Am J Hum Genet 35:845–860, 1983

Two Models for a Maternal Factor in the Inheritance of Huntington Disease

MICHAEL BOEHNKE,[1] P. MICHAEL CONNEALLY,[2] AND KENNETH LANGE[1]

SUMMARY

Huntington disease is a classic example of an autosomal dominant trait. Over the years, however, a number of investigators have reported anomalies regarding the age of onset of the disease that are inconsistent with this paradigm. We propose two models in which a maternal factor—cytoplasmic in one case, autosomal or X-linked in the other—acts to delay onset in a manner consistent with the previously reported anomalies. Relevant data from the Huntington's Disease Research Roster are presented that reinforce and extend the previous observations.

INTRODUCTION

Huntington disease is a degenerative neurological disorder with onset usually in adulthood. Clinical manifestations of the disease are variable in severity and order of appearance, but generally take the form of progressive motor disability and psychiatric disturbance. The hereditary nature of the disease was described by Huntington [1], and an autosomal dominant mode of inheritance for the disease has been accepted since shortly after the rediscovery of the work of Mendel. However, there are a number of puzzling population features of the disease that are inconsistent with a simple autosomal dominant model. On close examination, some of these features are simply artifacts of ascertainment bias and small sample size. Huntington's own suggestion that more men than women are afflicted falls in this category. But a number of these anomalies appear to be real, and a more complex model for the inheritance of Huntington disease is required to explain

Received November 16, 1982; revised January 5, 1983.

This research was supported in part by the University of California, Los Angeles; United States Public Health Service-National Research Service Awards GM-07104 and GM-07191; National Institutes of Health Research Career Development Award K04-HD00307; and Huntington's Disease Roster Contract NIH-NINCDS-79-06.

[1] Department of Biomathematics, University of California, Los Angeles, CA 90024.

[2] Department of Medical Genetics, Indiana University School of Medicine, Indianapolis, IN 46223.

them. These characteristics relate to the age of onset of the disease, and include: (1) differential age of onset in Huntington patients depending upon the sex of the parent who transmitted the disease; (2) stronger parent-offspring age-of-onset correlation when the mother is the affected parent; and (3) an excess of paternal transmission in cases of juvenile onset (age less than 21 years).

A number of genetic models have been considered in an effort to explain some or all of these anomalies. Among them are models postulating: multiple alleles at the disease locus [2, 3]; two or more major loci for the disease [4]; a modifying gene on the X chromosome [5], on the Y chromosome [6], or closely linked to the disease locus [7]. Explanations based on the social impact of Huntington disease on carriers and their families have also been suggested [8–10]. In our opinion, none of these models satisfactorily explains the reported anomalies in the inheritance of Huntington disease, and most appear to be inconsistent with the available data.

Here we consider two models in which a modifying factor alters the expression of the disease gene to delay onset. The first model proposes that this "protective factor" is cytoplasmic, and consequently is maternally transmitted, passing from a mother to all of her offspring. Such a factor could represent a mitochondrial gene, as previously suggested by Wallace [9], and by Goldman in [6]. The second model assumes that the protective factor is due to an allele at an autosomal or X-linked locus, and that the mother's genotype at this locus modifies age of onset of the disease in her offspring. This maternal protective effect could be provided to the fetus in utero or to the nursing infant. We present a mathematical formulation for the cytoplasmic factor model and demonstrate that this model predicts the anomalies in the inheritance of Huntington disease described in the literature. The maternal genotype model is dealt with at a more heuristic level since the mathematical development required is similar but much more complicated. Relevant new data from the Indiana University Huntington's Disease Research Roster are also presented.

METHODS

Statistical analysis was performed on data from the Huntington's Disease Research Roster, an ongoing project of the Department of Medical Genetics at the Indiana University School of Medicine. Roster information is obtained by two mailed questionnaires: a family-history questionnaire providing general information on an affected or at-risk individual and his or her family; and an affected questionnaire, giving detailed background, clinical, social, and psychiatric information on a specific Huntington patient. Questionnaires are usually completed by the spouse or some other close relative of the affected individual, although occasionally this task falls to the patient. Diagnosis is verified where possible through hospital records or autopsy reports. Age of onset is defined by the question: "At what age did symptoms first appear?" As of March 1982, the Roster contained data on 472 families, including responses from 616 affected questionnaires, representing 46 states and several foreign countries.

MODELS

In the cytoplasmic factor model, we suppose that a cytoplasmic element modifies the expression of the disease gene, so as to delay onset. Individuals lacking the cytoplasmic factor we shall call unprotected (U); individuals possessing this factor we shall call protected

(P). We assume that the mean age of onset for unprotected carriers is u years, while that for protected carriers is $u + v$ years. We further assume that protected carriers are more fit, leaving more offspring in the next generation than their unprotected counterparts. It follows from this last assumption that the equilibrium frequency α_H of the ctyoplasmic factor among Huntington carriers will be greater than its frequency α in the remainder of the population (see APPENDIX).

For the maternal genotype model, we suppose that two alleles, A and a, at the modifier locus act so that mean age of onset increases with the number of A alleles in the mother's genotype. We assume that a carrier's fitness increases with the degree of protection provided by the mother so that carriers with aa mothers are least fit and those with AA mothers most fit. It can be shown under this assumption that the frequency of the A allele and hence the frequency of the protective genotypes will be greater among Huntington carriers than in the normal population.

