

ORIGINAL ARTICLE

Female Predominance and Transmission Distortion in the Long-QT Syndrome

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ABSTRACT

BACKGROUND

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Congenital long-QT syndrome is a disorder resulting in ventricular arrhythmias and sudden death. The most common forms of the long-QT syndrome, types 1 and 2, are caused by mutations in the potassium-channel genes *KCNQ1* and *KCNH2*, respectively. Although inheritance of the long-QT syndrome is autosomal dominant, female predominance has often been observed and has been attributed to an increased susceptibility to cardiac arrhythmias in women. We investigated the possibility of an unbalanced transmission of the deleterious trait.

METHODS

We investigated the distribution of alleles for the long-QT syndrome in 484 nuclear families with type 1 disease and 269 nuclear families with type 2 disease, all with fully genotyped offspring. The families were recruited in five European referral centers for the long-QT syndrome. Mutation segregation, sex ratio, and parental transmission were analyzed after correction for single ascertainment.

RESULTS

Classic mendelian inheritance ratios were not observed in the offspring of either female carriers of the long-QT syndrome type 1 or male and female carriers of the long-QT syndrome type 2. Among the 1534 descendants, the proportion of genetically affected offspring was significantly greater than that expected according to mendelian inheritance: 870 were carriers of a mutation (57%), and 664 were non-carriers (43%, $P < 0.001$). Among the 870 carriers, the allele for the long-QT syndrome was transmitted more often to female offspring (476 [55%]) than to male offspring (394 [45%], $P = 0.005$). Increased maternal transmission of the long-QT syndrome mutations to daughters was also observed, possibly contributing to the excess of female patients with autosomal dominant long-QT syndrome.

CONCLUSIONS

Positive selection of the mutated alleles that cause the long-QT syndrome leads to transmission distortion, with increased proportions of mutation carriers among the offspring of affected families. Alleles for the long-QT syndrome are more often transmitted to daughters than to sons.

CONGENITAL LONG-QT SYNDROME IS A rare cardiac disorder; affected persons present with prolongation of the QT interval corrected for heart rate (QTc interval). These patients are at increased risk for syncope and sudden death due to life-threatening ventricular arrhythmias. In the majority of cases, inheritance of the long-QT syndrome is autosomal dominant but can also be recessive, with or without associated deafness. The genetic causes of the long-QT syndrome have been well characterized.¹ Mutations in the potassium-channel genes *KCNQ1* and *KCNH2* cause the most frequent forms of the long-QT syndrome: types 1 and 2, respectively.

Female predominance among patients with the long-QT syndrome has been reported,²⁻⁶ and results of studies of patients with the long-QT syndrome show a persistent excess of affected women.^{7,8} Reasons underlying the observed female predominance have not been thoroughly explored, and unanswered questions remain. Because the QTc interval is the main criterion for a diagnosis of the long-QT syndrome, women might be more likely to receive the diagnosis because their QTc interval is longer than that of men.⁹ It is unclear whether the observed unbalanced distribution between men and women in the population with clinically recognized long-QT syndrome is due to ascertainment bias or whether mutations causing the long-QT syndrome might have an increased penetrance among women.

An abnormally high rate of maternal transmission has been reported in a limited number of families with the long-QT syndrome.⁴ However, although most investigations have focused on correlations between phenotype and genotype, on prognostic markers, or on both in patients and their family members with symptomatic long-QT syndrome,^{5,8,10} the transmission of mutations causing the long-QT syndrome has not been studied in a systematic manner.

Our retrospective study investigated the transmission and distribution of the mutated alleles in a large number of families with the long-QT syndrome who were genotyped, after correction for ascertainment bias. We aimed to elucidate whether the autosomal dominant mutations that cause the long-QT syndrome types 1 and 2 follow classical mendelian inheritance or whether female predominance could be influenced by an unbalanced sex ratio in the population carrying the deleterious allele.

METHODS

STUDY POPULATION, GENOTYPING, AND PHENOTYPING

All family members with the long-QT syndrome who participated in the study gave written informed consent before the genetic and clinical investigations, in accordance with the standards of the Declaration of Helsinki and local ethics committees.

