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Report

A Genome Scan for Modifiers of Age at Onset in Huntington Disease: The HD MAPS Study

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Huntington disease (HD) is caused by the expansion of a CAG repeat within the coding region of a novel gene on 4p16.3. Although the variation in age at onset is partly explained by the size of the expanded repeat, the unexplained variation in age at onset is strongly heritable ($h^2 = 0.56$), which suggests that other genes modify the age at onset of HD. To identify these modifier loci, we performed a 10-cM density genomewide scan in 629 affected sibling pairs (295 pedigrees and 695 individuals), using ages at onset adjusted for the expanded and normal CAG repeat sizes. Because all those studied were HD affected, estimates of allele sharing identical by descent at and around the *HD* locus were adjusted by a positionally weighted method to correct for the increased allele sharing at 4p. Suggestive evidence for linkage was found at 4p16 (LOD = 1.93), 6p21–23 (LOD = 2.29), and 6q24–26 (LOD = 2.28), which may be useful for investigation of genes that modify age at onset of HD.

Huntington disease (HD [MIM 143100]), a dominantly transmitted neurodegenerative disorder that involves the basal ganglia and cerebral cortex, typically develops in midlife but can occur at any age. The characteristic symptoms of HD—involuntary choreiform movement (Huntington 1872), cognitive impairment (White et al. 1992), and psychiatric disorders (Hayden 1981)—begin insidiously and worsen, without periods of remission, until death. The nature of the underlying defect, an unstable, expanded CAG repeat within the coding region of a novel 4p16.3 gene (HDCRG 1993), explains many of

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the puzzling genetic features of the disorder, including the variable age at onset, the tendency for juvenile disease to be inherited from fathers, and the appearance of new mutations.

Many studies have examined the relationship of the CAG repeat to age at onset for motor symptoms in HD (Andrew et al. 1993; Duyao et al. 1993; Snell et al. 1993; Ranen et al. 1995; Brinkman et al. 1997), and it is commonly recognized that the correlation between repeat size and age at onset accounts for ~70% of the variation in age at onset. Our recent studies and those of others suggest that the remaining variation in age at onset of HD is strongly heritable (Djoussé et al. 2003). These findings indicate that the onset of HD is substantially influenced by factors other than repeat size, and other modifier genes may determine the remaining variation in age at onset.

To identify genetic modifiers that influence age at onset of motor symptoms of HD, siblings affected with HD were ascertained from 16 clinical sites specializing in HD. Neurologists or psychiatrists from the participating sites examined and confirmed the HD diagnosis for each of the index cases and affected siblings. The Mammalian Genotyping Service typed 403 autosomal markers (Set 10, Marshfield Medical Research Foundation) in 722 individuals from 645 sibling pairs affected with HD in 303 sibships. The genotyping data were first evaluated by the sib_kin program in the ASPEX package to verify sibling relationships. Sixteen pairs in 8 sibships, reported as full sibs but not confirmed as such, were deleted from subsequent analyses, which left 629 sibling pairs in 295 families. Mendelian inconsistencies were then identified using GENTEST, a precursor of INFER, in the PEDSYS package. Genotypes for the entire nuclear family were deleted for the particular marker when an inconsistency was detected. A total of 411 genotyping errors was detected, for a 0.15% error rate.

The quantitative trait utilized in linkage analysis was adjusted for the effects of the CAG repeat expansion on age at onset of motor symptoms. The variability in age at onset attributable to the CAG repeat number was adjusted by linear regression. The relationships of age at onset to the *HD* repeat size is best represented by a logarithmic relationship (Duyao et al. 1993; Ranen et al. 1995; Brinkman et al. 1997). Regression analysis was performed using the logarithmically transformed age at onset as the dependent variable and the size of (*a*) normal CAG repeat, (*b*) expanded CAG repeat, and (*c*) their interaction as independent variables [$\log(\text{onset}) = \alpha + \beta_1(\text{HD})\,\text{CAG} + \beta_2(\text{Normal})\,\text{CAG} + \beta_3(\text{HD})\,\text{CAG} \times (\text{Normal})\,\text{CAG}$] (Djoussé et al. 2003).

