinary people that influence research into Huntington disease

Research into Huntington disease has been accelerated owing to the involvement of remarkable people working in the non-professional organizations. In the 1960s two foundations were established in the United States that had a major impact for patients with Huntington disease, by promoting scientific research, care provision and raising the profile of Huntington disease in the community. The Committee to Combat Huntington's Disease (now the Huntington's Disease Society of America (HDSA)) was founded in 1967 by Marjorie Guthrie, the widow of the folk singer Woody Guthrie who suffered from Huntington disease and died at the age of 55. Marjorie Guthrie promoted the formation of similar non-professional organizations in other countries, which resulted in the establishment of the International Huntington's Association (IHA) in 1978. The second organization was the Hereditary Disease Foundation (HDF), which was founded by Milton Wexler in 1968 after his wife was diagnosed with Huntington disease and continued by his daughter Nancy Wexler, who is the current president. Milton Wexler brought a unique approach to helping scientific research with the aim of finding potential treatments or a cure[10]. He organized small workshops with an informal structure in which energetic and creative scientists were invited to participate in free-association discussions to explore new mechanisms that might underlie the aetiology and progression of Huntington disease. The HDF and HDSA were both supported by the exceptional Dennis Shea, who raised US$1 million for the Care and Cure of Huntington's Disease Foundation at a single dinner in New York in 1989. Since the identification of the Huntington disease gene (*HD*), Nancy Wexler established the Cure HD Initiative of the HDF, and Barbara Boyle provided the energy and expertise to drive the Coalition for the Cure programme of the HDSA. More recently, the High Q Foundation has established important resources and initiated programmes that are devoted to developing a cure for Huntington disease.

disease within a normal lifespan, whereas alleles of $(CAG)_{36–39}$ confer an increasing risk of developing Huntington disease[32,33]. There is an inverse relationship between the age of onset of Huntington disease and the CAG-repeat size, with alleles of $(CAG)_{70}$ repeats and above invariably causing a juvenile onset[8,9,26]. The largest repeat that has been reported so far had approximately $(CAG)_{250}$ (REF. 34), although alleles of $(CAG)_{80}$ and above are extremely rare[8,9]. From the outset it was clear that the CAG-repeat size was not the only determinant of the age of onset, and it was estimated to contribute 50–77% to the variance in different populations[8,30,31]. A recent study of the Venezuela pedigree showed that 59% of the residual variability in the age of onset can be attributed to genetic or shared environmental factors[16]. LD studies have shown that DNA variation that is close to the GluR6 kainate receptor contributes significantly to this residual variation among individuals with mid-life onset[35,36]. The GluR6 kainate neurotransmitter receptor binds the excitatory amino-acid glutamate, and this finding supports the idea that EXCITOTOXICITY contributes to the pathogenesis of Huntington disease.

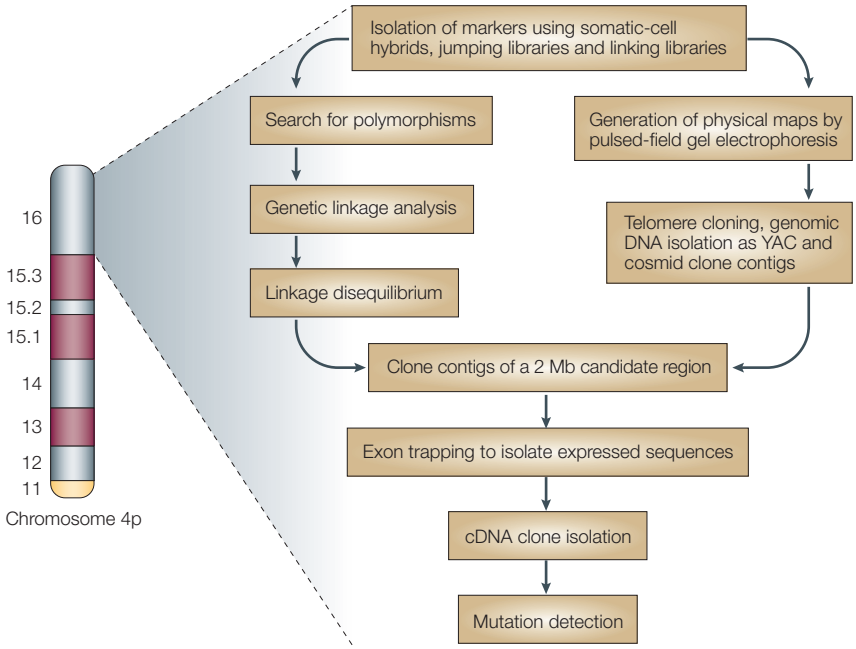
The CAG repeat is unstable and changes size during transmission from one generation to the next[8,26]. Although this instability and high variability is independent of paternal or maternal inheritance, large expansions are more likely to occur during male transmission. This is reflected in the large variation in repeat size in sperm[8,37]. The fact that large expansions occur during male transmission and that the age of onset of Huntington disease is inversely related to the size of the CAG-repeat expansion explains why juvenile patients almost exclusively inherit the disease gene from their fathers[8,38]. However, the molecular mechanism that causes large expansions to occur during male gametogenesis remains unknown.

