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Maternal Factors in Onset of Huntington Disease

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SUMMARY

Analyses of father-offspring and mother-offspring similarity in onset age suggest that nuclear genes account for a significant portion of the modification of onset age in Huntington disease. The effects of non-nuclear modifiers are supported by the finding that the offspring of affected women have significantly older mean ages of onset than offspring of affected men irrespective of the onset age in the parent. The absence of increased father-daughter similarity indicates that modification is not X-linked. The absence of reproductive advantage for late-onset individuals and the absence of a multigenerational maternal-lineage effect suggest that the modifying effect of the sex of the affected parent occurs in a single parental generation. Offspring of affected women with onset between ages 35 and 49 had a significantly older mean onset age than their mothers. This suggests that a protective effect may be conferred upon the offspring of affected women.

INTRODUCTION

Huntington disease (HD), an inherited neurodegenerative disease with onset in midlife, is transmitted as an autosomal dominant disorder [1, 2]. The average age at which symptoms of HD first appear is close to 40 [3–6], but the range in age at onset is wide and initial symptoms may occur as early as age 4 [7] and as

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late as age 65 [4]. Several patterns related to onset in HD have been noted. Variability in onset within families is significantly less than variability between families [4, 8], suggesting that either common within-family environmental or genetic mechanisms modify the onset of HD. Age at onset [6] and the rate of progression [9] in monozygotic twins concordant for HD is highly similar, suggesting that the modification of onset age in HD is primarily influenced by genetically transmitted mechanisms. Farrer et al. [10] suggested that genes controlling aging may account for the similarity of onset within HD families.

The sex of the affected parent in HD has been observed to exert considerable influence on the onset age of HD in the offspring. A significantly greater proportion of persons with juvenile- or adolescent-onset of HD (onset before age 20) have inherited the gene from an affected father than from an affected mother [4, 8, 11–13]. In addition, significantly more cases of HD with late-onset (initial symptoms after age 50) have inherited the HD gene from an affected mother than from an affected father [14, 15]. No preponderance of affected mothers was found for persons with age of death over age 65 [16], but a late age of death may indicate only long survival rather than late-onset age. The correlation in mother-offspring onset age is reported to be greater than that for father-offspring [12]. It is not clear whether the effect of the sex of the affected parent is confined to the juvenile-onset or if onset for all progeny of affected males is younger than that for all offspring of affected females [17].

The above findings have led to the hypothesis that maternally transmitted factors may modify onset in HD. Hypotheses proposed for maternal modifiers include extrachromosomal or cytoplasmic [12, 14], X-linked [13], or intrauterine effects [12]. Maternal effects upon offspring may be divided into two categories: those which represent multigenerational transmission and those which occur in a single generation. The multigenerational class of modifiers would include the maternally derived extrachromosomal organelles that are transmitted unchanged through a maternal lineage. Forms of mitochondrial cytopathy are believed to be transmitteed in this manner [18]. Alternatively, maternal effects may occur in a single generation. In utero effects upon the fetus that are transmitted across the placenta (such as maternal PKU) may be classified as single-generation. In addition, any preconceptual modification of the maturing oocyte would be a single-generation effect. This study evaluates hypotheses and expectations of maternally transmitted modification of HD onset age based upon multigeneration (cytoplasmic or extrachromosomal), single generation (intrauterine or preconceptual), and X-linked modifiers.

METHODS

History of neurologic impairment was collected for members of 165 apparently unrelated families for whom the diagnosis of HD was confirmed by neurologic evaluation of the proband. The families contained 5,480 individuals both living and deceased; 611 of these had been diagnosed HD-affected. An additional 104 deceased persons were highly probably HD-affected. These individuals had definitely diagnosed HD-affected descendants but were themselves given other diagnoses (progressive palsy, St. Vitus dance, chronic brain syndrome). Eight persons were "obligate carriers," having a parent and

offspring affected, but died before onset of symptoms. The above 723 individuals were grouped as "HD gene carriers," and their 1,642 offspring were designated as "at risk." An additional 156 persons with ambiguous clinical features were designated "question of HD," and their 167 offspring were designated "questionable at risk." The 2,787 grandchildren and great-grandchildren of HD gene carriers or question of HD and more distant relatives were designated "unknown status." Five individuals with clinical features of HD but without other family member similarly affected were designated "spontaneous HD" and are not included in this analysis (two are reported adopted but biologic family appears not affected). No individual is included in more than one category above. Precedures for collection of family history through interviews with family members and medical records review are described [14].

