

Review

Huntington's disease: the case for genetic modifiers

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Abstract

For almost three decades, Huntington's disease has been a prototype for the application of genetic strategies to human disease. *HD*, the Huntington's disease gene, was the first autosomal defect mapped using only DNA markers, a finding in 1983 that helped to spur similar studies in many other disorders and contributed to the concept of the human genome project. The search for the genetic defect itself pioneered many mapping and gene-finding technologies, and culminated in the identification of the *HD* gene, its mutation and its novel protein product in 1993. Since that time, extensive investigations into the pathogenic mechanism have utilized the knowledge of the disease gene and its defect but, with notable exceptions, have rarely relied for guidance on the genetic findings in human patients to interpret the relevance of findings in non-human model systems. However, the human patient still has much to teach us through a detailed analysis of genotype and phenotype. Such studies have implicated the existence of genetic modifiers - genes whose natural polymorphic variation contributes to altering the development of Huntington's disease symptoms. The search for these modifiers, much as the search for the *HD* gene did in the past, offers to open new entrées into the process of Huntington's disease pathogenesis by unlocking the biochemical changes that occur many years before diagnosis, and thereby providing validated target proteins and pathways for development of rational therapeutic interventions.

Huntington's disease: a lifelong disease process

Huntington's disease (HD) is a dominantly inherited disorder in which all affected individuals have precisely the same type of mutation, the expansion of a normally polymorphic CAG trinucleotide repeat in the *HD* gene, which lengthens a variable polyglutamine tract in the huntingtin protein [1]. Huntingtin is a large HEAT-domain protein expressed in both neuronal and peripheral tissues whose precise function is not known, though dozens of interactions with other proteins have been documented [2]. Despite widespread expression of mutant huntingtin from the time of conception, most individuals with HD are not diagnosed until mid-life, based upon the emergence of adventitious, involuntary movements that progress to a characteristic, all-consuming chorea, due to the gradual

loss of neurons, most notably in the striatum and, less distinctly, in the cerebral cortex. The age at which HD can be diagnosed based upon motor symptoms is largely determined by the precise length of the expanded CAG tract, as the two are inversely correlated, with longer CAG repeats leading to earlier onset, sometimes even in the juvenile years (Figure 1) [3]. However, though it is recognized by the movement disorder produced by neuronal dysfunction and degeneration, HD has many other less specific manifestations, including psychiatric disturbances and cognitive decline, as well as non-neuronal phenotypes detected in the periphery. Indeed, the careful examination of *HD* mutation carriers has revealed a variety of subtle effects (such as cognitive, motor and sensory changes, as well as inflammatory markers) that are detectable many years before clinical diagnosis [4-8]. Characterization of precise genetic mouse models with the equivalent mutation introduced by knock-in techniques into *Hdh*, the mouse *HD* ortholog, indicates that molecular differences are evident even at the embryonic stem (ES) cell stage [9,10]. Thus, inheritance of the *HD* mutation initiates a lifelong pathogenic process (Figure 2) whose early stages are only beginning to be explored and whose later stages entail clinical diagnosis, progression of neurodegeneration and of disease symptoms, and decline to death, as there is currently no effective treatment for preventing or delaying these. The ultimate goal of HD research is to identify an effective therapy for this devastating disorder (namely, an intervention capable of modifying either the nature or pace of the pathogenic process), recognizing that different modifiers might be required for subjects at the different stages shown in Figure 2.

Genetic modifiers - variation in disease expression determined by genes other than *HD*

Even though all those with HD have the same type of mutation, two individuals with precisely the same *HD* CAG length are unlikely to present with movement disorder at exactly the same age (for example, Figure 1), display the identical psychiatric, cognitive or peripheral phenotypes, show equivalent progression of phenotypes, or suffer death

BDNF, brain-derived neurotrophic factor; ES cells, embryonic stem cells; HD, Huntington's disease; iPS cells, induced pluripotent stem cells; SNP, single-nucleotide polymorphism; UTR, untranslated region; YAC, yeast artificial chromosome.

