ARTICLE

***TTR* familial amyloid polyneuropathy: does a mitochondrial polymorphism entirely explain the parent-of-origin difference in penetrance?**

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The Val30Met transthyretin familial amyloid polyneuropathy (*TTR*-V30M-FAP) is the most frequent familial amyloidosis, with autosomal dominant transmission. This severe disease shows important differences in age of onset and penetrance. Recently, a difference in penetrance according to the gender of the transmitting parent was elicited in different geographic areas with a higher penetrance in case of maternal transmission of the trait. In addition, differences in mitochondrial haplogroup distribution in early and late onset Swedish and French cases of *TTR*-V30M-FAP suggested that a polymorphism of mitochondrial DNA could be one underlying mechanism of the phenotypic variation. We further investigated this hypothesis by modeling the penetrance function with a parent-of-origin and/or a mitochondrial polymorphism effect in samples of Portuguese ($n=33$) and Swedish families ($n=86$) with *TTR*-V30M-FAP in which several individuals had been tested for mitochondrial haplogroups. Our analysis showed that a mitochondrial polymorphism effect was sufficient to explain the observed difference in penetrance according to gender of the transmitting parent in the Portuguese sample, whereas, in the Swedish sample, a clear residual parent-of-origin effect remained. This study further supported the role of a mitochondrial polymorphism effect that might induce a higher penetrance in case of maternal inheritance of the disease. In clinical practice, these results might help to better delineate the individual disease risk and have a significant impact on the management of both patients and carriers.

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INTRODUCTION

Transthyretin familial amyloid polyneuropathy (*TTR*-FAP) is a severe neuropathy of adulthood with autosomal dominant transmission most frequently due to the pathogenic *TTR*-V30M substitution of the gene. The disease is characterized by intratissular deposition of amyloid fibrils made up of misfolded *TTR*. Most patients present with a progressive sensorimotor and autonomic axonal polyneuropathy in the setting of multisystem manifestation. Cardiac involvement is often associated, including a restrictive cardiomyopathy along with conduction blocks and rhythm disturbance. Carpal tunnel syndrome can be inaugural. In addition, renal manifestations or visual impairment may occur, although less frequently. Overall, the course of the disease is pejorative in 8–15 years. Liver transplantation, if performed early in the course, by suppressing the main source of abnormal *TTR*, is the only therapeutic procedure known to stabilize the disease. Initially described in northern Portugal,^{1,2} the affection was subsequently reported in two other endemic foci, in Sweden and Japan.^{3,4} Since then, thanks to the development of genetic testing, patients have been diagnosed outside these areas and in many other countries worldwide.^{5,6} In Japan, previous studies have elicited differences according to geographical distribution, that is, endemic vs nonendemic areas.^{7,8} In endemic foci, characteristic features of V30M *TTR*-FAP patients include early age at onset from the late 20s to the early 40s. Clinically,

there is marked superficial sensory loss and autonomic dysfunction associated with cardiac conduction block requiring pacemaker implantation. In contrast, patients from nonendemic areas usually show an older age at onset of more than 50 years. The clinical picture shows diffuse sensory loss with mild autonomic dysfunction, whereas cardiomegaly is prominent.⁷ Interestingly, a similar figure was reported in Portugal.⁹

In a previous work, we showed that important differences in disease expression, and in particular in penetrance estimation, exist among countries.^{10–12} The cumulative risks by age 70 years were estimated to be 91% in Portuguese carriers, 64% in French carriers, and 36% in Swedish carriers.

In addition, Hellman *et al*¹¹ found a marked difference in penetrance according to the gender of the transmitting parent in the Swedish carriers, which was confirmed in the Portuguese populations where the difference was highly significant.¹³ Indeed, the risk of disease in carriers was significantly higher when the mutation was inherited from the mother. The same trend was observed in the French population but the difference did not reach significance. This observation might be due to various mechanisms. On the one hand, there could be a difference in the expression of the mutated allele according to the gender of the parent who transmitted the mutation, such as an imprinting phenomenon. We will refer to this mechanism as a

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parent-of-origin effect. On the other hand, given the maternal inheritance of the mitochondrial DNA (mtDNA), this observation might fit with the recent finding of different mitochondrial haplogroup distribution in early and late onset Swedish and French cases of TTR-FAP.¹⁴ The latter work suggested that a mtDNA polymorphism could be one underlying mechanism of the phenotypic variation in the disease through its impact on the amyloid-generating process.