All analyses are made from the 723 persons identified as "HD gene carriers." Age at onset of HD was defined as the onset of motor disturbance (gait or handwriting disturbance, subtle twitches, frequent accidents, dropping objects, or incoordination that subsequently evolved into unambiguous impairment). While some persons reported earlier symptoms of affective disorder or cognitive impairment, motor impairment was emphasized in our designation of age at onset because family instability or work-related stress may substantially influence behavioral changes observed in HD [9, 19].

The designation of a precise age at onset in HD is difficult because of the insidious nature of the initial signs of the disease. For this reason, we divided our sample of HD patients by age at onset into four 15-year age groups: (1) 4–19 years, (2) 20–34 years, (3) 35–49 years, and (4) 50 years and over. The 15-year age grouping was selected because the average duration of HD in our sample is 15 years [20].

RESULTS

Age at onset could be estimated for 306 of the 723 persons affected by HD with a mean onset age of 39.36 years. The mean onset for the 151 affected men was 39.27 years (SD = 13.99) and 39.45 years (SD = 12.89) for the 155 affected women.

Sex of Affected Parent

The mean age at onset of the 122 affected offspring of HD affected men was 32.98 years (SD = 13.29) and was significantly less than the mean onset of the 120 affected offspring of affected women at 41.59 years (SD = 11.85) ($P < .0001$). No differences were found between male and female offspring (table 1).

The effect of the sex of the affected parent on offspring onset was evaluated

TABLE 1

MEAN AND STANDARD DEVIATION OF ONSET AGE IN OFFSPRING

	Fathers affected		Mothers affected	
Sons	32.4 ± 13.8	(60)	41.8 ± 12.1	(62)
Daughters	33.5 ± 12.8	(62)	41.4 ± 11.7	(58)
All offspring ...	33.0 ± 13.3	(122)	41.6 ± 11.8	(120)

NOTE: No. cases in parentheses. No difference is found between onset of sons and daughters of affected fathers or between sons and daughters of affected mothers. The sex of the affected offspring has no effect upon age at onset while the sex of the affected parent exerts a significant effect ($P < .0001$).

TABLE 2

ONSET AGE OF OFFSPRING

	Juvenile/ Adolescent 4–19	Early 20–34	Midlife 35–49	Late 50–70	Total
Mean paternal onset	27.2	36.0	46.9	49.8	...
(No. offspring)	(16)	(24)	(23)	(5)	...
Paternal onset unknown (no. offspring)	(4)	(21)	(20)	(9)	...
Proportion paternal	83%	64%	41%	33%	...
(No. offspring)	(20)	(45)	(43)	(14)	(122)
Mean maternal onset	15.0	33.3	42.1	51.7	...
(No. offspring)	(1)	(10)	(29)	(18)	...
Maternal onset unknown (no. offspring)	(3)	(15)	(33)	(11)	...
Proportion maternal	17%	36%	59%	67%	
(No. offspring)	(4)	(25)	(62)	(29)	(120)

NOTE: One hundred twenty-two HD-affected individuals inherited the gene from an affected father, and 120, from an affected mother. These 242 offspring were divided into four groups by their age at onset. The proportion of cases inheriting HD from an affected father within the groups is significantly different from 50% ($\chi^2 = 24.1$, $P < .01$). There is a significant linear trend of proportion by sex of affected parent across age groups ($Z = 4.81$, $P < .01$).

by dividing the 242 cases for whom the sex of the affected parent was known into the four onset-age groups: juvenile and adolescent (onset 4–19 years), early (onset 20–34 years), midlife (onset 35–49), and late (50 years and older). The number of offspring within each age group inheriting HD from an affected father or affected mother was determined, as was the mean parental onset age (table 2). Within the different age groups, the proportion of cases inheriting HD from affected fathers and affected mothers is significantly different from the expected 50% ($P < .01$). Not only do a significantly greater number of persons with onset before age 20 inherit HD from affected fathers but those with onset before age 35 also are predominantly of paternal descent. The inverse occurs for the late-onset cases.