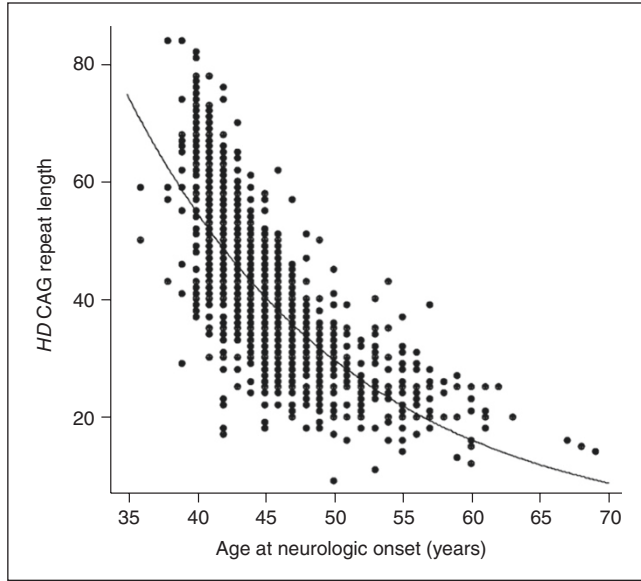


Figure 1

Inverse correlation of age at neurologic onset and *HD* CAG repeat length. The plot shows data points from 1,200 HD subjects of known age at neurologic onset. For each individual, the measured CAG repeat length in blood DNA (*x*-axis) is plotted against age at neurologic onset (*y*-axis). The line represents the best-fit simple logarithmic regression to the data. The CAG repeat length accounts for approximately 67% of the overall variation in age at neurologic onset, and the remaining variation shows a heritability of approximately 0.56.

after an equal disease duration. Although the primary determinants of whether and when a person will exhibit HD are the presence and length, respectively, of the expanded CAG tract, the precise disease manifestations and their timing are clearly modifiable by other factors. These could theoretically be stochastic, environmental/experiential or genetic, and while all three are likely to be involved to some degree, the latter factors offer the promise of being identified using modern genetic techniques and of then targeting particular biochemical pathways/processes for development of therapeutic interventions. If the genetic modifiers are discovered directly in studies of humans, then the pathways/processes revealed will already be validated to modify the pathogenic process in HD patients, surmounting a major hurdle early in the drug development process.

A gene is a disease modifier if altering its structure or expression alters the manifestation of phenotypes associated with the primary disease mutation, in this case, the *HD* CAG expansion. In studies in model systems, it is possible to manipulate gene structure or expression through a variety of techniques, but in humans, investigation of genetic modifiers is currently limited to the naturally occurring genetic variation that occurs in human popula-

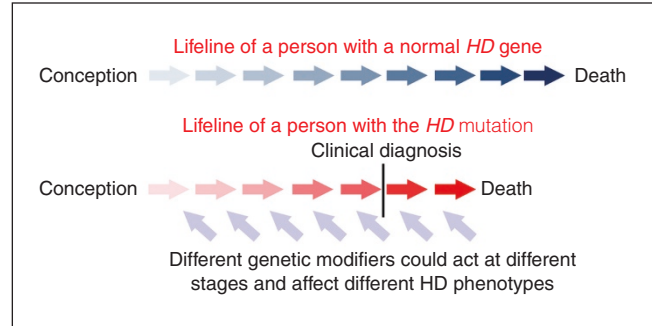


Figure 2

Huntington's disease is a lifelong disorder. The schematic diagram depicts the lifelines of a typical normal individual and a typical individual carrying the *HD* mutation. The darkening arrows illustrate the changes that occur during the lifetime of each individual as they proceed from conception to death. The use of different colors denotes that the HD subject is never the same as the normal individual, differing even shortly after conception in the expression of mutant huntingtin and its biochemical consequences. The differences lead over time to a variety of phenotypes whose order of appearance and interdependence are not well defined, particularly prior to clinical diagnosis, which is currently based upon the characteristic movement disorder. Death ensues after an inexorable clinical decline, usually approximately 15 years after the appearance of diagnostic movements. Genetic modifiers (blue upward arrows), which could theoretically act at any stage and on any phenotype, are currently being sought for the phenotype of diagnostic motor onset, as the residual variation in this phenotype after accounting for the effect of the *HD* CAG repeat is highly heritable.

tions. Evidence that heritable factors in humans can alter the course of HD came initially from the HD-MAPS (Modifiers of Age at onset in Pairs of Sibs) study, in which sibling pairs and small families from an international collaborative group were investigated for age at motor onset [11]. It was found that while the length of the *HD* CAG repeat accounted for 67% of the variance in age at motor onset, the remaining variance showed a high degree of heritability ($h = 0.56$). This effect was later confirmed in large HD pedigrees from Venezuela, where approximately 40% of the variation in age at onset remaining after accounting for the effect of CAG repeat length was due to other genetic factors [12]. Other phenotypes have not yet been examined as completely for genetic modifier effects, but it is likely that there will be some degree of impact of human gene variation on each disease feature.

Genetic modifiers - the candidate approach

The favored strategy to identify genetic modifiers in HD has been a candidate approach in which genes connected to pathways/processes suggested to be involved in HD pathogenesis are examined for genetic variation in humans, and variants are chosen for genotyping in DNAs from manifest HD individuals to test for an effect of genotype on age at motor onset. The results have at best been mixed.