The existence of *de novo* mutations in *HD* is another issue that had long been debated. Mutation analysis resolved this argument as it clearly showed that non-pathogenic alleles in the high normal range ($(CAG)_{27–35}$) could expand into the pathogenic range[39]. It is now known that $(CAG)_{27–35}$ alleles can be unstable during transmission[33,40] and extensive analysis has predicted a relatively high mutation rate for *HD* of ≥10% in each generation[41]. Instability of the CAG repeat in somatic tissues has been also reported. Small changes in repeat size were first detected in 1994 (REF. 42), but large expansions have recently been demonstrated in brain tissue[43]. The cause of these somatic expansions and their potential role in influencing the onset of disease remains to be determined.

Huntingtin and its self association

The *HD* gene encodes a large protein (huntingtin) of 348 kDa in which the CAG repeat is translated into a stretch of polyglutamine residues. It is expressed ubiquitously throughout the CNS, peripheral tissues and during embryonic development[44–48]. In 1993 amino-acid sequence searches revealed no homology to sequences held in protein databases and therefore gave no further insights into the function of huntingtin[26]. In 1995 three independent groups engineered knockout mice and showed that huntingtin is essential for embryonic development as null mice die during embryogenesis[49–51]. Around the same period, it was shown that huntingtin contains HEAT repeats —

Box 2 | **Cloning the *HD* gene**



After the Huntington disease gene (*HD*) was mapped in 1983, it was essential to develop approaches that would increase the chance of isolating DNA clones from the short arm of chromosome 4p. The first approach was to develop SOMATIC-CELL HYBRID (and later RADIATION HYBRID) panels that contained the human chromosome region of interest in a rodent cell background. This approach can be used to create a physical map of the donor genome and helped to localize DNA segments that were near the *HD* gene[108–110]. Jumping library technology was also developed to isolate DNA fragments that lay a few hundred kilobases away from a starting marker[111–113]. This technology was based on the isolation of fragments at the ends of RARE CUTTER RESTRICTION FRAGMENTS (used in PULSED-FIELD GEL ELECTROPHORESIS) and was complemented by LINKING LIBRARIES[114]. It was therefore possible to move along a chromosome by jumping from one end of a rare cutter restriction fragment to the other, crossing the restriction site in the linking library and then jumping to the end of the adjacent fragment[111,113]. Restriction fragment-length polymorphisms (RFLPs), VARIABLE NUMBER OF TANDEM REPEATS LOCI (VNTRs) and dinucleotide repeat polymorphisms were used to generate linkage maps[17,18]. Pulsed-field gel electrophoresis was used in parallel to generate physical maps[24,113]. Linkage disequilibrium and mapping relative to rare recombination events were used to position the *HD* gene more precisely within this physically defined candidate region[19,21–23]. The ability to clone large fragments of DNA (hundreds of kilobases) as YACs [115] transformed the entire field of gene cloning. The DNA within the *HD* candidate region was isolated as a YAC CLONE CONTIG[116], which was used to generate a 2 Mb cosmid DNA contig[117]. Exon trapping was developed to efficiently isolate expressed sequences from total genomic DNA[25]. The isolated cosmids were put through the exon-trapping system and the exons that were identified were used to screen cDNA libraries, which led to the isolation of the *HD* (IT15) gene[26].