In a second analysis of the effect of the sex of the affected parent, affected male and female parents are divided into the four onset-age groups (table 3). Eighty-six parents with ascertained onset ages had 122 offspring with ascertained ages at onset. The number of parents with onset before age 20 is too few to interpret. Affected fathers in the three older-age groups produce offspring with a significantly younger mean onset age than offspring of mothers of corresponding age groups. The offspring of affected fathers also have significantly younger mean onset ages than the fathers themselves. Affected mothers with onset between 35 and 49 years produce offspring with a significantly older mean onset age than the mothers.

Nuclear Gene Effects

The variance in age at onset within families is significantly less than the variance between families ($F_{123,182} = 4.42$, $P < .0001$) as has been previously

TABLE 3

ONSET AGE OF PARENT

	Juvenile/ Adolescent 4–19	Early 20–34	Midlife 35–49	Late 50–70
Mean onset of affected fathers	16	28.8	41.6	57.9
(No. fathers)	(1)	(15)	(20)	(10)
Mean onset of offspring	10	20.0	34.8	46.2
(No. offspring)	(1)	(26)	(31)	(10)
		$P < .002$*	$P < .002$*	$P < .0001$*
Mean onset of affected mothers	15	30.2	39.4	55.7
(No. mothers)	(1)	(10)	(17)	(12)
Mean onset of offspring	19	32.7	43.5†	53.4
(No. offspring)	(1)	(13)	(24)	(20)
		$P < .0002$‡	$P < .001$‡	$P < .03$‡

NOTE: Fathers and mothers with HD were divided into four groups by age at onset. The mean ages at onset for the offspring are reported for each group of parents. Very few persons with onset between ages 4 and 19 (juvenile/adolescent) had children, and this age group cannot be interpreted. Fathers with early-onset, between the ages of 20 and 34, had offspring with significantly younger mean onset ages than themselves and significantly younger onset ages than the offspring of mothers with early-onset. Similarly, the offspring of fathers with midlife and late-onset have significantly younger onset ages than their fathers and significantly younger onset ages than the offspring of mothers with midlife and late-onset. Thus, the paternal effect of earlier onset age of HD in offspring is not confined to juvenile-onset cases.

* *t*-test comparison of onset for offspring of affected fathers vs. affected fathers.

† *t*-test comparison; offspring of midlife onset mothers have significantly older onset than their mothers ($P < .05$).

‡ *t*-test comparison of onset for offspring of affected mothers vs. offspring of affected fathers.

reported [4, 8]. This is consistent with the hypothesis that common genetic mechanisms shared within families modify the onset of HD. Multiple regression analysis reveals that while the prediction of onset in the offspring is significantly related to the sex of the affected parent (beta weight = 0.35, $P < .0001$), age at onset of the parent is a more powerful predictor of onset in the offspring (beta weight = 0.65, $P < .0001$). The larger beta weight for parental onset age suggests that intrafamilial similarity is a stronger determinant of offspring onset age than is sex of affected parent. The correlations of onset for fathers with their offspring of r = .72 ($P < .0001$) and for mothers with their offspring of r = .68 ($P < .0001$) are statistically significant. The high parent-offspring correlations suggest that much of the modification in offspring onset is not sex-related but is apparently autosomal. The sex of the affected parent accounts for only a portion of the variability in onset of HD in offspring. The primary modifiers are presumably nuclear genes.