The assumption of increased fitness for protecteds over unprotecteds required by both models is supported by the observation that fitness among Huntington patients increases with age of onset for the disease. This relationship has been empirically demonstrated in a number of studies [11–13]. Table 1 presents number of offspring by onset age for Huntington patients from the Roster who were either dead or beyond 50 years of age. These criteria were intended to insure that only individuals who had completed reproduction would be included in the sample. The number of offspring appears to initially increase with increasing age of onset, then level off for onsets during middle age, and, perhaps, finally increase again for older onset ages. The rank correlation coefficient [14] between number of offspring and age of onset is .184 for these data. Applying Fisher's Z transformation [15] shows this correlation to be significantly different from zero ($Z = 5.92$, $P < .000001$).

ANTICIPATION IN THE MALE LINE

A genetic disease exhibits anticipation if recognizable characteristics of the disease—for example, onset or death—occur at progressively younger ages in successive generations [16]. Observations of this phenomenon for a number of dominant disorders, including myotonic dystrophy and Huntington disease, have long been a source of controversy in the genetics literature. For the most part,

TABLE 1

AVERAGE NO. OFFSPRING BY AGE OF ONSET

Age of onset (yrs)	Cases*	No. offspring Mean ± SD
≤ 15	24	0.12 ± 0.44
16–20	50	1.86 ± 2.26
21–25	55	1.85 ± 2.71
26–30	130	2.99 ± 2.79
31–35	158	3.18 ± 2.15
36–40	196	3.31 ± 2.55
41–45	140	3.13 ± 2.40
46–50	142	2.73 ± 2.22
51–55	64	3.97 ± 2.78
56–60	44	4.18 ± 3.05
≥ 61	14	4.21 ± 4.44
Total	1,017	3.01 ± 2.60

* Cases include those individuals who were either dead or at least 50 years of age.

anticipation has been dismissed as an artifact on the grounds that no genetic mechanism could account for it. Certainly, bias in ascertainment may be at least partly responsible. For example, onset ages for parents and grandparents are more likely to be remembered if onset has occurred only recently. This can result in an inflated estimate of mean age of onset in previous generations and apparent anticipation. Anticipation may also result from a positive correlation between age of onset and fitness. Parent-offspring age-of-onset comparisons involve all affecteds from the current generation, but only those affecteds in the previous generation who actually had children. Since the parents represent a biased subset, mean age of onset for the previous generation is again overestimated.

An interesting characteristic of Huntington disease first reported by Bird et al. [17] is that anticipation is much more pronounced when the disease is inherited from the father. This difference cannot be explained by the previous arguments, which are independent of sex. Stevens, Wallace, Newcombe et al., and Myers et al. [5, 10, 18, 19] all reported the related observation that offspring of affected fathers show earlier age of onset or death than offspring of affected mothers. Brackenridge [12] also noted this latter effect, but concluded that it was an artifact. In no case did the sex of the individual affect age of onset; only the sex of the transmitting parent appeared to make a difference.

These observations are strongly supported by data from the Roster. Table 2 displays age of onset by sex of the individual and sex of the transmitting parent. Offspring of affected fathers had onset approximately 4 years earlier than offspring of affected mothers. A two-way analysis of variance showed this differrence in age of onset by sex of the transmitting parent to be highly significant ($F = 34.1$ on 1 and 995 df, $P < .0001$). There was no effect due to sex of the individual ($F = 0.26$, $P = .61$) or to parent sex-offspring sex interaction ($F = 0.14$, $P = .71$). In table 3, degree of anticipation by sex of the affected parent is shown. Anticipation averaged 8.06 years when the father was affected, and only 1.41 years when the mother was affected, based on samples of 276 and 281, respectively. To compare these means while allowing for a statistically significant difference in the variances ($F = 1.48$ on 275 and 280 df, $P < .01$) [20], we employed a two-sample t-test which does not assume equality of variances [21]. We found the difference in means to be highly significant (two-sample $t = 8.14$,

TABLE 2

AGE OF ONSET BY INDIVIDUAL AND PARENTAL SEX

AFFECTED PARENT	INDIVIDUAL SEX	
	Male*	Female*
Father	33.57 ± 12.04 (234)	33.68 ± 12.00 (255)
Mother	37.47 ± 10.26 (240)	38.10 ± 10.58 (270)

NOTE: Effect of parental sex: $F = 34.1$; df = 1 and 995; $P < .0001$. Effect of individual sex: $F = 0.26$; df = 1 and 995, $P = .61$. Interaction: $F = 0.14$; df = 1 and 995; $P = .71$.

* Mean age of onset in years ± 1 SD. Sample sizes in parentheses.

TABLE 3

ANTICIPATION BY SEX OF THE AFFECTED PARENT

Affected parent	Sample size	Anticipation (yrs) Mean ± SD
Father	276	8.06 ± 11.27
Mother	281	1.41 ± 7.62

NOTE: Effect of parental sex: $t = 8.14$; df $\doteq 484$ (see text); $P < .000001$.

df $\doteq$ 484, $P < .000001$). Since both offspring and parent ages of onset were required to calculate anticipation, the total sample for table 3 is less than that for table 2.

Both models predict the related effects of more pronounced anticipation in the male line and differential age of onset depending on the sex of the transmitting parent. Under each model, the protective state of the mother specifies the mean age of onset for her offspring. Since either protective factor would be present at a higher frequency in the Huntington population than among normals, a carrier mother is more likely to provide protection to her offspring than a normal mother would. Thus, children of carrier mothers are more likely to be protected than children of carrier fathers, yielding the differences in anticipation and age of onset by sex of the transmitting parent.

