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Genetic Testing for Early-Onset Atrial Fibrillation–Is It Time to Personalize Care?

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Atrial fibrillation (AF) is the most common arrhythmia, affecting more than 33 million people worldwide. AF is associated with increased risk of stroke and all-cause mortality and often co-occurs with or is caused by heart failure (HF). Because AF can often be asymptomatic and frequently underdiagnosed until a major adverse cardiovascular event occurs (eg, stroke, decompensated HF), identifying individuals at increased risk of AF (and AF recurrence[1]) creates an opportunity to intervene and reduce AF-related morbidity and mortality. Although several clinical risk prediction models for AF have been developed (eg, Cohorts for Heart and Aging in Genomic Epidemiology-Atrial Fibrillation [CHARGE-AF]),[2] these risk estimates are highly dependent on age and limit the relevance for those with early-onset AF (EOAF; age ≤66 years). Indeed, in the US, the mean age for AF is 67 years for men and 75 years for women with 1 in 25 individuals having a diagnosis of AF before the age of 60 years.[3] However, there is increasing awareness that individuals with EOAF may harbor pathogenic or likely pathogenic (P/LP) variants in cardiomyopathy and arrhythmia genes, which may represent unique risk markers to focus efforts on primary and secondary prevention of AF and AF-related cardiovascular disease (eg, stroke, HF).

It is well established that AF is heritable. Having a parent with AF is associated with increased risk for AF. Like most common diseases or complex traits, risk for AF is polygenic.[4] Consistent with this, polygenic risk scores are associated with a near doubling of AF risk (1.5-2 × population risk).[5] Although familial AF has been linked to ion channel genes (eg, *KCNQ1*) and structural protein-encoding genes (eg, *MYL4*), it is rare.[6] Other genes implicated in AF encode proteins important for heart function and include transcriptional regulators (*PITX2*, *TBX5*) in addition to ion channel genes.[6] Perhaps unexpected but now validated in many studies, there is considerable overlap between genes associated with risk for AF and cardiomyopathy, including genes encoding structural

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proteins like *TTN*, *MYH7*, and *LMNA*. Now with the availability of large data sets with both clinical and broad genetic information, it has become possible to query the population effect of rare genetic variations. Several recent studies now underscore that subset of EOAF is associated with cardiomyopathy gene variants.

Considerable advances in our understanding of genetic signatures for AF have come from the Trans-Omics for Precision Medicine Program (TOPMed), which is a National Heart, Lung, and Blood Institute initiative aimed at uncovering the genetic contributions to common disorders like AF, asthma, and chronic obstructive pulmonary disease. In 2018, Choi et al[7] reported truncation variants in the giant gene *TTN* (referred to as *TTNtv*) associated with EOAF (2047 EOAF cases). *TTNtv* are observed in approximately 1% of the general population but in this case control study, *TTNtv* were observed twice as often in patients with EOAF compared with controls.

A more recent TOPMed study evaluated rare variants in arrhythmia and cardiomyopathy genes in 1293 patients with EOAF (median age of AF diagnosis, 50 years) and expanded the list of cardiomyopathy genes implicated in EOAF beyond *TTNtv*.[8] Just over 10% (n = 131) of the EOAF cohort was found to carry P/LP variants. Although *TTNtv* was the most frequent gene identified (29%), it was followed closely by *MYH7* (13.7%), *MYH6* (7.6%), *LMNA* (6.9%), and *KCNQ1* (6.1%). The majority of P/LP variants were in cardiomyopathy genes, rather than arrhythmia genes, emphasizing the potential of atrial myopathies as contributors to AF. Indeed, it may be that AF is the first clinical manifestation in an individual's disease trajectory before the onset of cardiomyopathy, but data on lifetime risk of both AF and HF in individuals with *TTNtv* or variants in other cardiomyopathy genes remain limited.

In this issue of *JAMA Cardiology*, Yoneda et al[9] now report the clinical outcomes in EOAF, comparing P/LP gene carriers with noncarriers and demonstrating that these P/LP variants are associated with poorer outcomes. Over 10 years of follow-up, 219 individuals or 17% of the overall EOAF cohort (n = 1293) died. Having a disease-associated P/LP genetic variant was associated with higher all-cause mortality (HR, 1.5; 95% CI, 1.0-2.1). Other risk factors for poorer outcome included younger age at AF diagnosis, as well as higher body mass index and lower ejection fraction at diagnosis. For those with the earliest-onset AF, those younger than 30 years, the yield of genetic testing was greatest (16.7%). The "riskiest" genes were *TTNtv*, *MYH7*, and *LMNA*. *LMNA* variants, which are known to carry risk for ventricular arrhythmias before the onset of reduced left ventricular function, and guidelines exist to personalize device management recommendations in the setting of *LMNA* P/LP variants.