Test for X-Linkage

Stevens ([13], p. 253) proposed that X-linked modifiers influence the age at onset in HD. Because men always transmit their X chromosome to their daughters, one test for X-linkage is to compare father-to-son with father-to-daughter transmission. If X-linked modifiers are involved, one would expect the following patterns: (1) Father-daughter correlations should exceed father-son correla-

tions in onset age. (2) Affected fathers should produce more juvenile/adolescent-onset daughters than sons. (3) Early-onset fathers should produce more juvenile/adolescent-onset daughters than sons. (4) Late-onset fathers should produce more late-onset daughters than late-onset sons.

Results of X-linkage. (1) Father-daughter (no. = 36) onset-age correlation is r = .80 ($P < .0001$), while father-son (no. = 34) onset-age correlation is r = .67 ($P < .0001$). These correlations are not statistically different from one another ($P < .47$). The increase in the similarity of father-daughter onset ages when compared with father-son onset-age correlation is not statistically significant. Brackenridge [21] reported no difference between father-daughter and father-son correlations.

(2) Twenty-four cases of HD with onset before age 20 were contained within this sample. Twenty of these inherited HD from affected fathers, nine were daughters, and 11 were sons. The mean onset for these daughters is 11.44 years, and for the sons, 11.00 years. There is no preponderance of daughters with juvenile/adolescent-onset.

(3) Fathers with early-onset (20–34 years) had 26 affected children; 14 of these were sons (mean onset = 21.14 years) and 12 were daughters (mean onset = 18.58, $P < .60$). Of these 26, 19 had initial symptoms before age 20 (juvenile/adolescent)—nine were daughters and 10 were sons. There is no preponderance of juvenile/adolescent-onset daughters.

(4) Fathers with late-onset (50 years and older) had 10 affected children; five were sons with a mean onset age of 48.0 years and five were daughters with a mean onset age of 44.4 years ($P < .33$). There is no preponderance of late-onset daughters for late-onset fathers.

There is no apparent increase in similarity between fathers and daughters when compared with fathers and sons. X-linkage of modifying factors is therefore not supported by these data.

Tests for Maternally Transmitted Modifiers

It has been proposed that a maternally transmitted factor may modify the onset of HD [14]. According to this hypothesis, cytoplasmic factors or extrachromosomal organelles (such as the mitochondria), which are believed to be transmitted exclusively from mothers to offspring [22], may influence the expression of the HD gene.

The expected patterns for a maternally transmitted modifier would be as follows: (1) The sex of the affected offspring should have no effect upon the onset age of the offspring, but the sex of the affected parent should exert an effect. (2) For offspring of affected males, the offspring age at onset would be determined by the maternally transmitted factors of their unaffected mothers; thus, the sex of the affected grandparent would be expected to be insignificant. (3) Mother-offspring correlation of age at onset should exceed father-offspring correlation of age at onset. (4) Late-onset mothers would be expected to produce late-onset offspring, but late-onset fathers would produce late-onset offspring only with the frequency that the late-onset maternally transmitted form

occurs in the unaffected mates of these men. Thus, more late-onset offspring would be expected for late-onset mothers than for late-onset fathers.

Results of tests for maternally transmitted modifiers. (1) The sex of the offspring, as expected, exerts no effect upon age at onset of the offspring (tables 1 and 4). Modifying factors are transmitted to sons and daughters in similar fashion. Sex of the parent is significant (table 2). (2) For offspring of affected males, the sex of the affected grandparent, as expected, exerts no significant effect (table 4). (3) Contrary to expectation, there is no significant difference between mother-offspring correlation r = .68 and father-offspring correlation r = .72 ($P < .50$). (4) Twelve women with late-onset had 20 affected offspring, and their average age at onset was 53.35 years. Ten late-onset men had 10 affected offspring with an average age at onset of 46.2 years, which was significantly younger than the onset for offspring of late-onset women ($P < .03$). Fifty-five percent of the offspring of late-onset women were also late-onset, but only 20% of the offspring of late-onset men were late-onset.

Multigenerational vs. Single-Generation Effects

Three of the four analyses above suggest that the effect of the sex of the affected parent upon onset age in the offspring may be due to a maternally transmitted factor. One would expect extrachromosomal or cytoplasmic factors to be passed through multiple generations of affected female ancestors while in utero effects would not reflect multigenerational influences. Multigenerational influences may be expressed through a reproductive advantage or through an effect of the sex of affected grandparent as described below.