sequences of around 40 amino acids that form hydrophobic α-helices, which assemble into an elongated superhelix[52]. This structure indicated that huntingtin is a large multifunctional scaffold protein[53]. To identify the proteins that interact with huntingtin, the yeast two-hybrid (Y2H) system has been widely used[53]. More recently, a huntingtin protein–protein interaction network map comprising 186 proteins has been compiled using a high-throughput Y2H approach[54].

In 1994 Max Perutz predicted that polyglutamine stretches could self-associate to form cross β-sheet structures, which he called polar zippers, by hydrogen bonding between side-chain and main-chain amides[55] (FIG. 2). This was an intriguing proposal because this is the structure of the amyloid deposits that are found in many late-onset neurodegenerative disorders including Alzheimer disease, Parkinson disease and the prion-associated diseases. Three years later it was shown that the protein encoded by exon 1 of the *HD* gene, which contains polyglutamine repeats in the pathogenic range, could spontaneously aggregate into amyloid fibrils *in vitro*[56]. Since then, there has been much debate about the stages within the misfolding and aggregation pathway that are pathogenic[57].

Genetic models of Huntington disease

In 1996 the first mouse model of Huntington disease was generated in which exon 1 of the *HD* gene was expressed under the control of human *HD* promoter sequences[58]. One year later, neuropathological analysis of the mouse brains revealed the presence of ubiquitylated proteinaceous aggregates[59], which were subsequently detected in the brains of patients with Huntington disease[60]. In addition, the analysis of neurotransmitter receptor levels in these mice provided the first indication that transcriptional dysregulation might be an early event in the pathogenesis of Huntington disease[61]. Since then, several transgenic mouse models that express fragments of the human *HD* gene or the full-length human *HD* gene have been generated[62,63]. 'Knockin' models, in which a pathogenic CAG repeat has been introduced into the mouse homologue of the *HD* gene (*Hdh*)[62,63], and a transgenic rat model[64], have also been analysed. Mouse models have been valuable for predicting the neuropathological and molecular changes that occur in the brains of patients with Huntington disease, and they have recently led to useful insights into the peripheral pathogenesis of Huntington disease through identification of muscle and possibly pancreatic pathologies[65,66]. In 2000

Figure 2 | **Max Perutz at the Royal Institution in London in 1994.** Photograph taken by A.R. Fersht of the MRC Laboratory of Molecular Biology, Cambridge.

Ai Yamamoto created an inducible mouse model in which exon 1 of the *HD* gene with $(CAG)_{94}$ repeats was expressed under the control of a promoter that could be switched off after adding doxycycline to the drinking water[67]. This remarkable study revealed that if symptoms were allowed to develop and then the gene was switched off, huntingtin aggregates were rapidly cleared from the mouse brains and the motor symptoms were reversed. Most importantly, it provided the first indication that treatment in the early stages of Huntington disease might be able to reverse the clinical symptoms.

Perhaps surprisingly, it has been possible to model Huntington disease in many single-cell and invertebrate systems including *Saccharomyces cerevisiae*[68], mammalian cells[69,70], *Caenorhabditis elegans*[71–73] and *Drosophila melanogaster*[74–76]. It is remarkable that the CAG-repeat threshold that separates the unaffected and pathogenic repeat ranges is maintained in *C. elegans*[77]. One consistent finding from these models is that overexpression of chaperone proteins, which help to maintain polyglutamine in a soluble form, is beneficial[68,72,76,78,79]. Enhancer and suppressor screens have proved useful for identifying genes that modify polyglutamine toxicity in *S. cerevisiae*[80,81] and *D. melanogaster*[76], and a small interfering RNA (siRNA) screen has been used to identify genes that modify polyglutamine aggregation in *C. elegans*[82]. The genetic reduction of SIN3A, a co-repressor protein that is a component of histone deacetylases (HDAC) complexes, and the use of HDAC inhibitors for genetic and pharmacological approaches show that inhibition of transcriptional repressor complexes can rescue *D. melanogaster* phenotypes[83].