This retrospective study involving pedigrees of patients with clinically and molecularly diagnosed long-QT syndrome type 1 or type 2 is a collaborative project comprising five European referral centers. The smallest families included one parent with the long-QT syndrome and his or her fully genotyped offspring. The larger pedigrees were divided into nuclear families, consisting of the parent with the long-QT syndrome (either molecularly defined or an obligate carrier) and the offspring. All nuclear families with even one nongenotyped descendant were excluded, as were nuclear families in which two mutations for the long-QT syndrome were transmitted. We studied 240 pedigrees involving 142 distinct mutations (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Our study population consisted of 484 nuclear families with the long-QT syndrome type 1 and 269 nuclear families with the long-QT syndrome type 2. Genotyping and phenotyping were performed at each center according to standard methods. Mutations were defined as variations in DNA sequence that cosegregated with the disease phenotype, that were absent in 300 unrelated control subjects from the same ethnic background as the patient, and that induced an amino acid change or a premature stop codon. Information about phenotype — consisting of the measured QTc interval, clinical symptoms, and presence or absence of a family history of sudden death related to the long-QT syndrome — was available for 885 parental and descendant carriers (480 carriers of type 1 and 405 carriers of type 2). Clinical symptoms were defined as syncope of unknown cause, an aborted cardiac arrest, or documented torsade de pointes. Phenotypic characteristics of the Finnish carriers of the *KCNQ1* mutation resulting in the G589D amino acid substitution have been reported in detail elsewhere¹¹ and were thus not included in this study.

ANALYSIS OF MENDELIAN INHERITANCE AND CORRECTION OF ASCERTAINMENT BIAS

The offspring of nuclear families were analyzed to determine whether mendelian distribution ratios associated with autosomal dominant inheritance were observed in children of carriers of the long-QT syndrome. For mendelian inheritance, the expected findings were that 50% of the offspring carried the mutated allele, that the sex ratio was balanced among the sibship who were carriers, and that the frequencies of maternal and paternal transmission of the mutation were similar. We corrected for single ascertainment¹² to prevent bias toward families with large numbers of carriers by excluding from transmission analysis all probands in the ascertained sibships.

STATISTICAL ANALYSIS

We used the chi-square test to evaluate the observed distribution of offspring of parents carrying a long-QT allele. All P values were two-sided unless otherwise stated, and a P value of less than 0.05 was used to indicate statistical significance. The Bonferroni correction was applied to correct for multiple comparisons. Transmission analysis was conducted with the use of R statistical software.¹³ The phenotypic data (including clinical symptoms and the presence or absence of a family history of sudden death typical of the long-QT syndrome) were compared between probands and other family members carrying long-QT alleles, and the mean QTc intervals were calculated with the use of Stata SE 8.1 statistical software.

RESULTS

Our study included 240 pedigrees of families of European origin carrying 59 mutations causing the long-QT syndrome type 1 and 83 mutations causing the long-QT syndrome type 2. By definition, probands had markedly prolonged QTc intervals (mean [±SD], 493±44 msec for the long-QT syndrome type 1 and 505±53 msec for the long-QT syndrome type 2). The majority of probands had had syncope, aborted cardiac arrests, or both, whereas the symptoms were less prevalent and the QTc intervals were less prolonged among other family members who were carriers. Among family members who were not probands, 388 carriers of the long-QT syndrome type 1 had a mean QTc interval of 465±32 msec, and only 32% were symptomatic; 316 with the long-QT syndrome type 2

had a mean QTc interval of 470±39 msec and only 35% were symptomatic. Of the pedigrees studied, 37% of those with the long-QT syndrome type 1 and 47% of those with the long-QT syndrome type 2 involved a family history of sudden death typical of the long-QT syndrome. Among the pedigrees with type 1, 50 involved the same Finnish founder mutation (*KCNQ1* G589D) localized in the cytoplasmic C-terminal domain. In comparison, Fodstad et al. reported a mean QTc of 462±38 msec among carriers of that mutation, 30% of whom were symptomatic.¹¹ Of the Finnish pedigrees of the long-QT syndrome type 1 included in our study, 20% involved a family history of sudden death.

