Rare predicted loss-of-function (pLOF) variants and a polygenic risk score (PRS) are associated with increased atrial fibrillation (AF) risk, according to a study published online June 26 in *JAMA Cardiology*. 
Oliver B. Vad, M.D., from Copenhagen University Hospital–Rigshospitalet in Denmark, and colleagues examined rare pLOF variants associated with AF and elucidated their role in risk of AF, cardiomyopathy, and heart failure in combination with a PRS in a genetic association and nested case-control study. Data were included for 403,990 individuals from the U.K. Biobank (median age, 58 years).

Over a median follow-up of 13.3 years, 24,447 participants were diagnosed with incident AF. The researchers identified associations for rare pLOF variants in six genes (TTN, RPL3L, PKP2, CTNNA3, KDM5B, and C10orf71) with AF. In an external cohort, TTN, RPL3L, PKP2, CTNNA3, and KDM5B were replicated. Rare pLOF variants combined with high PRS conferred an odds ratio of 7.08 for AF.

PRS carriers also had a considerable 10-year risk of AF (16 and 24% in women and men older than 60 years, respectively). There was an association seen for rare pLOF variants with increased risk of cardiomyopathy before and subsequent to AF (hazard ratios, 3.13 and 2.98, respectively).

"These findings may contribute to possible future genetic risk stratification and improved clinical practice," the authors write.

Several authors disclosed ties to the biopharmaceutical and medical device industries.

More information: Oliver B. Vad et al, Rare and Common Genetic Variation Underlying Atrial Fibrillation Risk, JAMA Cardiology (2024). DOI: 10.1001/jamacardio.2024.1528

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