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EDITORIAL

Rare Things Being Common

Implications for Common Genetic Variants in Rare Diseases Like Long-QT Syndrome

Article, see p 324

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Although individually rare, Mendelian genetic diseases are collectively common, affecting 25 to 30 million people in the United States. Research exploring the causes of these orphan diseases has led to discoveries with broad impact on medicine. Long-QT syndrome (LQTS) affects 1 in 2500 individuals, manifesting as pathological prolongation of the QT interval reflecting an abnormal delay in cardiac repolarization.[1] LQTS has traditionally been considered a Mendelian or monogenic disease whereby a single pathological variant in a gene is sufficient to cause disease. These variants cause disruption of proteins encoding ion channels, affecting the coordinated flow of ions needed to repolarize the cardiac myocyte. Variants in *KCNQ1* (I_{Ks} potassium channel [Kv7.1]), *KCNH2* (I_{Kr} potassium channel [Kv11.1]), and *SCN5A* (I_{Na} sodium channel [Nav1.5]) are the most frequently implicated in LQTS; given their highly disruptive nature on protein function, these variants are rare (frequency <0.001) or absent in the general population. Combined, these 3 genes account for approximately 65% of all LQTS cases and approximately 80% of genotype-positive LQTS cases.[2]

Despite a quarter century of investigation in this extreme phenotype, unanswered questions remain that hamper the care of patients with LQTS. What is the cause in the approximately 20% of patients with negative genetic testing? What explains variable manifestations of disease within families? Given the extreme nature of monogenic diseases, studies have historically focused on rare coding variants, but can the full genome be leveraged to answer these questions? In this issue of *Circulation*, Lahrouchi and colleagues[3] perform an elegant study in a large international consortium of patients with LQTS to do just that, identifying common genetic variations that may account for some of the clinical variability seen in LQTS.

RARE SINGLE GENETIC VARIANTS ARE IMPORTANT BUT ONLY TELL PART OF THE STORY

The 3 major LQTS genes were identified decades ago through painstaking studies in families burdened with the disease. Now, even with genetic testing expanded to 14 additional genes (some of which are disputed for association with LQTS[4]), approximately 1 in 5 patients remains genotype negative. Because each of the genes discovered after *KCNQ1*, *KCNH2,* and *SCN5A* account for a paltry 5% to 10% of cases,[5] it is increasingly unlikely that another single gene will be identified that explains the remaining 20% of LQTS. Other issues also hamper the care of patients and families with LQTS. Even before the first actual gene was identified, it was recognized that members of the same family who inherited the LQTS locus did not always get the disease.[6] This phenomenon of incomplete penetrance is

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now a well-accepted feature of LQTS, with penetrance ranging from 40% to 80% in families.[7] Furthermore, a variant can manifest a variety of electric cardiac abnormalities, even in the same family.[8] The mediators of this incomplete penetrance and variable expressivity remain poorly understood. As our understanding of the noncoding genome has increased, attention toward monogenic diseases has likewise begun to shift from rare coding variants to the full genome looking for answers to these important questions.

COMMON GENETIC VARIANTS AND POLYGENIC RISK SCORES IN MONOGENIC DISEASES

Genome-wide association studies (GWAS) have been used for almost 2 decades as an unbiased method for identification of novel disease genes. By their nature, GWAS focus on common, less deleterious variants. As such, GWAS historically were felt to be more applicable to common diseases and population variation of traits. In 2009, the QTSCD and QTGEN studies collectively conducted GWAS on approximately 30 000 individuals and identified variants in genes influencing QT timing; chief among them was a common variation in *NOS1AP*.[9,10] Unfortunately, most individual GWAS variants did not have large effect sizes. More recently there has been growing appreciation for the role of genetic or polygenic risk scores (PRS) derived from GWAS, where common variants are aggregated in a more strongly associated risk score, as has been constructed for coronary artery disease inclusive of thousands to millions of variants.[11]

