Editorial

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

Is Bigger Always Better?

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In this issue of *Circulation Cardiovascular Genetics,* Weng et al[1] 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.[2] 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,[3–5] 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.[6–11] 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.[12,13]

Those numbers raised some concerns because studies performed in families might not adequately mirror the situation in the general population and might hence overestimate the true heritability. Also, it is in contrast to the experience from daily clinical practice where AF is predominantly seen in older patients with comorbidities, that is, in patients with several likely causes for AF, making a genetic cause of the disease less likely. It, therefore, remained unclear to which degree AF can be attributed to common genetic variants identified by genome-wide association studies (GWAS).

To overcome this gap in evidence, Weng et al[1] analyzed a total of 8.5 million genetic variants in 120 286 individuals from the UK Biobank, 2987 of whom were diagnosed with AF.[1] First, they performed GWAS on their study cohort and found 7 loci exceeding the genome-wide significance threshold. Five of the loci had been reported before. Of the novel ones, 1 locus is located on chromosome 5q31 downstream of *PITX1*, and the other locus is on chromosome 12p12 upstream of *RASSF8*. Second, they analyzed the 25 known risk loci for AF in the current cohort and could nominally confirm 20 of those risk loci. Third, they evaluated the single nucleotide polymorphism heritability of AF and demonstrated an overall AF heritability of 22.1% with common variants (minor allele frequency ≥5%) accounting for 20.4%. However, all 25 risk loci identified from prior GWAS could only explain 5.3% of the estimated heritability. Combined with additional 37 putative AF susceptibility genes, the estimate increased to 5.4% and together with additional 82 genes implicated in cardiac arrhythmias and cardiomyopathies to 6.4%. Interestingly, no differences were found between early- and older-onset AF or men and women.

As mentioned above, several studies have analyzed the heritability of AF before. The Danish Twin Study reported an AF heritability of 62%,[12] and data from the Framingham Heart Study demonstrated a 40% risk for AF.[13] The current study by Weng et al,[1] however, has several strengths: first, their calculations are based on a large cohort of unrelated patients, thereby minimizing potential bias that might affect results of smaller or family-based studies resulting in robust data. Second, an AF heritability of 22.1% seems to be more realistic than >60%, especially if considering that the heritability of other comparably common diseases, such as type 2 diabetes mellitus, hypertension, or hyperlipidemia, has a reported heritability estimate ranging from 25% to 30%.[14] Third, the authors revealed that 20.4% of the AF heritability can be attributed to common genetic variants, but the currently known risk loci can only explain ≈5% (one fourth of it).

The authors argue that their results can be seen as justification for more and even larger studies. But is bigger always better? And when is it big enough or too big to fail? 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 AF 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,[6] 896 AF cases and 15 768 controls to identify 3 risk loci,[7] 1335 AF cases and 12 844 controls to identify 3 risk loci,[8] 6707 AF cases and 52 426 controls to identify 9 risk loci,[9] and most recently 17 931 AF cases and 115 142 controls to identify 21 risk loci.[11] Assuming a linear relationship between genotyped

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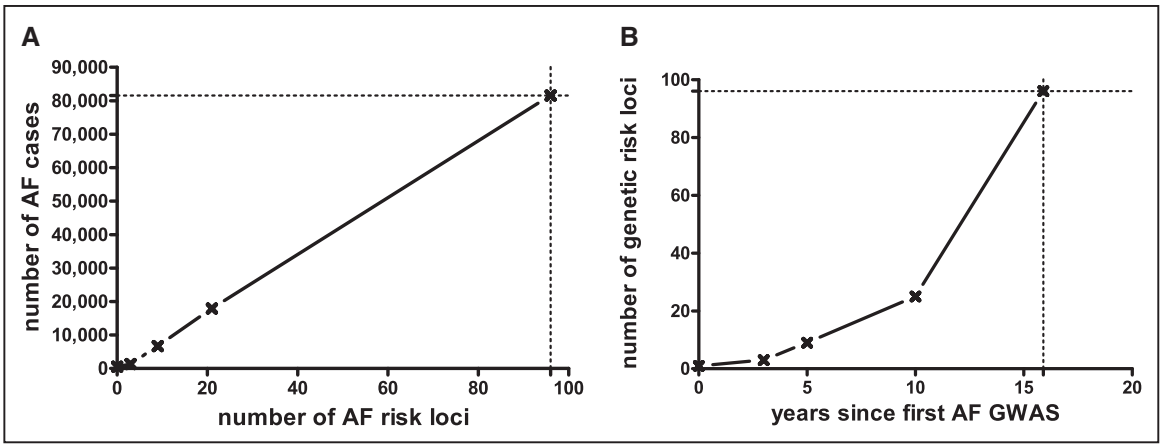