To verify that the cytoplasmic factor model predicts these differences, consider first the case of a carrier father and his carrier offspring. A randomly chosen individual from the Huntington population has protection probability α_H. As noted earlier, α_H is greater than α, the frequency of the cytoplasmic factor in the surrounding population. The protection probability α_{HF} of the father is actually greater than α_H, since protected carrier males are more likely to reproduce than are unprotected carrier males. Applying Bayes' theorem, α_{HF} can be computed explicitly as the conditional probability

$$\alpha_{HF} = \frac{\alpha_H c_{PY}}{\alpha_H c_{PY} + (1 - \alpha_H) c_{UY}}, \quad (1)$$

where $c_{PY} > c_{UY}$ are the average numbers of children born to protected and unprotected carrier males, respectively. (Y will represent male and X female in the following.) The expected age of onset for the father is $(1 - \alpha_{HF})u + \alpha_{HF}(u + v) = u + \alpha_{HF} v$. The offspring receives the cytoplasmic factor from a normal mother so that his or her expected age of onset $(1 - \alpha)u + \alpha(u + v) = u + \alpha v$ is less than that of the father. The result is anticipation.

The case of a carrier mother and her carrier offspring is simpler. Since the cytoplasmic factor is maternally transmitted, the offspring is protected exactly when the mother is, and no anticipation is predicted. In analogy to the previous case, the frequency of the cytoplasmic factor among carrier mothers is

$$\alpha_{HM} = \frac{\alpha_H c_{PX}}{\alpha_H c_{PX} + (1 - \alpha_H) c_{UX}}, \quad (2)$$

where $c_{PX} > c_{UX}$ are the average numbers of children born to protected and unprotected carrier females, respectively. Since $\alpha_{HM} > \alpha_H > \alpha$, the offspring's expected age of onset $u + \alpha_{HM} v > u + \alpha v$, so that offspring of carrier mothers experience later onset than offspring of carrier fathers.

The cytoplasmic factor model further predicts that the frequency of the protective factor should progressively increase with each consecutive generation of female-to-female transmission of the disease. In the 3-generation case, this means that Huntington patients with a carrier mother and a carrier grandmother (group I) should show later onset than those with a carrier mother and a carrier grandfather (group II), while those with a carrier father (group III) should have earliest onset. Application of Bayes' theorem as in calculating equations (1) and (2) shows that the protection probabilities for these three groups of carriers are

$$\frac{\alpha_H c_{PX}^2}{\alpha_H c_{PX}^2 + (1 - \alpha_H) c_{UX}^2} > \frac{\alpha c_{PX}}{\alpha c_{PX} + (1 - \alpha) c_{UX}} > \alpha ,$$

respectively. The maternal genotype model predicts no such age-of-onset difference based on the sex of the carrier grandparent, at least under the assumption that the modifier locus is autosomal. Under this model, both maternal grandparents contribute equally to the mother's genotype at the protecting locus, so that the question of which grandparent is a carrier becomes irrelevant.

Age-of-onset data from the Roster for the 3-generation transmission groups suggested by the cytoplasmic model are presented in table 4. As before, mean age of onset for the offspring of affected fathers (group III) was significantly less than that for the offspring of affected mothers (groups I and II). Since sample variances were significantly different ($F = 5.73$ on 1 and 533 df, $P = .02$), we again used the two-sample t-test in which the variance of each group is estimated separately, and found $t = 6.37$ on approximately 522 df, $P < .000001$. However, while the mean age of onset for group I patients was greater than that for group II patients, the difference was slight (0.46 years) and did not approach statistical significance; $t = 0.38$ on 262 df, $P = .71$. Since information on 3 generations was required for inclusion in this analysis, fewer observations were available

TABLE 4

AGE OF ONSET BY 3-GENERATION TRANSMISSION GROUP

Group	Sample size	Age of onset (yrs) Mean ± SD
I.....	117	36.62 ± 10.22
II.....	147	36.16 ± 9.87
III.....	271	30.31 ± 11.92

NOTE: Difference between groups I and II and group III: $t = 6.37$; df = 522; $P < .000001$. Difference between group I and group II: $t = 0.38$; df = 262; $P = .71$. Group I: Affecteds with an affected mother and an affected grandmother. Group II: Affecteds with an affected mother and an affected grandfather. Group III: Affecteds with an affected father and an affected grandparent of known sex.

than in the 2-generation case shown in table 3. Data of Newcombe et al. [18] yield similar results.

PARENT-OFFSPRING AGE-OF-ONSET CORRELATION

A second prediction of both models is that affected mother-offspring pairs should exhibit more strongly correlated onset ages than affected father-offspring pairs. Under the cytoplasmic factor model, mother and offspring share the same protection state, while the father and offspring protection states are unrelated. According to the maternal genotype model, the genotypes protecting mother and offspring are those of the maternal grandmother and mother, respectively. These two genotypes share one allele identical by descent. The genotypes protecting father and offspring are from unrelated women, the paternal grandmother and the mother. According to both models then, mother and offspring protection states should be dependent, father and offspring protection states independent.