In accordance with previous reports, we observed a marked female predominance among the 234 clinically diagnosed probands (159 [68%], vs. 75 male probands [32%]; $P < 0.001$) (Table 1). Correction of ascertainment bias led to the exclusion from transmission analysis of 157 probands within the sibships; more female than male probands were excluded (103 vs. 54).

Transmission analysis was first limited to one nuclear family per pedigree in order to maximize the correction for ascertainment bias, as well as to minimize the potential bias of mutations in large pedigrees that contributed multiple nuclear families to the study population. We observed marked female carrier predominance among the descendants (for the long-QT syndrome type 1, 65 female vs. 46 male carriers; for the long-QT syndrome type 2, 69 female vs. 43 male carriers) (Table 1). The proportion of mutation carriers in nuclear families with type 1 or type 2 was higher than expected, indicating that transmission of mutations causing the long-QT syndrome was skewed. When both subpopulations were combined, we identified 134 female carriers and 89 male carriers of the long-QT syndrome and 84 female and 88 male noncarriers (Bonferroni-corrected $P < 0.001$) (Table 1).

Transmission analysis was then extended to all eligible nuclear families with the long-QT syndrome (753 families). Assessment of sex ratio and mutation segregation in the entire study population after correction for ascertainment bias revealed that similar numbers of females (52%) and males (48%) were born to parents with the long-QT syndrome (Table 1 and Fig. 1). As in the single nuclear families, distortion of mutation transmission was observed among all nuclear families with the long-QT syndrome. More off-

Table 1. Study Population and Transmission Analysis Corrected for Ascertainment Bias.

| Category | Total | | | Female Proportion | | |
|---|------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| | Long-QT Syndrome | Long-QT Syndrome Type 1 | Long-QT Syndrome Type 2 | Long-QT Syndrome | Long-QT Syndrome Type 1 | Long-QT Syndrome Type 2 |
| | <i>number</i> | | | <i>number (percent)</i> | | |
| Study population | | | | | | |
| Pedigrees | 240 | 143 | 97 | — | — | — |
| Mutations | 142 | 59 | 83 | — | — | — |
| Probands | 234* | 137* | 97 | 159 (68) | 88 (64) | 71 (73) |
| Excluded probands | 157 | 93 | 64 | 103 (66) | 59 (63) | 44 (69) |
| Transmission analysis in one nuclear family per pedigree | | | | | | |
| Nuclear families | 191 | 94† | 97 | — | — | — |
| Descendants | 395 | 191 | 204 | 218 (55) | 100 (52) | 118 (58) |
| Mutation carriers | 223 (56)‡ | 111 (58)‡ | 112 (55)‡ | 134 (60) | 65 (59) | 69 (62) |
| Noncarriers | 172 | 80 | 92 | 84 (49) | 35 (44) | 49 (53) |
| P value§ | <0.001 | 0.02 | 0.03 | | | |
| Transmission analysis in all nuclear families | | | | | | |
| Nuclear families | 753 | 484 | 269 | — | — | — |
| Descendants | 1534 | 1000 | 534 | 803 (52) | 514 (51) | 289 (54) |
| Mutation carriers | 870 (57)‡ | 566 (57)‡ | 304 (57)‡ | 476 (55) | 303 (54) | 173 (57) |
| Noncarriers | 664 | 434 | 230 | 327 (49) | 211 (49) | 116 (50) |
| P value§ | <0.001 | <0.001 | <0.001 | — | — | — |

* In six pedigrees, five from Finland, the proband belonged to a family branch not investigated by a genetic referral center participating in this study.

† These 94 families included 93 with various mutations causing the long-QT syndrome type 1 and 1 with the founder mutation *KCNQ1* G589D.

‡ The percentage is based on the total number of descendants for the syndrome or subtype.