Linkage analysis of these data uses age at onset of motor symptoms as the phenotype of interest. Cases with ⩾36 repeats were designated "*HD* mutation carriers," in accordance with published associations with disease expression (Duyao et al. 1993). Age at onset was known for all HD-affected individuals. Thirty-four unaffected persons were also included in the analysis to assist with identical-by-descent (IBD) calculation; age at onset was coded as "missing" for all unaffected individuals. Variance-component linkage analysis to age at onset was performed using GENEHUNTER (version 2.1) (Kruglyak et al. 1996; Pratt et al. 2000).

The power to detect linkage in our sample of 629 affected sibling pairs depends on the amount of the variation in age at onset that is explained by a single locus. We have 69% power to detect a LOD score of 3.0 if the locus explains 35% of the variance in age at onset but only 40% power to detect a LOD of 3.0 if the locus explains 30% of the variance in age at onset. We have 60% power to detect a LOD of 2.3 if the locus explains 30% of the variance in the age at onset and 83% power to detect a LOD of 2.3 if the locus explains 35% of the variance in age at onset. Thus, we have power to detect loci that may be expected to explain a substantial amount of the variance in age at onset of HD.

Linkage results are presented in figure 1 and summarized in table 1. Ten multipoint LOD scores and 13 single-point LOD scores >1.0 were found on six chromosomes. The highest multipoint LOD scores were 2.29 on chromosome 6p (33 cM from pter, at marker D6S1959, 6p22), 2.28 on chromosome 6q (138 cM from pter, at marker GATA184A08, 6q22), and 1.93 on chromosome 4p (7.8 cM from pter, at marker D4S3360, 4p16).

One of the strongest LOD scores is on the tip of chromosome 4 (4p16). Because the Huntington gene locus is in this region (4p16.3), it was unclear whether the linkage may be caused by increased allele sharing at the *HD* locus in this study of HD-affected family members. Normally, the expected allele sharing IBD for siblings is that 25% will share no alleles, 50% will share one allele, and 25% will share two alleles. However, because affected siblings always share the abnormal *HD* allele, it is expected that 50% of siblings will share one allele IBD (the *HD* allele), and 50% of siblings will share two alleles (both the *HD* and normal alleles). Current available methods for the mapping of quantitative traits in sibling pairs rely on comparing the observed allele sharing for the polymorphic marker with the expected allele sharing at the locus under investigation. Thus, estimates of IBD by these methods will be biased for all positions within 50 cM of the *HD* gene, but the extent of bias will decrease with increasing recombination distance from the *HD* locus until it converges to the traditional estimate at 50 cM. Here, we evaluated two approaches to accommodate this possible bias in linkage analysis. In both approaches, we first defined the expected allele IBD sharing at the *HD* locus as "0% share no alleles," "50% share one allele," and "50% share two alleles." We also modified methods to estimate the allele sharing IBD at the *HD* locus for each pair within 50 cM of the *HD* gene.