Reproductive advantage for late-onset. One hypothesis that has been advanced to account for the disproportionate numbers of juvenile/adolescent cases inheriting HD from fathers and late-onset cases inheriting HD from mothers is a selection factor. Stevens [13] proposed that the effect of the sex of the affected parent on onset age in offspring may be due to a reproductive advantage for persons with later-onset ages.

In a manner similar to that advanced by Stevens [13], let us propose a reproductive advantage for late-onset individuals but involving also a late-onset producing maternally transmitted modifier (such as a mitochondrial gene). The late-onset producing factor is designated as "L," and an alternate early-onset maternally transmitted modifier is designated as "l." In the general population, there occurs a certain frequency, X, of persons carrying the "L" factors while everyone else (frequency of 1 − X) will carry the "l" factor.

The number of offspring of HD-affected men inheriting the early-onset "l" maternally transmitted factor will depend upon the frequency of the "l" factor among the unaffected mates of these men; presumably 1 − X. However the number of offspring of HD-affected women inheriting the "l" factor would depend upon the relative reproductive rates of women who carry the early-onset "l" factor or late-onset "L" factor. If there is a reduced reproductive rate for affected women carrying the "l" factor when compared with affected women carrying the "L" factor, then a disproportionate number of offspring of

TABLE 4

MEAN AGE AT ONSET FOR 125 HD-DIAGNOSED INDIVIDUALS FOR WHOM THE SEX OF AFFECTED PARENT AND GRANDPARENT WAS KNOWN

Grandparent	Parent	Offspring	Mean ± SE	Combined offspring
Male	Male	Male	27.8 ± 3.5 (17)	
				29.4 ± 2.8 (39)
Male	Male	Female	30.6 ± 3.2 (22)	
Female	Male	Male	34.0 ± 2.9 (13)	
				30.61 ± 2.2 (31)
Female	Male	Female	28.2 ± 2.3 (18)	
Male	Female	Male	41.7 ± 2.2 (13)	
				39.3 ± 2.0 (26)
Male	Female	Female	36.9 ± 2.5 (13)	
Female	Female	Male	48.2 ± 3.7 (13)	
				43.8 ± 2.7 (29)
Female	Female	Female	40.3 ± 2.9 (16)	

NOTE: There were no significant differences in age at onset between sons and daughters within the four grandparent-parent combinations, and therefore sons and daughters were combined. Offspring of affected male parents had significantly younger onset ages than did offspring of affected female parents ($P < .0001$), but the sex of the grandparent was not significant as analyzed by two-way analysis of variance.

affected women will inherit the "L" factor and be late-onset. If there is no reproductive advantage for affected women of late-onset, then the number of offspring of affected women with the "L" or "l" factor would be the same as that found for the general population.

A reproductive advantage for late-onset affected women with a maternally transmitted factor (extrachromosomal or cytoplasmic inheritance) could account for the disproportionate number of late-onset cases inheriting HD from affected mothers. The lack of this reproductive advantage would suggest that the proposed maternally transmitted factor is not derived from selection through multiple generations of affected female ancestors. This model may be evaluated by the following comparison: Women with later ages at onset will be expected to be reproductively more successful than early-onset affected women, thereby producing the disproportionate number of late-onset offspring of affected women.

TABLE 5

MEAN REPRODUCTIVE RATES FOR HD-AFFECTED INDIVIDUALS

Onset age	Male	Female
4–19	1.0 (2)	(0)
20–34	3.42 (26)	2.66 (21)
35–49	3.08 (62)	3.46 (63)
50 and over	3.17 (34)	3.20 (34)

NOTE: ($F = 0.14$, $P < .7$). No significant effect of age at onset on reproductive rate was found for male or female affected individuals born before 1940. There were no affected women, with onset between ages 4 and 19, born before 1940 identified in our sample.

Results of reproductive advantage for late-onset. There is no apparent reproductive advantage for affected women with late-onset (table 5). The disproportionate number of late-onset cases inheriting HD from affected mothers does not appear to be dependent upon a reproductive selective advantage of late-onset affected women.