§ The P value was obtained from the chi-square test (with 3 degrees of freedom) of the distribution of mutations as compared with that predicted by mendelian inheritance (four equivalent groups: female carriers, female noncarriers, male carriers, and male noncarriers). The Bonferroni-corrected significance level for six comparisons was $P < 0.008$.

spring than expected were born with mutations causing the long-QT syndrome type 1 (566 persons [57%]) or with type 2 (304 persons [57%]). A persistent female predominance among mutation carriers was observed in both subgroups. Among the 870 carriers, the allele for the long-QT syndrome was transmitted more often to female offspring (476 [55%]) than to male offspring (394 [45%], $P = 0.005$).

Since most pedigrees involved unique mutations causing the long-QT syndrome, we separately investigated persons with the Finnish founder mutation that causes the long-QT syndrome type 1 (*KCNQ1* G589D). This subgroup represented 451 (45%) of the descendants of parents with the long-QT syndrome type 1 in the study population and 191 of the 484 nuclear families. Transmission of the *KCNQ1* G589D mutation was slightly in-

creased among the descendants in this subgroup, and 243 (54%) were carriers. A trend toward a higher number of female than male carriers of the mutation was also observed (131 women [54%]). In contrast, the 549 offspring who were heterozygous for mutations causing the long-QT syndrome type 1 carried 58 different mutations, many of them affecting transmembrane domains. This subgroup featured higher proportions of mutation carriers (323 [59%]) than noncarriers (226 [41%]) and of female carriers (172 [61%]) than female noncarriers (108 [39%]). In summary, mutation transmission was significantly distorted for all subgroups analyzed, with the exception of the Finnish subgroup that carried the *KCNQ1* G589D founder mutation, which nevertheless showed a similar trend toward higher proportions of mutation carriers and female carriers.

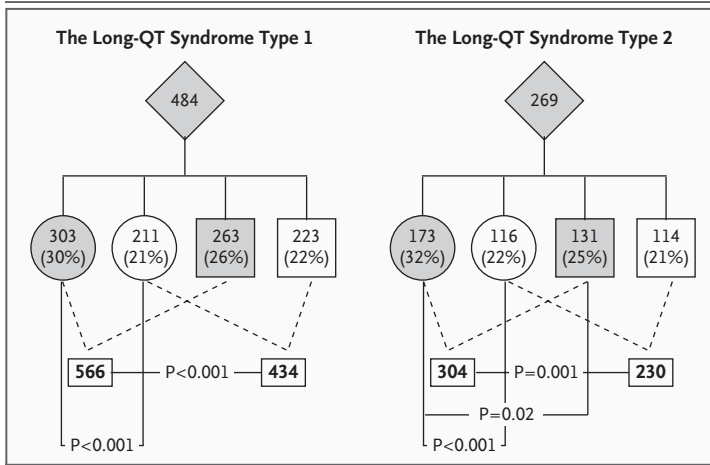


Figure 1. Transmission Analysis.

Female predominance and segregation distortion among offspring (corrected for ascertainment bias) of parents with the long-QT syndrome are shown. Shaded diamonds represent parental carriers of the long-QT syndrome, shaded circles female and shaded squares male offspring who are carriers, white circles female and white squares male offspring who are non-carriers, and white rectangles total numbers of offspring who are carriers or noncarriers. Percentages are calculated as the number divided by the total number. Percentages do not total 100 because of rounding.

Table 2. Parental Transmission of the Long-QT Syndrome to Proband.

| Syndrome | Probands | Transmission to Proband | | |
|------------------|----------|-------------------------|----------|---------|
| | | Maternal | Paternal | Unknown |
| <i>number</i> | | | | |
| Long-QT syndrome | 234 | 106 | 68 | 60 |
| Type 1 | 137 | 64 | 43 | 30 |
| Type 2 | 97 | 42 | 25 | 30 |

Although equal numbers of maternal and paternal transmission events are expected in mendelian transmission, we observed a higher number of maternal transmissions of mutations causing the long-QT syndrome. Indeed, among 837 offspring, the deleterious allele was inherited maternally in 516 children (62%) and paternally in 321 children (38%). The high number of mothers who were carriers, however, might have led to the observed increased maternal transmission. The parental origin of the mutation for the long-QT syndrome was known for 174 of 234 probands (Table 2). In this subgroup, we observed that mutations were inherited more often from the mother (106 probands [61%]) than from the father (68 probands [39%]). Increased maternal transmission

was observed among probands with the long-QT syndrome type 1 or type 2.