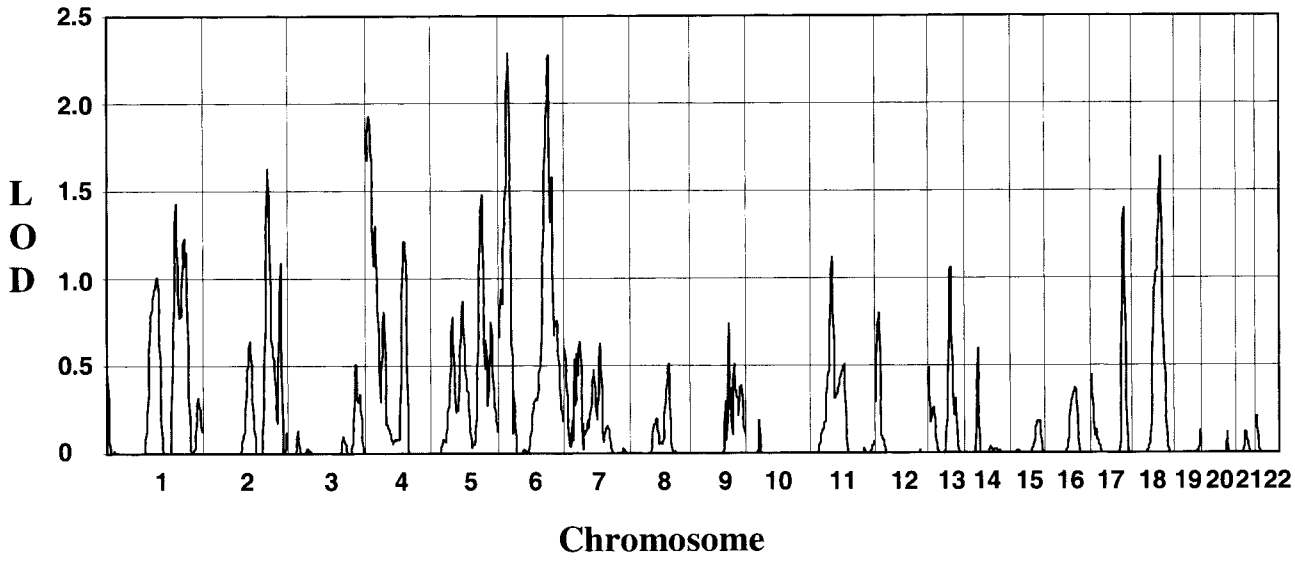

Figure 1 LOD score plots from multipoint variance component analyses of the whole genome in age at onset of HD. Peak LOD score >1.0 are summarized in table 1.

For the positionally weighted approach, each locus or marker under investigation is weighted on the basis of its distance from the *HD* locus. A portion of the original z_0 estimate is distributed to z_1 or z_2 estimates. The distribution of z_0 to z_1 and z_2 depends on two factors. The first is a weighted factor that is based on the distance from the *HD* locus. The distributed portion of z_0 is weighted by a linear function of distance in cM. As the distance from the *HD* locus increases, the chance of recombination increases, and the portion of z_0 allocated to z_1 or z_2 decreases. The distributed $z_0[D_{z0}(x)]$ and the remaining z_0 (adjusted z_0, $A[x]_{z0}$) could be described as follows: $A_{z0}(x) = z_0 \times x/50$ and $D_{z0}(x) = z_0 - A_{z0}(x)$, where x is the distance in cM from the *HD* locus and may vary from 0 cM—where all of z_0 is distributed to either z_1 or z_2—to 50 cM—where none of z_0 is distributed to either z_1 or z_2.

The second factor is determined by the allele sharing IBD at the *HD* locus and designates the distribution of $z_0[D_{z0}(x)]$. When the original z_2 estimate is not equal to 0, it means that, for this pair, the allele sharing for the loci close to the *HD* locus is likely to be two alleles. Under this scenario, at the *HD* locus, all of $D_{z0}(x)$ is allocated to z_2. However, as the distance from the *HD* locus increases, the chance of sharing two alleles decreases because of possible recombination. Therefore, some portion of $D_{z0}(x)$ would be contributed to z_1. When the distance reaches 50 cM from the *HD* locus, the estimates converge to the original estimates generated by GENEHUNTER. The following function describes the distribution of $D_{z0}(x)$ to z_1 and z_2, when the allele sharing at the *HD* locus is 2 (i.e., $z_2 \neq 0$). $A_{z1}(x) = z_1 + D_{z0}(x) \times 1/2 \times (x/50)$ and $A_{z2}(x) = z_2 + D_{z0}(x) \times [1 - 1/2 \times (x/50)]$, where x is the distance in cM from the *HD* locus and may vary from 0 cM—where all of $D_{z0}(x)$ is allocated to z_2—to 50 cM—where none of the $D_{z0}(x)$ is allocated to both z_1 and z_2. $A_{z1}(x)$ and $A_{z2}(x)$ are the adjusted estimates of z_1 and z_2, respectively, at the x position.