Predictive testing

Mapping the *HD* gene to chromosome 4 in 1983 paved the way for pre-symptomatic and prenatal testing using linkage analysis; however, these tests required DNA samples to be obtained from several family members[84–87]. After the cloning of the gene, accurate testing required only DNA from the at-risk individual. Predictive testing presented choices that had not previously been available to patients, but it also raised significant ethical issues. Perhaps initially surprising, both positive[86] and negative[88] outcomes could cause tremendous upheavals within families because of feelings of guilt, and through challenging perceived roles and family dynamics.

International guidelines to recommend procedures for predictive testing were prepared by the lay members and scientific groups of the International Huntington Association (IHA) and Working Group on Huntington disease of the World Federation of Neurology (WFN) after extensive consultation. These guidelines were first published in 1989 and revised in 1994 (REF. 89). The recommendations suggest that pre-symptomatic testing should only be offered to at-risk individuals who have had the appropriate counselling, are fully informed and wish to proceed. There is now an extensive literature on the impact of pre-symptomatic testing for Huntington disease[90–93], which has provided the model for establishing pre-symptomatic testing programmes for other diseases.

There are also specific situations that pose further ethical dilemmas. First, it has been generally recognized that testing in childhood for adult-onset untreatable disorders holds the potential of more harm than benefit[94], and the International Guidelines recommend against this. Second, there are instances when testing an individual at a 25% risk (for example, a young adult) might inadvertently diagnose a symptom-free at-risk individual (for example, their parent) who does not wish to know their genetic status[95]. Finally, the test also allows prenatal diagnosis for Huntington disease. The uptake of prenatal testing has been relatively low[93,96], which is most likely due to a combination of factors. The recent advent of pre-implantation genetic testing provides a new option to at-risk couples who wish to avoid the selective termination of pregnancies, even if there is a low success rate and possible complications[97].

The advent of predictive testing also has social, political and economic consequences. Genetic discrimination has become a pertinent issue over the past decade with the

advent of genetic testing for many diseases, and is set to become more controversial as the Human Genome Project realizes its predictive potential. Over the past few years, many countries and certain states in the United States have passed legislation to prevent access by employers or insurers to the results of predictive genetic tests[92]. In the United Kingdom the Association of British Insurers (ABI) published an agreement with the government in 2001 that set out a 5-year moratorium on the use of DNA genetic tests by insurers, except when very large sums are insured (over £500,000 for life insurance). This anonymity is important as the adverse financial consequences, and also the fear of genetic discrimination, can lead at-risk individuals to seek anonymous genetic testing (in the United States at least), which is often carried out without the appropriate genetic counselling.

Future perspectives

Over the past 25 years, our understanding of the molecular pathogenesis of Huntington disease has increased exponentially through the application of molecular genetic approaches and the cloning of the *HD* gene. However, as was true at the time of George Huntington, there are still no interventions that can be used to halt or slow the progression of Huntington disease, and treatment is limited to managing some of the symptoms. The inducible mouse model has revealed that it might be possible not only to slow down disease progression but in some situations even reverse it. Developing treatments that could slow down or reverse the symptoms would represent a major breakthrough. However, given that predictive testing can identify most individuals who will develop Huntington disease, interventions that might postpone the age of disease onset to beyond a natural lifespan present the most attractive scenario.

One therapeutic approach that is currently under development is the use of siRNAs to decrease the level of the huntingtin transcript[98]. Because increasing amounts of mutant *HD* — for example, by breeding mouse models to homozygosity — accelerates the onset of a phenotype, it is logical to assume that a decrease in the level of mutant *HD* should delay the onset of disease symptoms. Application of this approach relies on the development of a procedure to deliver siRNAs throughout the brain. As the consequences of reducing the huntingtin protein levels to less than 50% in the adult brain are unknown, it might be necessary to specifically target the mutant transcript or devise a system that simultaneously delivers normal huntingtin.

