In this issue of Circulation: Cardiovascular Genetics, Barsheshet et al shed novel and unexpected light on the genetics of syncope, defined as a transient loss of consciousness caused by cerebral hypoperfusion with spontaneous recovery. Syncope is very common, with a cumulative incidence of 37% by age 60 years. In “young” patients, far the most common cause of syncope is vasovagal syncope, with a well-characterized symptom complex and a benign natural history. Hidden in the forest of vasovagal syncope are rare but more worrisome sentinel events that reflect more life-threatening arrhythmic disorders, particularly inherited arrhythmia syndromes such as long-QT syndrome (LQTS).

The genetics of these syndromes are now relatively clear. In contrast to the LQTS, relatively little is known about the genetics of vasovagal syncope, though there are numerous reports of fainting in families, and a parental history of syncope greatly increases the likelihood that offspring will have fainting. Despite these findings, the role of genetic factors and the model of inheritance of vasovagal syncope are unknown.

In this issue, Barsheshet et al present data that inadvertently shed tantalizing light on the possible genetics of vasovagal syncope. The purpose of their study was to examine the role of clinical factors and genetic polymorphisms in syncope in family members of subjects with known culprit mutations causing LQTS. To remove the influence of the culprit mutation, the authors focused on family members who did not have those particular mutations.

Barsheshet et al describe the symptom burden and natural history of 1828 subjects from 239 families in the international LQTs Registry who were not carriers of their family LQTS-causing mutation. Although the duration and rigor of follow-up are not presented, the cohort had an excellent outcome, with only 2 serious events. Both were aborted cardiac arrests in the context of exercise. Details regarding investigation for alternate causes of exertional arrest such as catecholaminergic polymorphic ventricular tachycardia were not provided. The cumulative incidence of reported syncope by the age of 40 years was 15%. It is interesting that the cumulative incidence of vasovagal syncope in 2 population-based studies is >30%. Although the reason for the lower reported cumulative incidence is not clear, the high cumulative incidence of vasovagal syncope in young people in the community suggests that Barsheshet et al detected genetic correlates of vasovagal syncope.

Basic demographic and family history parameters along with ECG variables were then analyzed to predict development of syncope. As is true in vasovagal syncope, female sex increased the likelihood of syncope. Surprisingly, members of families with culprit LQT2 mutations (compared with LQT1 and LQT3) and those with a family history of life-threatening cardiac event also increased the likelihood of syncope, as did the QTc interval, despite the absence of the “connecting” mutation in the study subjects. Whether this is due to genetic factors or selection and inclusion bias is unclear.

Barsheshet et al then studied a subgroup of 218 study subjects, asking whether there was a relationship between syncope and other associated polymorphisms in the 5 LQT genes tested, presented in their supplemental material. Six common polymorphisms were present in up to 56% of study subjects and would be expected to be present in roughly equal proportions in the 3 LQT family subgroups. This was not the case, with a striking difference in proportions (Figure). Two of these polymorphisms greatly increased the likelihood of syncope. There was an immense 11-fold increased relative risk of syncope for subjects with the K897T polymorphism in KCNH2 and an 8-fold increased relative risk for subjects with the G38S polymorphism in KCNE1.

The apparent conclusion is that the QT interval, the family history of QT-related events, and these polymorphisms are potent risk factors for vasovagal syncope. It appears that the authors have performed an inadvertent candidate gene association study for vasovagal syncope. A review of the literature does not suggest that the QT interval is prolonged in vasovagal syncope, and prolonged monitoring has not demonstrated QT-mediated arrhythmias in patients with vasovagal syncope.

What might QT gene polymorphisms in 2 different ion channels have to do with apparently unrelated vasovagal syncope? This may be a simple statistical error caused by a relatively small sample size, compared with typical genome-wide population studies. Having said this, the hazard ratios for the QT intervals and family history are compelling, and a simple χ² statistical comparison in 4 of the 6 polymorphisms.

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returns a probability value of $<0.0001$, making this highly unlikely.

Neither of the 2 most compelling polymorphisms have a recognized effect on the vasomotor axis, as incompletely understood as it is. The K879T polymorphism may or may not play a role in repolarization, with several reports suggesting a modest QT-prolonging effect, whereas others suggest a protective effect in patients with otherwise causative LQ mutations.12,13 Similarly, the G38S polymorphism has at most a very modest effect on the QT interval, and its reported association with the QT interval at the population level was a very modest effect on the QT interval, and its reported association with the QT interval at the population level was not validated in the KORA study.14 Thus, we are left with a persistent problem of how to connect the QT genes with vasovagal syncope. Although these polymorphisms may have a modest effect on the QT interval, they appear to have a clear effect on risk of vasovagal syncope, perhaps through some unrecognized impact on the autonomic nervous system that warrants exploration.

Previous studies have not detected a clear family history of vasovagal syncope in LQT family screening, perhaps because we have not looked for it. If this is the case, we would have expected that the incidence of syncope would be higher than 15% by the age of 40 years, a prevalence that is, if anything, lower than the ambient population risk. Consequently, this discovery that prompts us to better understand the genetics of vasovagal syncope and explore the overlap with the more mature QT realm.

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**Disclosures**

None.

**References**


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Genetics of the Faint-Hearted: Great Results, Alternate Hypothesis
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