Transmission analysis involving the entire study population was conducted, stratified according to the parental origin of the mutation (Table 3). This analysis revealed that the skewed transmission in nuclear families with the long-QT syndrome type 1 was due to the markedly increased female transmission of the mutated allele to offspring ($P<0.001$), whereas male carriers in this subgroup showed a balanced, mendelian transmission ($P=0.57$). Transmission analysis in nuclear families with the long-QT syndrome type 2 showed a different pattern of parental transmission, however. Fathers with the long-QT syndrome type 2 had a markedly skewed mutation transmission ($P=0.009$). Among their offspring, transmission of the mutated allele was favored (117 carriers [62%]), and there was a slight excess of female carriers (62 carriers [53%]) over male carriers (55 [47%]). Mothers with the long-QT syndrome type 2 had nonsignificant transmission distortion ($P=0.13$). They transmitted the mutated allele to 53% of their offspring, and transmission to daughters was favored: the proportion of female carriers (100 [58%]) was higher than the proportion of male carriers (73 [42%]). In summary, the transmission analysis according to parental origin of the mutation provided evidence of a trend of female carriers transmitting the deleterious alleles more often to their daughters than to their sons.

DISCUSSION

We analyzed mutation segregation, sex ratio, and parental transmission in a population composed of mutation carriers and all their offspring, in which the long-QT syndrome was genetically and clinically ascertained. Classic mendelian-inheritance ratios expected for an autosomal dominant trait were not observed among the offspring of female carriers of the long-QT syndrome type 1 allele or among mothers and fathers carrying an allele for the long-QT syndrome type 2.

We investigated the nuclear families of proband-ascertained pedigrees of the long-QT syndrome for which all offspring were genotyped and applied correction for single ascertainment. By these means, we corrected for selection bias due to incomplete or sex-specific penetrance of the mutations for the long-QT syndrome, such as the underdiagnosis of asymptomatic male carriers or

Table 3. Transmission Analysis According to Parental Origin of the Mutation.

| Subgroup | Total No. of Patients (N = 1489)* | Carriers | Female Carriers | Daughters | | Sons | | P Value† |
|-------------------------|-----------------------------------|----------|-----------------|-----------------------------|-------------|------------|-------------|----------|
| | | | | Carriers | Noncarriers | Carriers | Noncarriers | |
| | | | | <i>no. of offspring (%)</i> | | <i>no.</i> | | |
| Long-QT syndrome type 1 | | | | | | | | |
| Maternal | 587 | 343 (58) | 190 (55) | 190 | 120 | 153 | 124 | <0.001 |
| Paternal | 385 | 204 (53) | 102 (50) | 102 | 85 | 102 | 96 | 0.57 |
| Long-QT syndrome type 2 | | | | | | | | |
| Maternal | 328 | 173 (53) | 100 (58) | 100 | 80 | 73 | 75 | 0.13 |
| Paternal | 189 | 117 (62) | 62 (53) | 62 | 33 | 55 | 39 | 0.009 |

* The parental-transmission status was unknown for 45 descendants.

† The P value was obtained from the chi-square test (with 3 degrees of freedom) of the distribution of mutations as compared with that predicted by mendelian inheritance (four equivalent groups: female carriers, female noncarriers, male carriers, and male noncarriers). The Bonferroni-corrected significance level for four comparisons was $P < 0.013$.

the higher likelihood of cardiac events, diagnosis of the long-QT syndrome, or both among women, owing to their longer QTc intervals. The applied correction for ascertainment bias resulted in the exclusion of nearly twice as many female as male probands.