To verify this argument rigorously for the cytoplasmic factor model, it is necessary to calculate and compare the theoretical father-offspring and mother-offspring correlation coefficients. The father-offspring age-of-onset correlation

$$\rho_{FO} = \frac{\text{cov}(Z_F, Z_O)}{[\text{var}(Z_F)\ \text{var}(Z_O)]^{1/2}},$$

where Z_A is the age of onset for person A and where var $(\cdot)$ and cov$(\cdot,\cdot)$ represent variance and covariance, respectively. The various terms in ρ_{FO} can be computed by conditioning on the protection status of the father and the offspring [15]. For example, if S is the status of the father, $\text{var}(Z_F) = E[\text{var}(Z_F|S)] + \text{var}[E(Z_F|S)]$. Here $E(\cdot)$ represents expectation, and $E(\cdot|\cdot)$ and $\text{var}(\cdot|\cdot)$ represent conditional expectation and conditional variance, respectively. With $\sigma_P^2(\sigma_U^2)$ denoting the age-of-onset variance for a protected (unprotected) individual, it then follows that $\text{var}(Z_F) = \alpha_{HF}\,\sigma_P^2 + (1 - \alpha_{HF})\,\sigma_U^2 + \alpha_{HF}\,(1 - \alpha_{HF})v^2$. Application of the same conditioning principle allows calculation of $\text{var}(Z_O)$ and $\text{cov}(Z_F, Z_O)$. The resulting correlation

$$\rho_{FO} = \frac{\alpha_{HF}[\alpha\sigma_{PP} + (1-\alpha)\sigma_{PU}] + (1-\alpha_{HF})\,[\alpha\sigma_{UP} + (1-\alpha)\sigma_{UU}]}{[\alpha_{HF}\,\sigma_P^2 + (1-\alpha_{HF})\sigma_U^2 + \alpha_{HF}(1-\alpha_{HF})v^2]^{1/2}[\alpha\sigma_P^2 + (1-\alpha)\sigma_U^2 + \alpha(1-\alpha)v^2]^{1/2}},$$

where σ_{ST} is the parent-offspring age-of-onset covariance when the parent has protection status S and the offspring has protection status T. Parallel calculations show that

$$\rho_{MO} = \frac{\alpha_{HM}\,\sigma_{PP} + (1-\alpha_{HM})\sigma_{UU} + \alpha_{HM}(1-\alpha_{HM})v^2}{\alpha_{HM}\,\sigma_P^2 + (1-\alpha_{HM})\sigma_U^2 + \alpha_{HM}(1-\alpha_{HM})v^2}.$$

Sufficient conditions for $\rho_{MO} > \rho_{FO}$ are (1) $\sigma_P^2 = \sigma_U^2$ and (2) $\sigma_{PP} = \sigma_{UU} \geq \max\{\sigma_{PU}, \sigma_{UP}\}$. These assumptions are consistent, for example, with a model positing a constant increment of v years in age of onset due to the protective factor and polygenic inheritance determining the residual variation in age of onset.

Employing these assumptions yields

$$\rho_{FO} \leqslant \frac{\sigma_{PP}}{\sigma_P^2 + \min\{\alpha_{HF}(1 - \alpha_{HF}), \alpha(1 - \alpha)\}v^2}$$

$$\rho_{MO} = \frac{\sigma_{PP} + \alpha_{HM}(1 - \alpha_{HM})v^2}{\sigma_P^2 + \alpha_{HM}(1 - \alpha_{HM})v^2} .$$

Since $\sigma_{PP} \leqslant \sigma_P^2$, appropriate cross multiplication then gives $\rho_{FO} < \rho_{MO}$.

Data from the Roster clearly demonstrated this difference in age-of-onset correlations. Figures 1 and 2 plot age of onset for the offspring against age of onset for the father and mother, respectively [6]. Mother-offspring pairs exhibited much less scatter about the regression line than did father-offspring pairs. This difference was reflected in the age-of-onset correlations. Product-moment age-of-onset correlations were calculated to be .562 for father-offspring pairs, and .730 for mother-offspring pairs, based on sample sizes of 276 and 281. The difference in the observed correlations was highly significant ($Z = 3.44$, $P < .001$, two-tailed). The difference in rank correlations was also highly significant.

Previous studies by Brackenridge [22] and Myers et al. [19] failed to demonstrate a significant difference in parent-offspring age-of-onset correlations by sex of the affected parent. Brackenridge's data were historical, gathered from a large series of studies in the literature. Variability in methods between studies and possible problems in the reliability of the older data could have obscured a true difference. The data of Myers et al. included only 51 parent-offspring pairs, far too few to detect a difference of the magnitude seen in the Roster data.

