In this issue of *Circulation Cardiovascular Genetics*, Weng et al. present an interesting study evaluating the heritability of atrial fibrillation (AF).

**See Article by Weng et al**

AF is the most common arrhythmia worldwide, and substantial efforts have been made to elucidate mechanisms underlying its onset and progression. Over the past years, a growing body of evidence demonstrated that AF is heritable. Besides rare genetic mutations with strong effects and a clear phenotype, such as gain- or loss-of-function mutations in ion channel genes, there are common genetic variants or single nucleotide polymorphisms that have been shown to be associated with AF although a causal mechanistic role has not been identified for most of the risk variants. Several studies tried to evaluate the degree of heritability by family-based or population-based studies, such as the Danish twin study that reported an AF heritability of 62% or the Framingham Heart Study that showed a 40% risk to develop AF if a first-degree relative is affected. Extrapolating the characteristics of previously published GWAS and applying it to simplified calculations, the number of patients that have to be genotyped to explain the entire variance in AF risk can be estimated. Twenty-five current genetic risk loci account for 5.3% of heritable variance in AF risk. Assuming a linear relationship between the number of genetic risk loci and the proportion of AF variance explained by it, 96 genetic risk loci will be necessary to fully explain the heritability estimate. Prior GWAS have analyzed 550 AF cases and 4476 controls to identify 1 risk locus, 896 AF cases and 15768 controls to identify 3 risk loci, 71335 AF cases and 12844 controls to identify 3 risk loci, 6707 AF cases and 52426 controls to identify 9 risk loci, and most recently 17931 AF cases and 115142 controls to identify 21 risk loci. Assuming a linear relationship between genotyped

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Editorial

Genome-Wide Association Studies Revealing the Heritability of Common Atrial Fibrillation

Is Bigger Always Better?

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individuals and AF risk loci and a proportion of 10% AF cases, a total of 81500 AF cases and 733500 controls will be necessary (Figure A). The first AF GWAS in 2007 analyzed a total of 5026 individuals, and the most recent AF GWAS published in 2017 analyzed a total of 133073 individuals, suggesting an exponential recruitment of cases and controls. Extrapolating this timeline, within the next 5.9 years, the final GWAS can be expected (Figure B) that fills the knowledge gap in AF heritability.

Evidently, these calculations are based on highly simplistic assumptions, excluding the continuous technical advancements in the field of genotyping and sequencing. They can thus only be seen as rough estimations. Nevertheless, it clearly demonstrates the dynamic nature of the field that began only a few years ago but has compiled huge data sets already.

Despite those huge data sets derived from large patient cohorts, several challenges remain. The current study could not show any statistical difference between young and old patients with AF although a higher degree of heritability for early onset AF had previously been demonstrated. Similarly, given extreme differences in AF prevalence between men and women, it is hard to think that there are no heritability differences between sexes. A potential explanation could be that even a study on large cohorts as presented by Weng et al could be underpowered to detect such differences. Another unmet need is to stratify patients with AF by their underlying conditions and comorbidities that likely play a role in AF pathogenesis and might result in differences in heritability.

The present investigation enrolled participants with AF because of any cause and might not have had sufficient information on concomitant conditions available. Therefore, we clearly call for a continuous recruitment of patients with AF while at the same time, efforts to carefully phenotype our patients for potentially AF causing factors have to be intensified.

In sum, Weng et al thoroughly refined the degree of AF heritability in the general population and revealed that common as opposed to rare genetic variants are the major contributors. Further studies, however, are necessary to identify missing risk loci, to allow analysis of subgroups, to translate the knowledge from population-based studies to an individual risk, and to identify cellular and molecular mechanisms how these genetic variants lead to an increased risk for AF. Only then it will be possible to finally improve both diagnosis and treatment of patients with AF and thereby justifying all to date and future efforts to identify a genetic basis for AF.

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Disclosures
None.

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