Published in final edited form as:

Heart Rhythm. 2017 October ; 14(10): 1539–1540. doi:10.1016/j.hrthm.2017.07.021.

Germline versus somatic mutations in genetic atrial fibrillation

Mark McCauley, MD, PhD, FHRS and Dawood Darbar, MBChB, MD, FHRS

Division of Cardiology, University of Illinois at Chicago, Chicago, Illinois

Atrial fibrillation (AF) is a complex and incompletely understood disease. Great progress has been made in elucidating the genetic determinants of AF recently. Genome-wide association studies have identified a chromosome 4q25 locus that has consistently been associated with AF.^{1,2} Although the mechanism for this observed association remains unclear, the locus is adjacent to the paired-like homeodomain transcription factor 2 gene (*PITX2*), which is critical for cardiac left-right asymmetry.^{3,4} We have found that symptomatic response to antiarrhythmic drug therapy is at least partially modulated by common single-nucleotide polymorphisms at the chromosome 4q25 locus.⁵ Pérez-Hernández et al⁶ showed that patients with chronic AF have a significantly higher expression of Pitx2c messenger RNA vs normal sinus rhythm controls; enhanced Pitx2c expression in HL-1 atrial myocytes results in an increase in slow delayed rectifier potassium current (I_{Ks}) and decrease in L-type calcium current ($I_{Ca,L}$), which are hallmarks of AF. More recently, the AFGen Consortium has identified 12 new genetic loci associated with AF.⁷ In addition to known associations such as *PITX2*, variants in potassium channel subunits (*KCNJ5* and *KCNN2*) and genes encoding structural proteins (eg, *ANXA4* and *CEP68*) were shown to be associated with AF susceptibility. Thus, genome-wide association studies have validated the contribution of *PITX2* to AF and have identified new associations for further characterization.

Other strategies to define the genetic architecture of AF have included linkage analyses and candidate gene approaches with characterization of AF-associated variants in heterologous systems and mammalian systems. For example, expression of an early-onset AF-causing potassium channel mutation *KCNQ1* (V1414M) in *Xenopus* oocytes demonstrated a novel gain-of-function mechanism responsible for shortening of atrial and ventricular action potentials.⁸ Another showed that a gain-of-function mutation in *KCNE1* (Q147R) is associated with AF and that, conversely, a loss of function in ventricles leads to QT interval prolongation.⁹ More recently, the generation of human-induced pluripotent stem cells has emerged as a mammalian system that has great potential to model atrial disease.¹⁰ The development of atrial-like cardiomyocytes has recently been described and has the potential to address some of the limitations of using noncardiac cell lines and murine models.¹¹ Also, next-generation sequencing (NGS) has greatly expanded our ability to evaluate rare genetic variants as a cause of AF. To date, rare variants in more than 30 genes have been associated with AF (see Table 1 in Huang and Darbar¹²).

Although much progress has been made in the determination of germline mutations contributing to AF susceptibility, the role of somatic mutations in the pathogenesis of AF is less clearly defined. The contribution of somatic mutations to cancer genesis and progression is well defined.¹³ Gollob et al¹⁴ sequenced *GJA5* from resected cardiac tissue vs peripheral lymphocytes and found unique *GJA5* mutations, suggesting that atrial somatic mutations may contribute to early-onset AF. They also described genetic mosaicism and loss-of-function mutations in the connexin 43 gene *GJA1* in atrial tissue, leading to heterogeneous coupling patterns that may explain an early-onset AF mechanism.¹⁵ However, NGS of 560 genes related to cardiac function and AF have not shown pathogenic somatic mutations in 25 patients with AF.¹⁶ Roberts et al concluded that “atrial-specific mutations are rare and that somatic mosaicism is unlikely to exert a prominent role in AF pathogenesis.”¹⁶ Given conflicting reports as to whether somatic mutations are a significant contributor to AF susceptibility, more in-depth analysis is required.

In this issue of **HeartRhythm**, Gregors et al¹⁷ examined the prevalence of somatic variants in 110 AF candidate genes in 44 patients undergoing surgery for mitral valve regurgitation (MVR). This single-center study of patients with a presurgical history of AF consented to left atrial (LA) posterior wall biopsy during surgery for NGS. The group used MuTect software to identify somatic point mutations; however, there was no control group of patients without presurgical AF for comparison. This study concluded that there was no evidence of somatic variants located in the coding regions of LA posterior wall tissue, though 60 rare germline missense variants were found in 34 of the 110 genes sequenced. Functional characterization of a Kv7.1-G272S genetic variant was performed in *Xenopus* oocytes, which showed a gain-of-function mutation contributing to the AF phenotype. Gregors et al¹⁷ concluded that “somatic variants do not play a major role in the pathogenesis of AF.”

This study adds to the current body of literature by examining the prevalence of somatic mutations in the pathogenesis of valvular AF. This is the largest characterization of somatic mutations in patients with AF to date and appears to correlate with the recent results of Roberts et al,¹⁶ suggesting a minor role of somatic mutations/mosaicism in the pathogenesis of AF. However, it would be unwise to conclude that these data are a “nail in the coffin” for somatic mutation contribution to AF just yet, given several study limitations and also design differences from previous studies. First, the sample size is likely insufficient to truly assess the burden of rare variants in the 110 genes sequenced. Second, the lack of a control population of patients receiving MVR and without presurgical AF severely limits the interpretation of any (or no) somatic changes in the population with AF. Furthermore, data are lacking as to whether patients were in AF during the time of surgery. Finally, it is important to note that in this study, 100% of enrolled patients received MVR and thus by definition have valvular-associated AF. This study assayed tissue from the posterior LA wall, between the pulmonary veins. Previous studies examined patients with nonvalvular AF and assayed tissue from the LA appendage.^{14,16} Thus, direct comparisons with previous studies may be challenging.