In this paper, we further investigated the hypothesis that the difference in penetrance according to the sex of the transmitting parent could be attributed to a modifier effect of a mtDNA polymorphism on the expression of the TTR mutation. This was performed by modeling the penetrance function of TTR mutation carriers under various hypotheses of transmission of a modifier mtDNA polymorphism in the populations in which the parent-of-origin difference was the strongest, that is, the sample of Portuguese families and the sample of Swedish families. In the latter families, several individuals have been tested for mitochondrial haplogroups.

MATERIALS AND METHODS

Families

The sample of Portuguese families used for the analysis was already described by Planté-Bordeneuve et al.¹⁰ Briefly, 384 subjects, including 124 affected and 260 unaffected individuals, were recorded from 33 families. Among them, 139 were tested and 83, including probands, were found carriers of a TTR mutation.

The Swedish families used for the analysis included the 78 families already ascertained and described by Hellman et al.¹¹ and 8 additional new families. The 86 families totaled 1630 individuals among whom 271 were affected. Among all family members, 387 were tested for a TTR mutation; 368 were found to be carriers (including probands) and 19 were noncarriers. Among carriers, 30 individuals, all in different families, were tested for mitochondrial haplogroups and included in the study by Olsson et al.¹⁴. In both the samples, Val30Met was the only detected mutation.

Statistical methods

The method was based on the PEL (proband's phenotype exclusion likelihood),¹⁵ which we extended to include the homozygous genotypes and to take into account a parent-of-origin effect and a modifier effect of a mtDNA polymorphism.

The PEL is a maximum likelihood method based on survival analysis. The penetrance function is estimated by using the phenotypic information, conditioned on genotypes, from all family members, including those with unknown genotype. According to survival analysis, if $F(t)$ is the penetrance function by age t , the contribution of an individual i to the likelihood is $1 - F(t_i)$ if i is still unaffected by age t_i , and $F(t_{i+1}) - F(t_i)$ if i is affected with age of onset included between t_i and $(t_i + 1)$.

The age-dependent penetrance function $F(t)$ is modeled by a Weibull model with parameters λ (scale parameter), α (shape parameter), and κ (the fraction of individuals that would never be affected): $F(t) = (1 - \kappa)(1 - \exp(-\lambda t^\alpha))$.

Correction for ascertainment is performed by removing the phenotypic information of the individual who allowed the family to be detected (the proband) and by duplicating families in which there are several probands.

Let us denote Phen the vector containing all the individuals' phenotypes and Gen_{obs} the vector of the observed genotypes in family f . The PEL uses the probability of the phenotypes of the family members given the observed genotypes and the proband's phenotype P_p . For family f , the likelihood L_f is:

$$L_f = \Pr(\text{Phen}/\text{Gen}_{\text{obs}}, P_p) = \frac{\Pr(\text{Phen}, \text{Gen}_{\text{obs}})}{\Pr(P_p, \text{Gen}_{\text{obs}})}$$

Practically, L_f is computed using the Elston-Stewart algorithm¹⁶ separately for the numerator and the denominator.

The PEL had initially considered a dominant model with only two possible genotypes, carrier and noncarrier. The extension to any genetic model was performed by considering as many penetrance functions as possible genotypes.

As FAP is a dominant disease with no sporadic cases, the penetrance function was fixed at the same values for homozygous and heterozygous carriers and was set to nil for all noncarrier individuals.

To investigate all possible hypotheses, we defined eight models. The baseline model with the three-parameter penetrance described above is referred to as model 1.

To take into account a parent-of-origin effect, we split the heterozygous genotype into two genotypes according to the maternal (m) or paternal (p) origin of the mutated allele, and the corresponding penetrance functions were modeled by two sets of parameters $(\lambda_m, \alpha_m, \kappa_m)$ and $(\lambda_p, \alpha_p, \kappa_p)$, respectively (model 2).