Studies are now exploring whether PRS may help with some of the unanswered questions in monogenic diseases. In this issue, in the largest and most comprehensive such study in LQTS, Lahrouchi et al[3] pool 1656 LQTS cases, finding that common variants are associated with LQTS and may be a distinct genetic subtype of LQTS. The authors aggregate 68 primarily common variants previously associated with population QT variation into a polygenic risk score (PRS_{QT}) and find that PRS_{QT} is associated with LQTS in both European and Japanese ancestry cohorts (meta-analysis β=0.34, SE=0.03, P=1.1×10^{-38}). Heritability analyses demonstrate that 15% of the variance in LQTS susceptibility is attributable to this variation. They also show that genotype-negative individuals (ie, without an identified rare LQTS variant) have a higher PRS_{QT} than genotype-positive LQTS cases. This genotype-negative group had a robust phenotype (average QTc approximately 500 ms) and was well-adjudicated clinically, making it an ideal cohort for discovery of polygenic risk. These interesting results suggest that a significant proportion of LQTS disease burden is explained by common variation, and that a higher burden of common QT interval–associated variants increases risk of overt LQTS in genotype-negative patients. Last, the authors perform a discovery GWAS comparing the 1656 LQTS cases with 9890 non-LQTS controls, identifying common variation in the *NOS1AP, KCNQ1*, and *KLF12* genes as associated with LQTS.

HOW CAN THESE RESULTS HELP US TAKE CARE OF PATIENTS WITH LQTS?

Genetic testing for rare variants in genes strongly associated with LQTS is a class I recommendation[12] because it allows for risk stratification of family members. This binary finding can offer some diagnostic clarity, in particular, for family planning and in the evaluation of young children in whom provocative testing like treadmill stress testing is not feasible. The results of the study by Lahrouchi offer potential hope to the additional 20% of genotype-negative LQTS families.

One could envision a scenario where testing of a large number of common variants is performed in a patient with genotype-negative LQTS; if a set of variants is identified, family members could be screened and their risk of pathological QT prolongation could be predicted. While genetic testing and cascade screening is a mainstay in LQTS, there are challenges in this paradigm for polygenic disease and in bringing this scenario to reality. The study finds that genotype-negative individuals had a less frequent family history of sudden cardiac death than genotype-positive individuals, suggesting a compound heterozygous mode of inheritance: each parent carries a small number of common variants that are combined in the child and reach a variant dosage threshold to manifest LQTS. But how many (and which) common LQTS-associated variants are needed to be considered at risk? As the authors note, there is an overlap in the PRS distributions of genotype-negative and non-LQTS controls. Should a PRS be a binary or continuous liability? How should clinicians change the care of family members deemed at risk based on PRS? How does one track dozens of variants across a family while the field evolves?

Studies of PRS in common diseases are provocative across large populations but have likewise raised questions about clinical utility. Some suggest that PRS could change management of patients, for example, demonstrating that a coronary artery disease PRS in conjunction with a clinical risk score can identify patients who would benefit the most from PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors,[13] but others have shown that the coronary artery disease PRS does not add predictive capability to clinical scores.[14] The current study is an impactful contribution to the field, providing important data that PRS may have clinical utility in monogenic diseases, but the results also

bring to light important questions that will need to be addressed before translating to the clinic. Studies of common variation and PRS in genotype-negative families and variability in disease penetrance and expression in genotype-positive families will begin to address these questions. In fact, the current study finds, perhaps surprisingly, that PRS_{QT} is not associated with QT interval in unrelated LQTS probands only, but studies in LQTS probands and their family members are needed to determine the role of PRS in penetrance.

WHERE DOES THE FUTURE OF LQTS GENETICS LIE?

A paramount scientific pursuit in parallel to LQTS human genetics studies is the validation of the biological impact of GWAS-identified common variants. Induced pluripotent stem cell–derived cardiac myocytes in combination with advances in genome editing can allow for modeling of the complex PRS genomic architecture in patients with LQTS to vet the functional role of variants and help model therapies. Genetics is only 1 factor that can impact cardiac repolarization. Sex, age, medications, and comorbidities affect the QT interval and pose a challenge for integrating these factors over the lifespan of a person to predict risk. The interaction between common genetic variation and drug-induced QT prolongation and sudden death risk has been compelling and may be an early clinical application of the PRS.[15] The era of precision medicine will include technologies like induced pluripotent stem cells, and clinical and genetic models, as well, including PRS integrated longitudinally into electronic health records, with decision support tools for improved identification of patients and family members at risk of LQTS. The future for patients with LQTS holds great hope thanks to advances in genetics and to studies such as the one by Lahrouchi and colleagues.

ARTICLE INFORMATION

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Disclosures

None.

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