Perhaps the most clear-cut result with a profound impact on interpretation of HD pathogenesis is the demonstration that a functional polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene does not modify age at neurologic onset [13-16]. BDNF is a protein thought to be important for the maintenance of striatal neurons, and evidence has emerged in model systems that huntingtin may play a part in regulating BDNF expression [17]. The polymorphism, a Val to Met substitution at position 66, shows evidence of selection in human populations, has been demonstrated to have a significant effect on BDNF secretion, is associated with a number of altered phenotypes in behavioral disorders and brain imaging studies, and acts as a modifier of Parkinson's disease pathogenesis [18-24]. However, the absence of an effect in HD indicates that the demonstrated functional variant in this protein growth factor does not have a significant impact on the events in HD pathogenesis that lead to motor onset. Whether BDNF plays a critical role in the events that occur after motor onset, or in development of other disease features, remains to be tested.

Less clear in their implications for defining early steps in pathogenesis are a number of reported positive results that appear to implicate such processes as glutamatergic transmission (*GRIK2*, *GRIN2A*, *GRIN2B*) [25-31], protein degradation (*UCHL1*) [31,32], gene transcription (*TCERG1*, *TP53*) [33,34], stress response/apoptosis (*DFFB*, *MAP3K5*, *MAP2K6*) [34,35], lipoprotein metabolism (*APOE*) [36], axonal trafficking (*HAP1*) [37], folate metabolism (*MTHFR*) [38], and energy metabolism (*PPARGC1A*) [39,40] as having small effects on age at motor onset. In some cases, gender stratification implied a sex-specific effect (*APOE*, *GRIN2A*, *GRIN2B*, *MAP2K6*) [30,35,36]. Complicating the assessment of many of the modifier investigations is the small sample size in many studies, the failure to correct for multiple hypothesis testing when several polymorphisms, genes or models were examined, and the potential confounding effects of sample relatedness and population stratification. In many cases, initial positive reports have been followed by negative studies of the same polymorphisms (for example, *GRIN2B*, *UCHL1*, *TP53*, *DFFB*, *APOE*, *MTHFR*) [41-44] or have not yet been confirmed (*HAP1*, *MAP3K5*, *MAP2K6*). In others, a follow-up study has trended in the same direction or yielded marginally significant findings (*TCERG1*, *GRIN2A*) [41]. In the case of *PPARGC1A*, two independent positive reports appeared simultaneously, showing association of age at onset with an intronic polymorphism whose functional significance has not been determined [39,40]. *GRIK2*, the earliest reported genetic modifier, has shown an effect in multiple studies where a particular allele of a 3'UTR (untranslated region) TAA trinucleotide repeat appears to be associated with earlier onset of HD [26-28,31]. Sequencing of the *GRIK2* gene, and haplotype studies in individuals showing earlier than expected onset, suggest that the effect is due to

the TAA repeat allele itself, rather than to some nearby coding or regulatory polymorphism in the *GRIK2* gene.

None of these modifier studies has yet revealed a specific mechanism by which the genetic variation has its apparent effects, which will be required to use these findings as a guide to rational therapeutic development. In addition to these candidate processes, age-related instability of the HD CAG repeat, which is particularly evident in the brain, may increase the severity of the disease process and is correlated with an earlier than expected age at onset of motor symptoms, suggesting that factors involved in generating the repeat length differences merit exploration as potential modifiers of the insult that initiates the disease process [45,46].

Genetic modifiers - the unbiased approach

The alternative approach of performing unbiased searches for genetic modifiers to reveal potential unsuspected factors has begun to be employed in HD. In lower organisms, these have taken the form of genetic screens to identify genes that modify some specific phenotype in an engineered animal model. For example, screens in yeast, *Caenorhabditis elegans* and *Drosophila melanogaster* expressing an introduced fragment from human huntingtin consisting largely of polyglutamine have yielded a number of modifiers of the effects of this fragment [47-50]. Indeed, in the *Drosophila* system, the orthologs of proteins that interact physically with human huntingtin have been suggested to be over-represented among modifiers. While the non-human systems are certainly more manipulable and yield modifiers more readily, they have two major drawbacks.

The first is that in none of these systems is the mechanism that leads to the phenotype being screened necessarily the same mechanism that triggers the disease in humans. As the effects in humans begin with the expression of a full-length mutant huntingtin protein, much or all of the pathogenic pathway may not be reproduced in animals that express only a small fragment of foreign protein. The models that most closely match the genetic basis of HD are mouse models that express full-length mutant protein, particularly those generated by knock-in technology that uses *Hdh*, the endogenous mouse HD ortholog. Both yeast artificial chromosome (YAC) transgenic and knock-in HD mice display a variety of phenotypes that are modifiable by genetic background, but no systematic screen for modifiers has yet been performed [51,52].