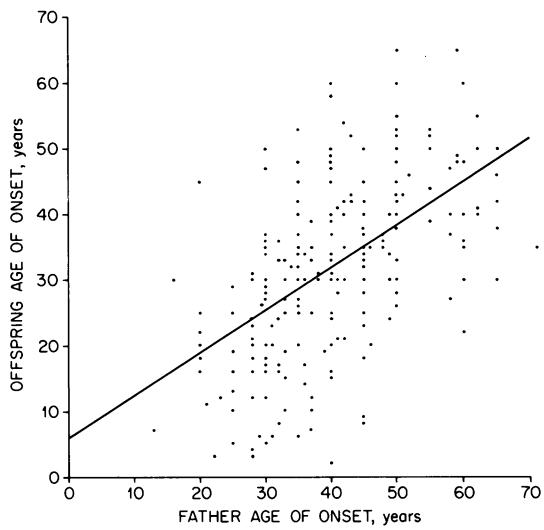

FIG. 1.—Father-offspring age of onset. No. pairs = 276

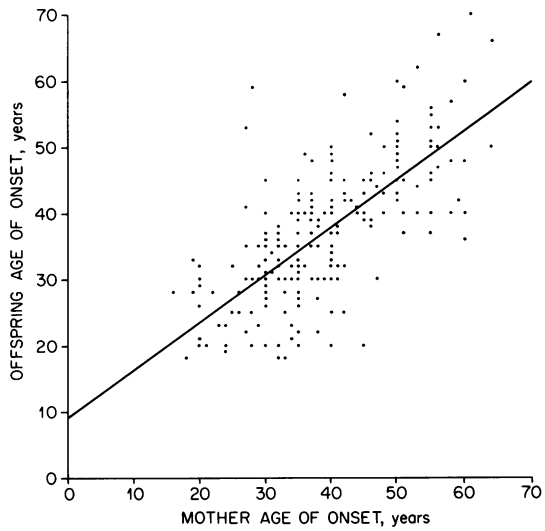

FIG. 2.—Mother-offspring age of onset. No. pairs = 281

EXCESS PATERNAL TRANSMISSION AMONG JUVENILE-ONSET CASES

Though Huntington [1] reported that onset of the disease never occurred prior to age 30, instances of juvenile onset have been known since Davenport and Muncey [23] observed two cases with onset shortly after birth. More recently, interest has centered on an observation first made by Merritt et al. [8]. They ascertained 106 sibships in which at least one individual showed onset of Huntington disease prior to age 21. Of the 106 affected parents, 84 were the father and only 22 were the mother. This 3.8-fold paternal excess is highly significant (χ^2_1 = 36.3, $P < .0005$). The sex ratio of the juvenile cases did not differ significantly from 1.0.

Many investigators have since confirmed these observations [7, 12, 19, 24–26]. Wallace [10] found no excess of paternal transmission, but his sample included only 13 sibships with cases of juvenile onset. Data from the Roster are presented in table 5. Of the 87 sibships with at least one onset before age 21, 62 were due to transmission from an affected father, a 2.5-fold excess of paternal transmission (χ^2_1 = 15.7, $P < .0005$). Among the 108 individuals with juvenile onset, 51 were male and 57 female, consistent with the hypothesis of a sex ratio of one (χ^2_1 = 0.33, $P > .50$). Pooling the Roster sibship data with the data from the literature cited gives a total of 358 cases of paternal and 109 of maternal transmission, for a ratio of 3.3 to 1.0. Caution is advisable when pooling the data in this manner since some individuals may have been included in more than one study, and since some authors report sibships with at least one juvenile-onset case while others include all parent-offspring pairs. Nonetheless, the evidence overwhelmingly favors a significant excess of paternal transmission among juvenile-onset cases.

One reasonable explanation for this observation would be that carrier males are relatively more fit than carrier females [8]. However, the data do not support

TABLE 5

JUVENILE-ONSET CASES OF HUNTINGTON DISEASE

A. Sibships with at least one juvenile-onset case

Affected parent	No. sibships
Father	62
Mother	25
Total	87

NOTE: Effect of parental sex: $\chi^2 = 15.7$; df = 1; $P < .0005$.

B. Individuals with juvenile onset

	INDIVIDUAL SEX		
AFFECTED PARENT	Male	Female	TOTAL
Father	37	41	78
Mother	14	16	30
Total	51	57	108

NOTE: Effect of individual sex: $\chi^2 = 0.33$; df = 1; $P > .50$.

this hypothesis. Studies carried out in Michigan, U.S.A. [27] and in Queensland, Australia [10] showed that affected females had on the average 1.5 times as many children as their male counterparts (2.82 to 1.85 in Michigan, 3.70 to 2.38 in Queensland). Jones [13] further demonstrated that the female reproductive advantage is maintained over all onset ages. These observations make the excess paternal transmission among juvenile cases appear even more striking.

Both the cytoplasmic factor model and the maternal genotype model can explain this excess in paternal transmission. For sake of argument, let us now assume that the age-of-onset distribution for unprotecteds is sufficiently shifted toward earlier onset relative to protecteds that only unprotected individuals may experience juvenile onset. This assumption will be approximately true if the left-hand tails of the distributions decline sharply enough, as illustrated for the cytoplasmic factor model in figure 3. Excess paternal transmission among juvenile-onset cases then occurs because the offspring of carrier fathers are less likely to be protected than are the offspring of carrier mothers. This effect must outweigh the observed excess female fitness among Huntington carriers.

In the case of the cytoplasmic factor model, the probability that the child of a carrier father is unprotected is $1 - \alpha$; with a carrier mother, this probability is $1 - \alpha_{HM}$. All carrier males are represented among the fathers of unprotected children, but only unprotected females can be found among the mothers. Hence, the paternal-to-maternal ratio among parents transmitting juvenile-onset disease is

$$\frac{[\alpha_H c_{PY} + (1 - \alpha_H) c_{UY}] (1 - \alpha)}{c_{UX} (1 - \alpha_{HM})} . \quad (3)$$

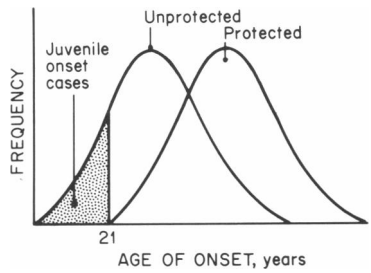

FIG. 3.—Hypothetical age-of-onset distributions: cytoplasmic factor model

Unfortunately, this ratio depends on a number of unobservable parameters. Two quantities that can be observed are the overall fitness of carrier males, $c_Y = \alpha_H c_{PY} + (1 - \alpha_H) c_{UY}$, and the overall fitness of carrier females, $c_X = \alpha_H c_{PX} + (1 - \alpha_H) c_{UX}$. Employing equation (2) together with equation (A-4) from the APPENDIX, the ratio (3) reduces after some algebra to $[c_X c_Y (2c - c_{UX})]/[c_{UX}^2 (2c - c_X)]$, where c is the average number of children born to a normal individual. In the case of the Michigan study, $c = 2.88$, $c_X = 2.82$, and $c_Y = 1.85$. For those data, values of c_{UX} between 1.4 and 1.6 (corresponding to fitnesses relative to normal females of between 0.49 and 0.56) predict a paternal-to-maternal juvenile-onset transmission ratio of between three and four. Thus, for appropriate choices of the parameters, the cytoplasmic factor model is consistent with observed excess of paternal transmission.