Similar functions could be used for allocating $D_{z0}(x)$, where the original z_2 estimate is equal to 0. At the *HD* locus, all of $D_{z0}(x)$ is allocated to z_1. As the distance from the *HD* locus increases, some portion of $D_{z0}(x)$ is contributed to z_1. For half sibs, since they share only one allele, the affected *HD* allele, $D_{z0}(x)$ is all contributed to z_1 at any position between the *HD* locus and 50 cM.

For the linear IBD estimate approach, the estimated IBD values between 0 cM and 50 cM were adjusted by a linear function. The IBD values at the *HD* locus were adjusted on the basis of the same principle as of the weighted method. The estimate of z_0 at the *HD* locus is fixed at 0, since they always share the affected *HD* allele, and z_1 depends on the value of the original z_2 estimate. If the original z_2 estimate is not equal to 0, which indicates that the sibling pair likely shares two alleles, then the adjusted z_2 estimate $[A_{z2}(0)]$ is the sum of the original z_0 estimate and z_2 estimate, and the adjusted z_1 estimate

Table 1

Maximum Multipoint and Single-Point LOD Scores and Flanking Markers for Regions with Multipoint LOD > 1.0

	Single-Point LOD Score			Multipoint LOD Score		Cytogenetic
Chromosome	Location[a]	Marker	LOD	Location[a]	Max LOD	Location
1	202	D1S518	1.22	196.60	1.43	1q31.1
2	200	D2S1384	1.57	196.90	1.63	2q33.3
	237	D2S427	1.38	236.70	1.09	2q37.1
4	0	D4S3360	1.37	7.80	1.93	4p16
	13	D4S2366	1.4	…	…	…
	35	D4S3403	1.09	29.64	1.3	4p15
	114	D4S2623	.8	107.94	1.3	4q25
5	139	D5S816	1.27	…	…	…
	147	D5S1480	2.02	146.66	1.48	5q31-32
	183	D5S211	1.36	…	…	…
6	34	D6S1959	1.84	33.00	2.29	6p22.3
	138	D6S1009	1.28	…	…	…
	146	GATA184A08	1.35	147.12	2.28	6q23-24
18	89	D18S1357	1.74	83.26	1.69	18q22

Note.—An ellipsis (…) indicates that the LOD score at the position is <1.0.

[a] Location is in relation to pter and uses the Marshfield Genetic Map, sex-averaged distances.

$[A_{z1}(0)]$ remains unchanged (original z_1 estimate). If the original z_2 estimate is equal to 0, then the sibling pairs share one allele, and $A_{z1}(0)$ is 1. The allele sharing at 50 cM was estimated by the traditional GENEHUNTER algorithm and was assumed to be unbiased. Allele sharing between 0 cM and 50 cM was determined as a simple linear function as follows: $A(x) = A(0) - x \times [A(0) - z_{50}]/50$, where x is the distance in cM from the *HD* locus and may vary from 0 to 50. $A(x)$ is adjusted $z_0 A_{z0}(x)$, $z_1 A_{z1}(x)$, or $z_2 A_{z2}(x)$ at x position. $A(0)$ is the adjusted z_0, z_1, or z_2 at 0 cM. z_{50} is the estimate of z_0, z_1, or z_2 at 50 cM. In this way, as the distance from the *HD* gene increases, the estimate of IBD approaches the estimate at 50 cM in a linear manner.