The problems that are associated with brain delivery make small-molecule therapeutics an attractive option. Over the past few years, several protocols have been established for screening compounds in genetic models of Huntington disease[99]. Compounds are selected by an hypothesis-driven approach; for example, histone deacetylase inhibitors have been shown to be effective in several model systems including *D. melanogaster*[83] and the mouse[100–102]. Alternatively, several compounds have been isolated by screening pharmaceutical libraries and have been evaluated in model systems[99,103]. These have been limited to identifying small molecules that inhibit the aggregation of mutant *HD* by either direct or indirect interactions[104–106]. Because phase III clinical trials for Huntington disease are long and expensive[107], it is essential that preclinical trials in mouse models are carried out rigorously and are shown to be reproducible[99]. In parallel to preclinical testing, the Huntington Study Group (HSG) and more recently the Huntington Project (in the United States) and the Euro-HD Network (in Europe) are investing considerable effort and resources to ensure that the infrastructure necessary to test promising compounds in the clinic is in place. With such efforts, there is every reason to expect that effective treatments for Huntington disease will become a reality for the next generation.

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Glossary

ANTICIPATION
A phenomenon whereby a disease develops an earlier onset, or more severe symptoms, as it is transmitted through the generations.

BIALLELIC
A locus at which there are two possible variations of a given DNA sequence that are detectable in the human population.

CLONE CONTIG
A linear series of DNA clones with overlapping inserts.

EXCITOTOXICITY
The over-stimulation of excitatory neurotransmitter receptors, which causes an influx of calcium in the postsynaptic neuron.

EXON TRAPPING
A specialized vector containing splice sites that will splice to and isolate exons that are contained within the genomic insert.

FRAGILE X SYNDROME
The most common form of human X-chromosome-linked mental retardation that is associated with a folate-sensitive fragile site at Xq27.3.

HETEROGENEOUS
A description of a genetic disease that is caused by mutations in different genes.

LINKAGE DISEQUILIBRIUM
Non-random association of alleles at genetically linked loci.

LINKING LIBRARIES
Genomic libraries of rare cutter restriction sites and their flanking DNA.

MYOTONIC DYSTROPHY
An autosomal-dominant disease with variable symptoms. The mild form exhibits cataracts that develop in mid to old age, the adult form shows myotonia and muscle weakness, and the most severe form is congenital with a high rate of neonatal mortality. Myotonic dystrophy shows pronounced anticipation on maternal inheritance.

PULSED-FIELD GEL ELECTROPHORESIS
An electrophoretic technique that is used to separate large fragments of DNA (>20 kb and up to 10 Mb) on an agarose gel by periodically changing the orientation of the electrical field that is applied to the gel.

RADIATION HYBRID
A type of somatic-cell hybrid in which fragments of chromosomes of one cell type are generated by exposure to X-rays and are subsequently allowed to integrate into the chromosomes of a second cell type.

RARE CUTTER RESTRICTION FRAGMENT
Fragments generated by restriction endonucleases that cut infrequently in the genome either because the recognition sequence is large or because it contains one or more copies of the CpG dinucleotide.

RESTRICTION FRAGMENT-LENGTH POLYMORPHISM
A fragment-length variant that is generated through the presence or absence of a restriction-enzyme recognition site. Restriction sites can be gained or lost by base substitutions, insertions or deletions.

SOMATIC-CELL HYBRID
An artificially constructed cell in which chromosomes have been stably introduced from cells of a different species.

SPINAL AND BULBAR MUSCULAR ATROPHY
An X-chromosome-linked mild form of motor neuron disease.

VARIABLE NUMBER OF TANDEM REPEATS LOCUS
A locus that contains a variable number of short tandemly repeated DNA sequences that vary in length and are highly polymorphic.

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Competing interests statement

The author declares no competing financial interests.

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