DISCUSSION

The two maternal factor models appear to explain the reported anomalies in the inheritance of Huntington disease rather well. They both explain the well-established differences in age of onset for Huntington disease by sex of the affected parent; the maternal genotype model is perhaps more in accord with the 3-generation transmission data. They predict that affected mother-child pairs should show a stronger age-of-onset correlation than father-child pairs, as is observed in the Roster data. They are also consistent with the highly significant excess of paternal transmission among juvenile-onset cases of the disease. Actually, either model is most likely a caricature of the true situation, representing the simplest version consistent with the observed data. Multiple cytoplasmic factors, or multiple alleles at the modifying locus, could be present; polygenic and environmental variability probably also influence the age of onset of the disease.

Both maternal factor models allow at least one further prediction. Half-sibs who share a carrier mother would necessarily be of identical protection status. They should, therefore, exhibit a stronger age-of-onset correlation than half-sibs sharing a carrier father. Data on this point are very limited. Brackenridge [28] actually found a stronger half-sib age-of-onset correlation given a common affected father (.649 based on 11 half-sib pairs) than for a common affected mother (.167 for 13 pairs). Age-of-death correlations showed the opposite result, with values of .269 and .703 for 18 half-sibs sharing an affected father and 16 sharing an affected mother, respectively. However, neither of these differences reaches sta-

tistical significance: for age of onset, $Z = 1.28$ for a one-tailed P-value of .10, and for age of death, $Z = 1.58$, $P = .06$ [14]. Currently, the Roster lacks sufficient data to test this hypothesis.

Other models have been suggested to explain the anomalies of the inheritance of Huntington disease. Models positing two distinct disease loci or multiple alleles at the disease locus are unsatisfactory, since they fail to predict any age-of-onset difference owing to the sex of the transmitting parent. A purely polygenic model for age-of-onset variability is inadequate for the same reason. The suggestion that a Y-linked modifier might be responsible is inconsistent with the observation that age of onset does not depend on the sex of an individual, but only on that of the transmitting parent. The above two arguments apply to an autosomal or X-linked modifier unless, as we have proposed, it is the mother's genotype at the modifier locus that alters age of onset in her offspring. Wallace [9, 10] suggests that differential reproduction among subgroups of carrier males might be responsible for the observed anomalies. However, he assumes that a group of males with early onset leaves more offspring than the early-onset females; this suggestion is difficult to reconcile with Jones' [13] observation that females are more fit over the entire range of onset ages.

The maternal factor models we propose are not without precedent. Cytoplasmic inheritance is common in plants [29], and has been suggested for a number of human traits including Leber's optic atrophy [30, 31] and the color blindness described by Cunier [32]. Human mitochondrial DNA is known to include 13 open reading frames [33]. One or more of these might code for the proposed protective factor. Hemolytic disease of the newborn provides an example in which the genotype of the mother strongly affects the developing child [34]. The increased risk of vaginal and cervical cancers among daughters of women who received diethylstilbestrol (DES) during pregnancy [35] demonstrates that the role of maternal factors may not become apparent until much later in life. Similar delayed effects due to the maternal genotype are certainly possible.

One might suppose that the observed excess in paternal transmission of juvenile-onset cases could be responsible for the other observations of differential anticipation and parent-offspring correlation on the basis of parental sex. The Roster data argue against this interpretation. When juvenile-onset cases are excluded, anticipation averages 5.65 years in the case of paternal transmission, and only 0.90 years for maternal transmission ($t = 5.74$ based on samples of 217 and 260, respectively, $P < .000001$). The father-offspring and mother-offspring age-of-onset correlations of .439 and .714 are also significantly different ($Z = 4.59$, $P < .00001$).

Possible ascertainment bias is an issue that must be considered, particularly when data gathering is by voluntary questionnaire. Our findings of differential age of onset by parental sex and excess parental transmission in cases of juvenile onset are supported by a number of other studies [5, 7, 8, 10, 12, 17–19, 24–26]. These other studies involved different sampling strategies and should, in general, be subject to different biases. Furthermore, it is difficult to imagine what sort of ascertainment bias could produce all the anomalies observed without also causing a difference between male and female mean ages of onset.

A final point that merits attention is the difficulty in defining age of onset. Problems arise because the question requires both a subjective evaluation by the patient and his or her family of what actually constitutes disease and an accurate recollection of when the change from "healthy" to "sick" took place. These problems are particularly severe in the case of Huntington disease, owing to the gradual nature of onset and to the tendency on the part of affecteds and their families to deny its presence.

An alternative to analyzing data on age of onset is to consider age of death. The obvious advantage of this approach is that death is much simpler to pinpoint. The primary disadvantage is the difficulty in deciding whether or not to include individuals whose primary cause of death is not Huntington disease, but may be related, for example, to suicide or accidental death.