Of all probands, 68% were female. This observation was in accordance with earlier evidence of the marked female predominance in symptomatic long-QT syndrome.^{2-4,6,14,15} The reasons for the increased risk among women of cardiac symptoms and of diagnosis of the long-QT syndrome on electrocardiography have been discussed at length. First, it is well established that the QTc interval is longer in women than in men.⁹ Thus, abnormal QT prolongation is more likely to be detected on electrocardiography in women. The biologic basis for this sex difference might be the down-regulation of expression of cardiac potassium-channel genes by female sex hormones, which has been shown to prolong the QT interval.¹⁶ Furthermore, women may be at higher risk for symptomatic arrhythmias and sudden death than men and, if cardiac events occur, may have a higher mortality rate, even after adjustment for age.¹⁷ Longer QTc intervals may predispose women to ventricular arrhythmias, torsade de pointes in particular. In addition to predisposing physiological factors, women have been shown to be more prone to torsade de pointes during exposure to QT-prolonging drugs.¹⁸ Finally, β -adrenergic blockade has been reported to be less effi-

cient in women with the long-QT syndrome than in men with the syndrome.¹⁹ Taken together, all these factors may contribute to the described female predominance among phenotypically affected populations.^{3-5,7,8,14,15,20,21}

The main finding of our study was that meiotic drive, which results in some alleles being over-represented, favors the transmission of mutant alleles to daughters even in subpopulations corrected for the method of proband selection. Therefore, increased penetrance of the mutation for the long-QT syndrome in women is not the only factor resulting in female predominance. The observed transmission distortion could be due to positive selection of the mutated allele during gametogenesis or during postfertilization processes. A selection bias that eliminates male carriers of the long-QT syndrome before birth could also result in an excess of genetically affected females. However, among persons with the long-QT syndrome, the greater number of mutation carriers (female and male) than noncarriers does not provide support for a negative-selection hypothesis.

Transmission distortion has previously been reported in invertebrates as well as in mammals. Specific genetic loci and molecular mechanisms involved in transmission distortion have been investigated in drosophila²² and mice.²³ Genome-wide transmission distortion involving numerous genetic loci was recently reported in a consanguineous human subpopulation.²⁴ The skewed segregation of disease-causing alleles has been

described in human genetic disease mediated by expanded trinucleotide repeats²⁵ and in recessive congenital disorders.²⁶

Our results revealed that the paternal mutation for the long-QT syndrome type 1 is neutral and has no positive selection effect at the population level, since transmission and sex ratios were found to be in accord with mendelian inheritance. A possible explanation for this finding is that the locus for the long-QT syndrome type 1, 11p15.5, is paternally imprinted during early ontogenesis. The exclusive maternal expression of *KCNQ1* has been reported for various fetal tissues.^{27,28} Although true gametic imprinting is thought to be conserved throughout development,²⁹ the paternal allele for the long-QT syndrome type 1 is expressed in mature cardiac muscle, as evidenced by the occurrence of paternally inherited long-QT syndrome type 1. We suggest that repression of the paternally inherited mutations for the long-QT syndrome type 1 due to the gametic imprint leads to the observed normal mendelian transmission.

Mechanisms resulting in the positive selection of mutations for the long-QT syndrome are unknown. The mutation might confer a reproductive advantage during the maturation, fertilization, implantation, and postimplantation development of the gamete by leading to variation in potassium flow and alteration of membrane potential. Yet the positive selection of the mutated allele seems to be independent of the detrimental cardiac effect later in life.

Though the observed transmission distortion may be directly linked to the deleterious effect of the mutation for the long-QT syndrome on potassium-channel function, we cannot rule out with

certainty that no hidden bias remains in our European study population, since the retrospective study design is inherently vulnerable to involuntary bias in population selection. Therefore, to shed light on these issues, future studies should be prospective and should involve systematic transmission analysis of the mutation for the long-QT syndrome in nuclear families ascertained through nonindex patients.

In conclusion, we report transmission distortion among persons with the long-QT syndrome, owing to positive selection of the mutated allele in a large population corrected for ascertainment bias and including a large proportion of asymptomatic persons. We found compelling evidence of the unbalanced transmission of the deleterious alleles causing the long-QT syndrome types 1 and 2. Our results show that the probability of inheriting a mutation for the long-QT syndrome is higher than expected according to mendelian inheritance and that in maternal transmission, daughters are favored. Therefore, the skewed segregation of the mutation from mothers to their daughters might contribute substantially to the observed female predominance in the long-QT syndrome.

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CLINICAL TRIAL REGISTRATION

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