Sex of affected grandparent. If a gene-carrying mother exerts an intrauterine protective effect (single generation) that produces a later onset in her offspring, then the sex of her affected parent, the grandparent of the offspring, would be expected to be insignificant. If an extrachromosomal or cytoplasmic maternally transmitted factor (multigeneration) delays onset, one would expect persons with multiple generations of affected female ancestors (affected mother and grandmother) to have later onset than those with a single affected female ancestor (affected mother and grandfather). This would be expected because for those offspring of affected women with affected grandfathers, the maternally transmitted factors would be derived from their unaffected grandmothers who would carry the general population frequency of early- and late-onset producing factors.

Therefore, according to a multigenerational hypothesis of maternal modification, onset ages of offspring of affected grandfathers and mothers should more closely resemble offspring of affected fathers than offspring of affected grandmothers and mothers. According to a single-generation hypothesis (in utero modification or oocyte modification), the sex of the affected maternal grandparent will be insignificant. This may be evaluated by the following comparison: For offspring of affected mothers and grandfathers, does the mean age at onset resemble that of offspring of affected fathers or that of offspring of affected grandmothers and mothers?

Results of sex of affected grandparent. For offspring of affected women, there is no statistical difference in onset age between those offspring with an affected grandfather and those with an affected grandmother (table 4). Offspring with affected grandfathers and mothers have a significantly older mean onset age than offspring of affected fathers. This suggests that the effect of the sex of the affected parent occurs with a single generation of an affected female ancestor.

Maternal Transmission of a Protective Agent or Organelle

The above analyses suggest that the effect of the sex of the affected parent upon onset age of HD in the offspring occurs with a single generation of an affected female ancestor (i.e., an affected mother). Because maternally transmitted modifiers appear to influence the onset of HD occurring 40–60 years later, the phenomenon may represent an event that is preserved over a lengthy period. A protective agent or a form of an organelle that protects or delays the deleterious effect of the HD gene may be selected for. This might occur by the selected propagation of a pre-existing subset of such an agent or organelle or through selective alteration or mutation of a pre-existing agent or organelle. The degree of selection for such a protective agent, and thus the degree of modification in onset of the offspring, may depend upon the composition of the population of pre-existing agents upon which selection or mutation will act. The stimulus for selection would be the effect of the mother's HD gene. According to this hypothesis, offspring of affected women might be expected to have more of a protective agent than do their mothers. Selection of a protective agent or organelle may be evaluated by the following comparison: Offspring of affected mothers would be expected to have an older onset age than that of the mothers.

Results of tests for selection of protective agent. These results are obtained in table 3. Only one mother has juvenile/adolescent-onset, so this age group cannot be assessed. The offspring of early-onset mothers are, on average, 2.49 years older than their mothers at the time of onset, but this difference does not reach statistical significance ($P = .23$). The offspring of midlife-onset mothers are, on average, 4.19 years older than their mothers at the time of onset; this difference is statistically significant at $P < .05$. Offspring of late-onset mothers are, on average, 2.32 years younger at the time of onset than their mothers.

DISCUSSION

The sex of the affected parent has been reported to exert a significant effect upon the age at onset in HD. The majority of cases with onset before age 20 inherit HD from an affected father [4, 8, 11, 12], and the majority of cases of late-onset inherit HD from an affected mother [14, 15]. Myers et al. [14] also reported that affected offspring of late-onset females had late-onset while those of late-onset males had significantly earlier ages at onset. Bird et al. [23] noted an earlier age of death for offspring of affected men.

Several hypotheses have been proposed to account for the effect of the sex of the affected parent upon the age at onset of offspring. These hypotheses include X-linked modification [13], extrachromosomal or cytoplasmic inheritance [12, 14], and in utero modification [12]. No evidence in support of X-linked modification was found in the present study, nor have others found evidence of X-linked modification [12].

In our present study, offspring of affected men are found to have earlier onset ages than their fathers, irrespective of the age at onset of the father, and to have earlier onset ages than the offspring of affected women (tables 1 and 3).