In fact, age of onset and age of death for Huntington disease are strongly correlated [19]. Furthermore, Hayden [36] found that their difference—that is, the duration of the disease—showed no significant sex-related variability. These observations suggest that similar results should be obtained if age of death is considered instead of age of onset. Indeed, both maternal-factor models could be reformulated to postulate a delay in age of death rather than in age of onset.

ACKNOWLEDGMENTS

We thank the participants in the Huntington's Disease Workshop held at UCLA in February, 1982. The workshop was organized by the Hereditary Disease Foundation under a contract from the State of California, and chaired by Drs. M. Anne Spence and P. Michael Conneally. Many of the ideas developed in this paper originated at the Workshop. Thanks also to Dr. Elliot Landaw for help with the maternal genotype model, to Kathy Neiswanger and Dr. M. Anne Spence for critically reading a previous manuscript and suggesting several improvements, to Keith Beidelman, Kay Rogers, and Kamton Joe for assistance with the data management and analysis, and finally to the many families who participated in the Huntington's Disease Research Roster.

APPENDIX

EQUILIBRIUM FREQUENCY OF THE CYTOPLASMIC FACTOR AMONG HUNTINGTON CARRIERS

To verify that the cytoplasmic factor should have a higher frequency among Huntington carriers than in the general population, let us determine the equilibrium frequency α_H of the cytoplasmic factor among Huntington carriers. We assume that the sex ratio is one, that the mutation rate is constant over time, and that generations are discrete. Define X_P^n, Y_P^n, X_U^n and Y_U^n as the expected numbers of carriers who are protected females, protected males, unprotected females, and unprotected males, respectively, at generation n. Let c_{PX}, c_{PY}, c_{UX}, and c_{UY} be the average numbers of children born to a carrier of each of these types. Let c be the average number of children born to a normal individual in the population, and let α be the frequency of the cytoplasmic factor in the normal population. For a sufficiently large population, the number of new mutations at the Huntington disease locus at generation n is the deterministic value $(c/2)^n w$, for some constant w.

We may now write recursive formulas for the expected numbers of protected and unprotected male and female carriers:

$$X_P^{n+1} = \tfrac{1}{4}c_{PY}\,\alpha\,Y_P^n + \tfrac{1}{4}c_{UY}\,\alpha\,Y_U^n + \tfrac{1}{4}c_{PX}\,X_P^n + \alpha\,(c/2)^{n+1}\,w/2$$

$$X_U^{n+1} = \tfrac{1}{4}c_{PY}\,(1-\alpha)\,Y_P^n + \tfrac{1}{4}c_{UY}\,(1-\alpha)\,Y_U^n + \tfrac{1}{4}c_{UX}\,X_U^n + (1-\alpha)(c/2)^{n+1}\,w/2\ .$$

Since $Y_P^n = X_P^n$ and $Y_U^n = X_U^n$, we need follow only the carrier females. If we write

$$\mathbf{C} = \tfrac{1}{4}\begin{bmatrix} c_{PY}\alpha + c_{PX} & c_{UY}\alpha \\ c_{PY}(1-\alpha) & c_{UY}(1-\alpha) + c_{UX} \end{bmatrix} \text{ and } \mathbf{D} = \begin{bmatrix} \alpha w/2 \\ (1-\alpha)w/2 \end{bmatrix},$$

then

$$\begin{bmatrix} X_P^{n+1} \\ X_U^{n+1} \end{bmatrix} = \mathbf{C}\begin{bmatrix} X_P^n \\ X_U^n \end{bmatrix} + (c/2)^{n+1}\,\mathbf{D}\ .$$

Under the reasonable assumption that $\frac{1}{2}(c_{PX} + c_{PY}) < c$, the dominant eigenvalue of $2/c\ \mathbf{C}$ is strictly less than unity [37]. It then follows as in Lange and Gladstien [38] that

$$\lim_{n\to\infty} (c/2)^{-n}\begin{bmatrix} X_P^n \\ X_U^n \end{bmatrix}$$

exists, and is given by $[\mathbf{I} - (2/c)\mathbf{C}]^{-1}\,\mathbf{D}$, where $\mathbf{I}$ is the 2×2 identity matrix.

The equilibrium frequency of the cytoplasmic factor among Huntington carriers is then

$$\alpha_H = \lim_{n\to\infty} \frac{X_P^n}{X_P^n + X_U^n} = \frac{\alpha}{\alpha + (1-\alpha)\dfrac{c - \frac{1}{2}c_{PX}}{c - \frac{1}{2}c_{UX}}}\ . \qquad (4)$$

Since $0 < \alpha < 1$ and $c_{UX} < c_{PX}$, $\alpha < \alpha_H$. It is interesting to note that the equilibrium frequency α_H depends neither on the fitnesses of the male Huntington carriers nor on the rates of mutation and population growth.