To include a modifier effect of a mtDNA polymorphism, we extended the set of genotypes to take into account both the TTR genotype and the mitochondrial genotype, with the constraint that the latter is always maternally inherited. To model the risks associated with the different genotype combinations, we hypothesized a mtDNA biallelic polymorphism M1/M2, with frequencies q and $1 - q$, respectively, with two sets of penetrance parameters $(\lambda_{M1}, \alpha_{M1}, \kappa_{M1})$ and $(\lambda_{M2}, \alpha_{M2}, \kappa_{M2})$ (model 3). Model 4 was defined by adding a residual parent-of-origin effect to model 3, thus combining models 2 and 3, with four sets of penetrance parameters $(\lambda_{m,M1}, \alpha_{m,M1}, \kappa_{m,M1})$, $(\lambda_{p,M1}, \alpha_{p,M1}, \kappa_{p,M1})$, $(\lambda_{m,M2}, \alpha_{m,M2}, \kappa_{m,M2})$, and $(\lambda_{p,M2}, \alpha_{p,M2}, \kappa_{p,M2})$.

In the Swedish sample where haplogroups were available in some families, we considered, in addition, n possible haplogroups,¹⁷ with corresponding penetrance functions modeled by $(\lambda_i, \alpha_i, \kappa_i)$, where i varies from 1 to n (model 5). In the model including the parent-of-origin effect and the haplogroup effect (model 6), there are $2n$ possible penetrance functions modeled by $(\lambda_{m,i}, \alpha_{m,i}, \kappa_{m,i})$ and $(\lambda_{p,i}, \alpha_{p,i}, \kappa_{p,i})$. Finally, to include the haplogroup information in the mitochondrial polymorphism effect, we assumed that the mtDNA polymorphism was not necessarily confounded with the haplogroups. Therefore, we considered a model in which the polymorphism (M1/M2) would have different frequencies q_i (and $1 - q_i$) in the n different haplogroups, with i varying from 1 to n (model 7). The complete model (model 8) was defined by adding a parent-of-origin effect as well as haplogroup information to model 7.

The frequency of the TTR mutation was set to 0.04 in the Swedish sample¹¹ and to 0.001 in the Portuguese sample.¹⁰ The frequencies of the different haplogroups in the Swedish sample were fixed at the values reported by Olsson et al.¹⁴. The *de novo* mutation rate was neglected as the PEL has been shown to be robust to a misspecification of this parameter.¹⁵

Tests of each set of nested hypotheses H_0 (null hypothesis) and H_1 (alternative hypothesis) were performed using the maximum likelihood ratio test. Twice the natural logarithm of this ratio follows a χ^2 distribution with degrees of freedom equal to the difference in the number of parameters estimated, respectively, under H_1 and H_0 .

RESULTS

The results of the analyses of the Portuguese and Swedish samples are shown in Table 1. In accordance with our previous analysis of the Portuguese sample,¹³ the parent-of-origin effect (model 2 vs model 1) was highly significant ($\chi^2 = 42.8$, d.f.=3, $P < 10^{-5}$). The mtDNA polymorphism model (model 3 vs model 1) provided a still better fit ($\chi^2 = 159.5$, d.f.=4, $P < 10^{-5}$). When accounting for both effects, the parent-of-origin effect (model 4 vs model 3) was no more significant ($\chi^2 = 4.4$, d.f.=6). The frequency of the at-risk M1 allele was estimated to be 0.69 under both models 3 and 4.

In the Swedish sample, the parent-of-origin effect (model 2 vs model 1) was clearly significant ($\chi^2 = 23.2$, d.f.=3, $P < 0.001$), but the mtDNA polymorphism model (model 3 vs model 1) was much better ($\chi^2 = 83.7$, d.f.=4, $P < 10^{-5}$). The model including both effects provided a still better fit, and the parent-of-origin effect (model 4 vs model 3) remained significant ($\chi^2 = 52.9$, d.f.=6, $P < 10^{-5}$). The frequency of the at-risk allele was estimated to be 0.25 under model 3 and 0.32 under model 4.