Figure. **A**, Extrapolation to estimate the number of individuals necessary for genotyping to identify 96 genetic risk loci assuming a linear relationship. **B**, Extrapolation of the time necessary to recruit enough individuals to allow identification of 96 genetic rick loci assuming an exponential recruiting. AF indicates atrial fibrillation; and GWAS, genome-wide association studies.

individuals and AF risk loci and a proportion of 10% AF cases, a total of ≈81 500 AF cases and 733 500 controls will be necessary (Figure A). The first AF GWAS in 2007 analyzed a total of 5026 individuals,[6] and the most recent AF GWAS published in 2017 analyzed a total of 133 073 individuals,[11] 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.[13] Similarly, given extreme differences in AF prevalence between men and women, it is hard to think that there are no AF heritability differences between sexes. A potential explanation could be that even a study on large cohorts as presented by Weng et al[1] could be underpowered to detect such differences. Another unmet need is to substratify 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[1] 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.

References

1. Weng L-C, Choi SH, Klarin D, Smith JG, Loh P-R, Chaffin M, et al. Heritability of atrial fibrillation. *Circ Cardiovasc Genet*. 2017;10:e001838. doi: 10.1161/CIRCGENETICS.117.001838.
2. Nattel S. New ideas about atrial fibrillation 50 years on. *Nature*. 2002;415:219–226. doi: 10.1038/415219a.
3. Andalib A, Brugada R, Nattel S. Atrial fibrillation: evidence for genetically determined disease. *Curr Opin Cardiol*. 2008;23:176–183. doi: 10.1097/HCO.0b013e3282fa7142.
4. Christophersen IE, Ellinor PT. Genetics of atrial fibrillation: from families to genomes. *J Hum Genet*. 2016;61:61–70. doi: 10.1038/jhg.2015.44.
5. Sinner MF, Clauss S, Wakili R, Meitinger T, Estner H, Kääb S. Recent advances in the genetics of atrial fibrillation: from rare and common genetic variants to microRNA signalling. *Cardiogenetics*. 2011;1:35–44.
6. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007;448:353–357. doi: 10.1038/nature06007.
7. Benjamin EJ, Rice KM, Arking DE, Pfeufer A, van Noord C, Smith AV, et al. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. *Nat Genet*. 2009;41:879–881. doi: 10.1038/ng.416.
8. Ellinor PT, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK, et al. Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet*. 2010;42:240–244. doi: 10.1038/ng.537.
9. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet*. 2012;44:670–675. doi: 10.1038/ng.2261.
10. Sinner MF, Tucker NR, Lunetta KL, Ozaki K, Smith JG, Trompet S, et al; METASTROKE Consortium; AFGen Consortium. Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes

for atrial fibrillation. *Circulation*. 2014;130:1225–1235. doi: 10.1161/CIRCULATIONAHA.114.009892.
11. Christophersen IE, Rienstra M, Roselli C, Yin X, Geelhoed B, Barnard J, et al; METASTROKE Consortium of the ISGC; Neurology Working Group of the CHARGE Consortium; AFGen Consortium. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet*. 2017;49:946–952. doi: 10.1038/ng.3843.
12. Christophersen IE, Ravn LS, Budtz-Joergensen E, Skytthe A, Haunsoe S, Svendsen JH, et al. Familial aggregation of atrial fibrillation: a study in Danish twins. *Circ Arrhythm Electrophysiol*. 2009;2:378–383. doi: 10.1161/CIRCEP.108.786665.
13. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA*. 2010;304:2263–2269. doi: 10.1001/jama.2010.1690.
14. Loh PR, Bhatia G, Gusev A, Finucane HK, Bulik-Sullivan BK, Pollack SJ, et al; Schizophrenia Working Group of Psychiatric Genomics Consortium. Contrasting genetic architectures of schizophrenia and other complex diseases using fast variance-components analysis. *Nat Genet*. 2015;47:1385–1392. doi: 10.1038/ng.3431.

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