The influence of the sex of the affected parent upon age at onset in offspring represents a modifying effect that operates at all ages of onset in HD.

Boehnke et al. [12] reported a small but statistically significant reproductive advantage for persons with later-onset ages. In agreement with Walker et al. [24], no support for a reproductive advantage among late-onset individuals was found in the present study (table 5). A reproductive advantage for late-onset individuals appears to be insufficient to account for the sex-of-the-affected-parent effect.

Maternal transmission of cytoplasmic or extrachromosomal factors modifying onset of HD has been proposed to explain the sex-of-the-affected-parent effect [14]. This hypothesis is not sufficient to account for all observations. Persons with affected mothers and affected grandfathers have onset ages similar to those of persons with affected mothers and affected grandmothers (table 4). The extrachromosomal or cytoplasmic factors of affected mothers with an affected male parent would be derived from the unaffected grandmothers. We find that the onset ages of the descendants of an affected male grandparent and affected female parent do not resemble the onset ages of the descendants of affected male parents. The absence of a multigenerational maternal-lineage effect together with the absence of a substantive reproductive or selective advantage among late-onset individuals suggests that the HD gene modification is a single-generation parental effect.

One mechanism that may account for the effect of the sex of the affected parent upon HD onset age in the offspring is the selection for a protective maternally transmitted factor, such as a form of mitochondria, which modifies the expression of the HD gene. Such a protective agent appears to be conserved and may exert an effect on onset of HD for an extended period of 40–60 years in the offspring. There is evidence supporting mitochondrial heterogeneity. It has been suggested that mitochondrial heterogeneity existing within the D-loop region of the mitochondrial genome may be selectively transmitted to progeny through maternal lineage [25]. Selective propagation of functional mitochondria from among a heterogeneous population of mitochondria has been proposed as a mechanism in reversible cytochrome oxidase deficiency [26]. The selective propagation of a subpopulation of a maternally derived protective agent, such as a mitochondria, might account for the patterns observed in onset age in HD. The offspring of affected women with midlife onset (ages 35–49) had older mean onset ages than did their mothers (table 3). This suggests that offspring of affected women are more protected than are the mothers. For selection of a protective agent to occur preconceptually or in utero, the maternal HD gene would presumably have to exert an influence upon the developing oocyte and/or fetus. Although abnormalities in erythrocytes [27] and fibroblasts [28] have been reported, effects of the HD gene in nonneuronal tissues have, however, not been established.

The modification of onset by nonmaternal, presumably nuclear genes, is demonstrated by the high father-offspring correlation in onset age. Because the onset ages of fathers and their offspring are highly similar, much of the modification of onset in HD cannot be of maternal origin. These presumably

nuclear gene effects may account for two observations. First, only 55% of the offspring of late-onset women are also of late-onset; the earlier onset of the remaining 45% may be the result of modifying nuclear genes inherited from their unaffected fathers. Second, offspring of late-onset mothers had a younger mean onset age than did their mothers. This observation may represent a shift toward the more prevalent midlife-onset produced by nuclear genes of paternal origin.

Boehnke et al. [12], in the study of a very large HD population, found an increase in the correlation of onset age for affected mothers and offspring when compared with affected fathers and offspring. No trend toward an increase in mother-offspring correlation was found, however, in our present study. Although onset ages of offspring of affected fathers were consistently younger than those of the fathers across all parental-age groups, the resulting father-offspring correlation was high and it was similar to that found for mother-offspring. Others [4, 21], studying smaller HD populations, have also not found evidence for an increase in mother-offspring correlation. A possible shift to later onset in the offspring of affected women may produce correlation coefficients of similar magnitude for mother-offspring and father-offspring pairs.

Effects of the sex of the affected parent upon onset age in offspring are found to occur across all onset ages in HD. The absence of multigenerational sex effects and the absence of a significant reproductive advantage for late-onset individuals suggest that modification occurs in a single parental generation. Maternal factors derived through preconceptual or prenatal selective modification might account for the patterns observed in offspring onset age.

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