REFERENCES

1. HUNTINGTON G: On chorea. *Med Surg Reptr* 26:317–321, 1872
2. PENROSE LS: The problem of anticipation in pedigrees of dystrophia myotonica. *Ann Eugen (Lond)* 14:125–132, 1948
3. WALLACE DC, HALL AC: Evidence of genetic heterogeneity in Huntington's chorea. *J Neurol Neurosurg Psychiatry* 35:789–800, 1972
4. HALDANE JBS: The relative importance of principal and modifying genes in determining some human diseases. *J Genet* 41:149–157, 1941
5. STEVENS DL: Huntington's chorea. A demographic, genetic and clinical study. M.D. thesis, University of London, 1976
6. NEISWANGER K: Heterogeneity and age of onset in Huntington's disease. Hereditary Disease Foundation Workshop, 1982

7. HAYDEN MR, BEIGHTON P: Genetic aspects of Huntington's chorea: results of a national survey. *Am J Med Genet* 11:135–141, 1982
8. MERRITT AD, CONNEALLY PM, RAHMAN NF, DREW AL: Juvenile Huntington's chorea, in *Progress in Neurogenetics*, vol 1, edited by BARBEAU A, BRUNETTE JR, Amsterdam, Excerpta Medica, 1969, pp 645–650
9. WALLACE DC: The social effect of Huntington's chorea on reproductive effectiveness. *Ann Hum Genet* 39:375–379, 1976
10. WALLACE DC: Distortion of Mendelian segregation in Huntington's disease, in *Advances in Neurology*, vol 23, edited by CHASE TN, WEXLER NS, BARBEAU A, New York, Raven Press, 1979, pp 73–81
11. WENDT GG, SOLTH K, LANDZETTEL HJ: Kinderzahl, Erkrankungsalter und Sterbealter bei der Huntingtonschen Chorea. *Anthropol Anz* 24:299–309, 1961
12. BRACKENRIDGE CJ: A genetic and statistical study of some sex-related factors in Huntington's disease. *Clin Genet* 2:267–286, 1971
13. JONES MB: Fertility and age of onset in Huntington's chorea, in *Advances in Neurology*, vol 1, edited by BARBEAU A, CHASE TN, PAULSON GW, New York, Raven Press, 1973, pp 171–177
14. SNEDECOR GW, COCHRAN WG: *Statistical Methods*, 7th ed. Ames, Iowa State Univ. Press, 1980, pp 191–193
15. RAO CR: *Linear Statistical Inference and Its Applications*, 2nd ed. New York, John Wiley, 1973, pp 97, 432–434
16. MURPHY EA, CHASE GA: *Principles of Genetic Counseling*. Chicago, Year Book Medical, 1975, pp 277–279
17. BIRD ED, CARO AJ, PILLING JB: A sex-related factor in the inheritance of Huntington's chorea. *Ann Hum Genet* 37:255–260, 1974
18. NEWCOMBE RG, WALKER DA, HARPER PS: Factors influencing age at onset and duration of survival in Huntington's chorea. *Ann Hum Genet* 45:387–396, 1981
19. MYERS RH, MADDEN JJ, TEAGUE JL, FALEK A: Factors related to onset age of Huntington disease. *Am J Hum Genet* 34:481–488, 1982
20. LEVENE H: Robust tests for equality of variances, in *Contributions to Probability and Statistics*, edited by OLKIN I, Stanford, Calif., Stanford Univ. Press, 1960, pp 278–292
21. BROWNLEE KA: *Statistical Theory and Methodology in Science and Engineering*. New York, John Wiley, 1965, pp 299–303
22. BRACKENRIDGE CJ: Familial correlations for age at onset and age at death in Huntington's disease. *J Med Genet* 9:23–27, 1972
23. DAVENPORT CB, MUNCEY EB: Huntington's chorea in relation to heredity and eugenics. *Am J Insan* 73:195–222, 1916/1917
24. BARBEAU A: Parental ascent in the juvenile form of Huntington's chorea. *Lancet* 2:937, 1970
25. JONES MB, PHILLIPS CR: Affected parent and age of onset in Huntington's chorea. *J Med Genet* 7:20–21, 1970
26. MYRIANTHOPOULOS NC: Huntington's chorea: the genetic problem five years later, in *Advances in Neurology*, vol 1, edited by BARBEAU A, CHASE TN, PAULSON GW, New York, Raven Press, 1973, pp 149–159
27. REED TE, NEEL JV: Huntington's chorea in Michigan. 2. Selection and mutation. *Am J Hum Genet* 11:107–136, 1959
28. BRACKENRIDGE CJ: A statistical study of half-sibships born to parents affected with Huntington's disease. *J Med Genet* 9:17–22, 1972
29. AYALA FJ, KIGER JA: *Modern Genetics*. Menlo Park, Calif., Benjamin/Cummings, 1980, pp 160–162
30. IMAI Y, MORIWAKI D: A probable case of cytoplasmic inheritance in man: a critique of Leber's disease. *J Genet* 33:163–167, 1936
31. VOGEL F, MOTULSKY AG: *Human Genetics. Problems and Approaches*. Berlin, Springer-Verlag, 1979, p 95

32. STERN C, WALLS GL: The Cunier pedigree of "color blindness." *Am J Hum Genet* 9:249–273, 1957
33. SLONIMSKI P, BORST P, ATTARDI G, EDS: *Mitochondrial Genes*, Cold Spring Harbor Monograph Series, vol 12. Cold Spring Harbor, N.Y., Cold Spring Harbor Laboratory, 1982
34. THOMPSON JS, THOMPSON MW: *Genetics in Medicine*, 3rd ed. Philadelphia, W.B. Saunders, 1980, pp 214–216
35. HERBST AL, ULFELDER H, POSKANZER DC: Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 284:878–881, 1971
36. HAYDEN MR: *Huntington's Chorea*. Berlin, Springer-Verlag, 1981
37. SENETA E: *Non-Negative Matrices*. New York, John Wiley, 1973, p 6
38. LANGE K, GLADSTIEN K: Further characterization of the long-run population distribution of a deleterious gene. *Theor Popul Biol* 18:31–43, 1980