The second major drawback of non-human model systems is inherent even in the genetically equivalent mouse models: modifiers identified in these systems must still be validated in humans, as they may reflect biology peculiar to the model organism used. The need for validation re-introduces a costly, time-consuming and inherently uncertain step in using the result for development of

therapeutics, a step that is obviated by identifying the genetic modifiers directly in humans. The attempt to validate findings in animal studies can be problematic and may never be definitive until an intervention based upon the result is tested in humans.

The initial unbiased scans for human modifiers have relied on genetic linkage to search for chromosome regions associated with alteration of age at neurologic onset from that expected based upon the CAG repeat length in the individuals tested. HD-MAPS, a large collaborative study involving HD groups from around the world, performed this analysis in sibling pairs and small families by genome-wide microsatellite genotyping, and identified a number of possible regions of genetic linkage [53]. A follow-up study with additional samples achieved a genome-wide significant score for a region of 6q, indicating the frequent presence of genetic variation in this region that modifies HD pathogenesis prior to neurologic onset [54]. Subsequently, a similar scan in sibships of the Venezuela pedigrees studied by the US-Venezuela Collaborative Group identified genome-wide significant genetic linkage to 2p, and several other possible regions of linkage, including 6q [55]. In both cases, the genomic regions implicated are quite large and have not yet yielded specific modifier genes responsible for the effect.

Advances in the understanding of overall human genetic variation and the technologies for rapidly assessing it in large numbers of individuals have led to the possibility of performing genome-wide studies using densely spaced single-nucleotide polymorphisms (SNPs) and copy number probes. These are now being applied in an expanded version of the HD-MAPS collaboration, to search for association with age at neurologic onset. These investigations, which will have a much larger sample size of several thousand HD subjects, should clarify the candidate human modifier genes described above, narrow the known linkage peaks, and identify new polymorphisms that exhibit association with age at neurologic onset.

Future directions

It is likely that capitalizing on the rapid advances in the capacity for genome-wide genetic research in humans will prove the most rapid and definitive way to identify validated genetic modifiers of HD pathogenesis. This approach has the added advantage that once the genome-wide genotyping has been performed, it will be possible to mine the same dataset to identify genetic modifiers of other phenotypes defined in the participating HD subjects. For example, modifiers of the disease progression that takes place after many of the vulnerable striatal neurons have already died may well reveal different pathways and targets for intervention. Similarly, genetic modifiers of behavioral symptoms may reveal targets for intervention that are applicable years before motor onset, but which

represent different branches of pathogenesis. Once a genetic variation has been found to affect a particular human HD phenotype, it can be incorporated into the design of clinical trials involving that phenotype. The interventions that these trials are designed to test are putative modifiers, chemical or otherwise, of HD pathogenesis, and the inclusion of genotype for important genetic variations that also modify HD pathogenesis will increase the power of the clinical trials to detect an effect of the intervention by controlling for the effect of the genetic background of each test subject.

Ultimately, for any genetic modifier to itself be useful in leading to an intervention, it will be necessary to define at least in part the mechanism of action of the genetic variation that has the modifier effect, in order to know how to use the implicated pathways or proteins as targets for therapeutic development. This will require the use of model systems, though the human must remain the gold standard, due to the critical importance of knowing that the mechanism being defined in the model actually occurs in human patients. A major hope in this regard is the development of induced pluripotent stem (iPS) cell technology, which offers the promise of providing pluripotent cells and differentiated products from individual human subjects. These will represent a tremendous resource both for defining the effect of validated genetic modifiers on *HD* mutation-dependent cellular phenotypes, as a route to discovering the mechanisms involved in genetic modification, and also for carrying out human cell-based genetic screens (for example, RNA interference, overexpression) to identify modifiers that were not found in the genome-wide genetic studies, perhaps due to a lack of inherent functional variation in the human population.

Conclusions

HD is a lifelong disorder whose genetic trigger was found by application of genetic strategies to DNA from human patients. The continued application of these strategies is a powerful way to identify genetic factors that are capable of altering disease pathogenesis. The same argument can be made for any late-onset disorder where the presence of an ongoing disease process can be predicted prior to diagnosis based upon genotype. Indeed, the approach is no longer limited by genetic technologies, but only by the need for detailed quantitative and qualitative phenotyping in large cohorts of individuals at all stages of the disease process, both pre-diagnosis and post-diagnosis. As the same detailed phenotyping of patient cohorts for defining natural history and biomarkers is required to design and carry out effective clinical trials, the increased emphasis in the HD community on examination of early phenotypic changes in human patients should support both the identification of validated targets and the testing of interventions aimed at these targets, in genetically stratified clinical trials.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JFG and MEM both drafted the manuscript and approved its final version.

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