Before adjustment, the maximum multipoint LOD score near the *HD* locus was 1.95 at 5.2 cM (from the 4p telomere), and the single-point LOD was 1.37. By use of a positionally weighted adjustment, the LOD score at the *HD* locus remained essentially unchanged at 1.93 (7.8 cM) for multipoint, and the single-point LOD was 1.51. When we employed a linear adjustment for the observed IBD estimation, the maximum multipoint LOD score at the *HD* locus was 1.67. The single-point estimate—which limits the allele sharing to 0.5 or 1.0, depending on whether siblings shared 1 or 2 alleles—was 1.51. Both approaches resulted in similar LOD scores, which suggests that the evidence for linkage near the *HD* locus is not a consequence of the increased allele sharing dictated by presence of the disease allele at the *HD* locus. The approaches we utilized may be used in other linkage-analysis studies for modifier genes at disease loci. These results are consistent with our previous report that the normal *HD* allele or a closely linked gene may influence age at onset (Farrer et al. 1993).

Our study detected two chromosomal regions that met genomewide threshold criteria for "suggestive linkage" (LOD $\geq$ 2.19 [Lander and Kruglyak 1995; Nyholt 2000]) to age at onset, adjusted for CAG repeat size in the *HD* and normal alleles (table 1). One candidate gene within these regions, distal to the *HD* locus in 4p16.3, that may modify age at onset is the corepressor c-terminal–binding protein (CtBP; 4p16.3). CtBP is a transcriptional repressor and may play a role during cellular proliferation. Recently, the *CtBP* gene was reported to interact with wild-type huntingtin in the nucleus, and the polyglutamine expansion in huntingtin reduced this interaction (Kegel et al. 2002). Some studies attempting to localize the primary site of cellular toxicity of abnormal huntingtin have suggested that this may occur in the nucleus (Saudou et al. 1998; Peters et al. 1999), which supports the potential for a modifying role for the *CtBP* gene.

Recently, the *UCHL1* gene, which encodes ubiquitin carboxyl-terminal hydrolase L1, was reported to influence age at onset of HD, with the S18Y polymorphisms accounting for 13% of the variance in age at onset in a case-and-control-study design (Naze et al. 2002). *UCHL1* (4p14; 51 cM in the Marshfield Genetics Map) is proximal to the peak on the tip of chromosome 4 (4p15-16; 0–35 cM) and unlikely to account for the effect observed.

Several previous studies have reported that the glutamate receptor gene (GluR6; *GRIK2*) acts as an HD modifier (Rubinsztein et al. 1997; MacDonald et al. 1999). A particular TAA repeat allele in the 3′ UTR of *GRIK2* was associated with younger age at onset of HD (Rubinsztein et al. 1997; MacDonald et al. 1999). When analyzed in conjunction with *UCHL1,* 7% of the variance in the age at onset of HD could be attributed to the *GRIK2* genotype variation, 13% to *UCHL1,* and 16% to both polymorphisms (Naze et al. 2002). *GRIK2* (6q16.3; 112.20 cM in the Marshfield Genetics Map) is located ~26 cM proximal to the peak observed here on chromosome 6 (6q23–24; 138–146 cM).

The findings of suggestive linkage to chromosomes 4 and 6, as well as marginal evidence for linkage to chromosomes 1, 2, 5 and 18, in a sample of 629 affected sibling pairs has provided a direction for the identification of candidate modifiers for onset of motor symptoms of HD that now may be explored in more detail. Similarly, this scan provides a baseline of comparison for genome scans to be carried out with independent populations with HD—and possibly other polyglutamine disorders—to define whether there is overlap in the chromosomal regions implicated to contain modifiers. Ultimately, discovering the identity of bona fide modifier loci will help to explain the steps in the HD pathogenetic process and will provide potential therapeutic targets already validated to have a relevant effect in human HD.

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Electronic-Database Information

URLs for data presented herein are as follows:

GENEHUNTER, http://www.fhcrc.org/labs/kruglyak/Downloads/

Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for HD)

PEDSYS package, http://www.sfbr.org/sfbr/public/software/pedsys/pedsys.html

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