Only six haplogroups were observed in the family sample: H (eight families), J (six families), K (six families), U (five families), X (three

Table 1 Likelihoods of hypotheses including parent-of-origin and mitochondrial effects in the Portuguese and Swedish families

Hypothesis	Model no	Estimated parameters	Number of parameters	−2Ln L	
				Portuguese	Swedish
Baseline model	1	$\lambda_i, \alpha_i, \kappa$	3	1715.2	3007.5
POO effect only	2	$\lambda_m, \alpha_m, \kappa_m$ $\lambda_p, \alpha_p, \kappa_p$	6	1672.4	2984.3
MiP effect only	3	$\lambda_{M1}, \alpha_{M1}, \kappa_{M1}$ $\lambda_{M2}, \alpha_{M2}, \kappa_{M2}$ q	7	1555.7^a	2923.8
MiP+POO effects	4	$\lambda_{m,M1}, \alpha_{m,M1}, \kappa_{m,M1}$ $\lambda_{p,M1}, \alpha_{p,M1}, \kappa_{p,M1}$ $\lambda_{m,M2}, \alpha_{m,M2}, \kappa_{m,M2}$ $\lambda_{p,M2}, \alpha_{p,M2}, \kappa_{p,M2}$ q	13	1551.3 ^a	2870.9
HAP effect only	5	$\lambda_i, \alpha_i, \kappa_i$ $i=1-7$	21		2917.8
HAP+POO effects	6	$\lambda_{m,i}, \alpha_{m,i}, \kappa_{m,i}$ $\lambda_{p,i}, \alpha_{p,i}, \kappa_{p,i}$ $i=1-7$	42		2861.1
MiP effect+HAP information	7	$\lambda_{M1}, \alpha_{M1}, \kappa_{M1}$ $\lambda_{M2}, \alpha_{M2}, \kappa_{M2}, q_i$ $i=1-7$	13		2912.8
MiP+POO effects+HAP information	8	$\lambda_{m,M1}, \alpha_{m,M1}, \kappa_{m,M1}$ $\lambda_{p,M1}, \alpha_{p,M1}, \kappa_{p,M1}$ $\lambda_{m,M2}, \alpha_{m,M2}, \kappa_{m,M2}$ $\lambda_{p,M2}, \alpha_{p,M2}, \kappa_{p,M2}$ q_i $i=1-7$	19		2857.6

POO, parent of origin; HAP, haplogroup; MiP, mitochondrial polymorphism
Bold characters, best model.

^aAccording to parsimony principle, as model 4 is not significantly better than model 3, one concludes for model 3.

families), and V (one family). The analysis was performed by considering seven possible haplogroups, the last category summarizing the nonobserved haplogroups. The haplogroup model (model 5 vs model 1) also provided a better fit than the baseline model ($\chi^2=89.7$, d.f.=18, $P < 10^{-5}$), but the parent-of-origin effect (model 6 vs model 5) remained significant ($\chi^2=56.7$, d.f.=21, $P < 10^{-4}$). Finally, when we included the haplogroup information into the mitochondrial polymorphism model (model 7 vs model 3), we did not obtain a significantly better fit ($\chi^2=11.0$, d.f.=6), and the parent-of-origin effect (model 8 vs model 7) again remained significant ($\chi^2=55.2$, d.f.=6, $P < 10^{-5}$).

The penetrance functions for the best model including a parent-of-origin effect and a mitochondrial polymorphism (model 4) are shown in Figure 1 for the Portuguese sample and in Figure 2 for the Swedish sample. These curves well illustrate that a mitochondrial polymorphism is sufficient to explain the difference in penetrance according to the transmitting parent in the Portuguese sample, where individuals carrying the M1 allele show the same penetrance level whichever parental mutation they received (only a small difference exists for the M2 allele carriers). Contrarily, a residual parent-of-origin effect clearly remains in the Swedish sample after taking into account a mitochondrial polymorphism, as M1 carriers show a large difference in penetrance according to the paternal or maternal origin of the mutation.

The penetrance by age 60 years according to haplogroup and gender of the transmitting parent (model 6) in the Swedish sample is shown in Figure 3. Haplogroup V was observed in only one family and results on this haplogroup are not shown in this figure.

DISCUSSION

Our study results showed that a mtDNA polymorphism may explain the observed difference in penetrance for *TTR*-FAP according to the gender of the transmitting parent. The explanation for such observation is not straightforward as a polymorphism is expected to exist for all individuals, independently of the *TTR* mutation. However, if a modifier polymorphism exists in mtDNA, then an affected individual is likely to carry mitochondrial at-risk alleles. If this individual is a woman, an offspring inheriting the *TTR* mutation necessarily receives her mitochondrial at-risk allele, and has therefore a high probability of being affected. This will not be the case if the *TTR* mutation is transmitted by the father. Under this hypothesis, one may expect that when the transmitting parent is detected, this would be more often the mother than the father. Indeed, in our data the gender of the transmitting parent was known for 144 of the 271 affected individuals in the Swedish sample, that is, the mother for 92 and the father for 52 of these. In the Portuguese sample the gender of the transmitting parent was known for 105 of the 130 affected individuals, that is, the mother in 67 and the father in 38 cases.

