Association study of atrial fibrillation clinical recurrence after catheter ablation with PR interval using a Mendelian randomization analysis

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**Introduction:** We previously reported that abnormality of PR interval was known to be a predictor of atrial fibrillation (AF) clinical recurrence and contributed to a high risk of AF. The purpose of this study is to investigate causal association between PR interval and the AF clinical recurrence.

**Methods:** PR interval (ms) and clinical recurrence of AF were monitored and measured in 1745 individuals who underwent AF catheter ablation (73.2% male, 58.6 with the standard deviation of 10.9 years old). Five single nucleotide polymorphisms (SNPs) that are known for PR interval loci were investigated for analysis. A Mendelian randomization analysis was used to examine the causal association of PR interval with the AF clinical recurrence.

**Result:** PR interval level (Quartile 4; PR>200 ms) in the upper quartile was associated with 2.24-fold (95% confidence interval [CI]:1.68-3.00, p = 4.75 × 10^{-8}) increased risk of AF clinical recurrence compared with the lower quartile. Weighted genetic risk score was associated with 0.147 (ms) increase in PR interval level per 1 Standard Deviation (SD) change (p = 5 × 10^{-11}) as well as increased (HR 1.17, 95%CI 1.08-1.27, p value = 1.38 × 10^{-4}) risk of AF recurrence, respectively. PR interval (ms) per risk allele indicated that 5 SNPs were associated with PR interval (p value<0.05). Among those 5 SNPs, clinical recurrence per risk allele demonstrated that FRMD4B (HR 1.24, 95%CI 1.06-1.44, p = 0.005) and CAV1 (HR 1.17, 95%CI 1.04-1.32, p=0.010) were associated with clinical recurrence of AF. The conventional association showed strong statistical significance (HR 1.01, 95%CI 1.00-1.01, p = 4.02 × 10^{-7}) between AF clinical recurrence and PR interval. Mendelian randomization analysis also exhibited the association with weighted Genetic Risk Scores (wGRS) of 5 SNPs (HR 1.02, 95%CI 1.00-1.03, p = 0.016).

**Conclusion:** PR interval is causally associated with AF clinical recurrence after catheter ablation at the genetic level.