Nevertheless, the data generated by Gregors et al¹⁷ are intriguing and suggest that somatic mutations in AF are rare and unlikely to contribute to AF susceptibility in the vast majority

of cases. The identification of rare variants in AF candidate genes may suggest a role for these genes in the pathogenesis of valvular AF. Further studies using multiple trial sites and in valvular vs nonvalvular AF will be necessary to clarify this complex issue of somatic vs germline mutations as a cause of AF.

Acknowledgments

This work was in part supported by the National Institutes of Health (grant nos. R01 HL092217, R01 HL138737, and K08 HL130587).

References

1. Perez-Serra A, Campuzano O, Brugada R. Update about atrial fibrillation genetics. *Curr Opin Cardiol*. 2017; 32:246–252.
2. Gudbjartsson DF, Arnar DO, Helgadóttir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007; 488:353–357.
3. Lubitz SA, Lunetta KL, Lin H, et al. Novel genetic markers associate with atrial fibrillation risk in Europeans and Japanese. *J Am Coll Cardiol*. 2014; 63:1200–1210. [PubMed: 24486271]
4. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. *Proc Natl Acad Sci U S A*. 2010; 107:9753–9758. [PubMed: 20457925]
5. Parvez B, Vaglio J, Rowan S, Muhammad R, Kucera G, Stubblefield T, Carter S, Roden D, Darbar D. Symptomatic response to antiarrhythmic drug therapy is modulated by a common single nucleotide polymorphism in atrial fibrillation. *J Am Coll Cardiol*. 2012; 60:539–545. [PubMed: 22726630]
6. Pérez-Hernández M, Matamoros M, Barana A, Amorós I, Gómez R, Núñez M, Sacristán S, Pinto Á, Fernández-Avilés F, Tamargo J, Delpón E, Caballero R. Pitx2c increases in atrial myocytes from chronic atrial fibrillation patients enhancing I_{Ks} and decreasing $I_{Ca,L}$. *Cardiovasc Res*. 2016; 109:431–441. [PubMed: 26714926]
7. Christophersen IE, Rienstra M, Roselli C, et al. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet*. 2017; 49:946–952. [PubMed: 28416818]
8. Hong K, Piper DR, Diaz-Valdecantos A, et al. De novo *KCNQ1* mutation responsible for atrial fibrillation and short QT syndrome in utero. *Cardiovasc Res*. 2005; 68:433–440. [PubMed: 16109388]
9. Lundby A, Ravn LS, Svendsen JH, Olesen SP, Schmitt N. *KCNQ1* mutation Q147R is associated with atrial fibrillation and prolonged QT interval. *Heart Rhythm*. 2007; 4:1532–1541. [PubMed: 17997361]
10. Goedel A, My I, Sinnecker D, Moretti A. Perspectives and challenges of pluripotent stem cells in cardiac arrhythmia research. *Curr Cardiol Rep*. 2017; 19:23. [PubMed: 28220464]
11. Devalla HD, Schwach V, Ford JW, Milnes JT, El-Haou S, Jackson C, Gkatzis K, Elliott DA, Chuva de Sousa Lopes SM, Mummery CL, Verkerk AO, Passier R. Atrial-like cardiomyocytes from human pluripotent stem cells are a robust preclinical model for assessing atrial-selective pharmacology. *EMBO Mol Med*. 2015; 7:394–410. [PubMed: 25700171]
12. Huang, H., Darbar, D. Genetic heterogeneity of atrial fibrillation susceptibility loci. *Eur Heart J*. 2017 Jun 14. <http://dx.doi.org/10.1093/eurheartj/ehx289>. [Epub ahead of print]
13. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015; 373:1697–1708. [PubMed: 26510020]
14. Gollob MH, Jones DL, Krahn AD, et al. Somatic mutations in the connexin 40 gene (*GJA5*) in atrial fibrillation. *N Engl J Med*. 2006; 354:2677–2688. [PubMed: 16790700]
15. Thibodeau IL, Xu J, Li Q, Liu G, Lam K, Veinot JP, Birnie DH, Jones DL, Krahn AD, Lemery R, Nicholson BJ, Gollob MH. Paradigm of genetic mosaicism and lone atrial fibrillation:

physiological characterization of a connexin 43-deletion mutant identified from atrial tissue. *Circulation*. 2010; 122:236–244. [PubMed: 20606116]

16. Roberts JD, Longoria J, Poon A, Gollob MH, Dewland TA, Kwok PY, Olgin JE, Deo RC, Marcus GM. Targeted deep sequencing reveals no definitive evidence for somatic mosaicism in atrial fibrillation. *Circ Cardiovasc Genet*. 2015; 8:50–57. [PubMed: 25406240]
17. Gregors E, Ahlberg G, Christensen T, et al. Deep sequencing of atrial fibrillation patients with mitral valve regurgitation shows no evidence of mosaicism but reveals novel rare germline variants. *Heart Rhythm*. 2017; 14:1531–1538. [PubMed: 28549997]