The tests of the different hypotheses in the samples of Portuguese and Swedish families did not lead to the same conclusions. Whereas a mitochondrial polymorphism entirely explained the difference in penetrance according to the sex of the transmitting parent in the Portuguese sample, we observed a residual parent-of-origin effect in the Swedish sample. Moreover, when the haplogroup information was taken into account in the Swedish sample, we did not obtain a significantly better fit to the data and there still remained a significant parent-of-origin effect.

Figure 1 Penetrance function according to mitochondrial allele (*M1* or *M2*) and gender of the parent having transmitted the transthyretin (*TTR*) mutation (*pat* for paternal and *mat* for maternal) in the Portuguese population.

Figure 2 Penetrance function according to mitochondrial allele (*M1* or *M2*) and gender of the parent having transmitted the transthyretin (*TTR*) mutation (*pat* for paternal and *mat* for maternal) in the Swedish population.

Figure 3 Penetrance by age 60 according to mitochondrial haplogroup and to gender of the parent having transmitted the transthyretin (*TTR*) mutation (*pat* for paternal and *mat* for maternal) in the Swedish population.

One possible explanation for our study results is that the underlying model that we assumed for the mitochondrial polymorphism may be far too simple. In particular, it is possible that several loci are involved. When we increased the number of possible alleles by considering a three-allele polymorphism in the Swedish sample, we found a significantly better fit to the data, but this model did not cancel the parent-of-origin effect (data not shown).

The absence of better fit to the observed data when including the haplogroups may be due to the fact that these haplogroups were defined on a phylogenetic basis¹⁷ on a limited number of specific polymorphisms that are probably not directly involved in the mitochondrial modifier effect. Such haplogroups are defined by using nine primer pairs covering a small part of the mtDNA, that is, the control region of the mtDNA (nt15678–16569 and nt1–850). We hypothesize

that this polymorphism is probably complex and that candidate genes, different from the polymorphisms that determine the haplogroup classification, should be looked for.

The biological mechanisms that could explain the role of mitochondria in processing misfolded proteins appear rather complex. TTR is a soluble protein that is secreted from the cell throughout the endoplasmic reticulum (ER) where it undergoes folding. ER function is highly sensitive to ER stress. Misfolded proteins cause ER stress with increased reactive oxygen species (ROS) production.¹⁸ This ROS production further enhances ER stress creating a feedback loop.¹⁹ Polymorphisms in the mtDNA lead to tighter coupling of the OXPHOS system thereby increasing ROS production.^{20,21} This also affects the ER due to the close relationship between the ER and the mitochondria. These two sources of ROS production could alter the efficiency of ER in eliminating misfolded proteins.¹⁹

At present, there is no explanation for the important difference in penetrance estimation between countries.^{10–12} One might speculate that a mitochondrial polymorphism could account for at least part of this difference if the at-risk alleles had different frequencies among countries. The results of our study on the Portuguese and the Swedish families favor this hypothesis as the estimated frequency of the at-risk allele was much higher in the Portuguese (0.69) than in the Swedish (0.32) populations.

In clinical practice, our study results might have a significant impact on the management of both patients and carriers. Presently, the main challenge is to offer treatment, that is, liver transplantation and/or future upcoming oral drugs at the earliest stage of the disease manifestations. Unraveling the possible influence of a mitochondrial modifier gene on the phenotype of TTR-FAP, and in particular on the distribution of ages of first symptoms, might give a major clue to delineate the individual disease risk. Accordingly, such mtDNA marker could be one important factor of the phenotypic variation, particularly in the Portuguese families. So far, we cannot accurately foresee the onset of symptoms in a carrier. On the basis of our penetrance estimation in the different populations, we can only expect a dramatic increase in risk within particular age intervals, which will incite to enhance the clinical follow-up, from this time. Such molecular genetic marker could help pointing at those individuals with higher risk of developing the disease, to be able to detect and treat them as early as possible. Further studies are now needed to better delineate the role of the mitochondrial genome in this setting.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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