In a related study, Patel et al[10] evaluated outcomes associated with carrying rare cardiomyopathy gene P/LP variants in a community-based sample: the Atherosclerosis in Risk Communities (ARIC) cohort.[10] Although this study did not specifically evaluate EOAF, AF was seen more frequently in cardiomyopathy P/LP gene carriers. The authors examined 13 cardiomyopathy genes (*ACTC1*, *FLNC*, *GLA*, *LMNA*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *PRKAG2*, *TNNI3*, *TNNT2*, *TPM1*, and *TTN*) and found an increased risk for AF (HR, 2.9; 95% CI, 1.9-4.5), HF (HR, 1.7; 95% CI, 1.1-2.8), and all-cause

mortality (HR, 1.5; 95% CI, 1.1-2.2) over a median follow-up of 24 years. The authors additionally examined the UK Biobank and compared cardiomyopathy P/LP gene carriers with noncarriers finding similarly greater risk of AF, HF, and all-cause mortality by age 75 years. Consistent with this, a prior study by Choi et al[4] in the UK Biobank demonstrated that *TTNtv* were more likely to manifest as AF compared with HF within the setting of the limited follow-up to date. Additionally in the UK Biobank, ventricular tachycardia risk was elevated (HR, 3.7; 95% CI, 1.9-7.1).[10] Together, these data support the concept that AF can be an early presentation of P/LP cardiomyopathy gene variants with sequelae, including progression to HF and other major adverse cardiovascular events.

To date, a majority of the evidence for risk associated with P/LP variants is based on samples largely comprising individuals of European ancestry. Indeed, the UK Biobank and the Vanderbilt AF registry in the Yoneda study[8,9] are mainly inclusive of participants who self-reported White race in contrast with the Patel study that now extends similar conclusions to participants of African ancestry from the ARIC cohort.[10] A prior genotype-first, electronic health records study using the Geisinger and University of Pennsylvania biobanks demonstrated that *TTNtv* were associated with diagnostic codes for AF, HF, ventricular arrhythmias, and sudden death.[11] Notably, this study was unable to associate *TTNtv* with dilated cardiomyopathy in individuals of African ancestry. In contrast, a recent study of African American and Hispanic patients with EOAF did identify a significant proportion of individuals with *TTNtv* in these participants, but here the clinical finding was AF, not HF.[12] Together these data suggest that one of the major risks with P/LP variants in classically labeled “cardiomyopathy” genes is EOAF, perhaps more than or at least before the onset of dilated cardiomyopathy, and this holds true for many racial and ethnic groups. A caveat of studying racial composition in older US cohorts is the overrepresentation of White patients compared with nearly all other groups. The racial and ethnic skewing of cohorts of adults older than 65 years toward White individuals may make it challenging to see signals of HF and dilated cardiomyopathy in African American and Hispanic groups. It is possible that EOAF presentation may be similar across diverse groups with differential progression to other adverse cardiovascular outcomes, including ventricular arrhythmias, stroke, and HF, which may limit life span in distinct ways. More data from diverse samples are needed and are coming with the All of Us data, which have emphasized enrollment of racial and ethnic minority groups and will include whole-genome sequencing from 98 500 participants and array data from over 165 000 participants in the first release.[13]

Together, these studies recognize that AF may be the first clinical presentation of carrying a P/LP variant in cardiomyopathic genes. These studies also distinguish that carriers of P/LP cardiomyopathy gene variants have worse long-term outcomes compared with noncarriers. In light of these data, is it time to personalize care for EOAF and incorporate panel-based rare-variant genetic testing into the clinical management framework as is currently recommended for cardiomyopathy? Even with incomplete penetrance, can these genetic variants be incorporated as key risk-enhancing factors to inform a precision approach to screening, prevention, and management of a variety of cardiovascular diseases, including AF?[14] Genetic testing is well positioned to inform clinical management through stratification of patients with EOAF into lower and higher risk for AF recurrence, other arrhythmias, and progression to HF. Although clinical trials are needed to test whether

and how management should be altered by genetic risk stratification, it is reasonable to hypothesize that a higher-risk EOAF group may benefit from closer screening and more intensive traditional cardiovascular risk factor modification. In a higher-risk EOAF group, it will be important to evaluate whether better blood pressure control, including choice of agent, or management of weight or obstructive sleep apnea, can reduce AF and AF-related morbidity and mortality. Additional imaging and telemetry surveillance might additionally benefit a gene-positive EOAF group. As monitoring capabilities for AF now extend to smart watches and other patientenabling devices, these trials are even more feasible. Additionally, cascade genetic testing for family members offers additional opportunities for further risk mitigation and ultimately even primary prevention of AF, stroke, and cardiomyopathy.

Conflict of Interest Disclosures:

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