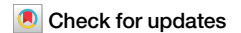


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A genome-wide association between foveal thickness and arrhythmia



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Abstract

Background The fovea is one of the most crucial parts of the visual system and has a special structure. We aimed to identify susceptibility single nucleotide polymorphisms (SNPs) for foveal thickness in a large Japanese cohort.

Methods Genome-wide association study (GWAS) and replication studies were conducted in 9850 individuals from the Nagahama Study (from 2013 to 2016) and 935 individuals from the Hisayama Study. Genome-wide quantitative trait loci analyses and phenome-wide association study (PheWAS) were conducted using Biobank Japan Data for novel susceptibility SNPs. Finally, phenotypic associations were evaluated in the Nagahama Study.

Results Here we show that rs4903064, located in *Double PHD Fingers 3 (DPF3)*, is genome-wide significantly associated with foveal thickness, which is confirmed by replication studies and meta-analysis ($\beta = 2.18$, standard error = 0.59, $P = 2.93 \times 10^{-13}$). PheWAS identifies that the SNP was phenome-wide significantly associated with arrhythmia ($\beta = -0.049$, SE = 0.012, $P = 2.50 \times 10^{-5}$). In the Nagahama Study, individuals with a thicker fovea have a significantly lower risk of premature atrial/ventricular contraction (odds ratio = 0.86, 95% confidence interval = 0.75 to 0.98, P -value = 0.022).

Conclusions We identify a novel foveal thickness susceptibility gene that is also associated with arrhythmia. Individuals with premature atrial/ventricular contraction may be advised to undergo ophthalmological evaluation as necessary.

Plain language summary

The fovea is one of the most crucial parts of the visual system and has a special structure. Foveal thickness can vary between individuals, and understanding the genetic factors behind this variation is important. In this study, we analyzed data from a large Japanese population cohort to identify genetic variants associated with foveal thickness. We identified a genetic variant in the *Double PHD Fingers 3 (DPF3)* gene associated with foveal thickness. Interestingly, individuals with this genetic variant were also associated with arrhythmia. These findings suggest there may be an association between eye and heart health, although further research is needed to better understand this relationship and its implications.

The macula, located in the central part of the retina, plays an important role in visual function. The center of the macula is called the fovea, which is the most crucial part of the visual system because it has a special structure for distinguishing between fine objects and colors. Recently, spectral-domain optical coherence tomography (SD-OCT) has enabled the noninvasive and sensitive detection of macular thickness and abnormalities. Many ocular diseases, including age-related macular degeneration (AMD)¹, central serous chorioretinopathy (CSC)², and glaucoma³ involve structural changes in the macula. Although studies have identified factors associated with macular

thickness, such as age, sex, and axial length^{4,5}, twin studies have indicated that ~80% of macular thickness is determined by genetic factors⁶. Given that macular abnormalities can directly affect visual function, genomic studies on macular thickness are important. However, progress in this area has been hindered due to limited sample sizes with both genetic information and precise OCT scans.

Recently, Gao et al. conducted the first genome-wide association analysis (GWAS) for 6 mm-wide macular thickness using UK Biobank data, identifying macular thickness susceptibility single nucleotide

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polymorphisms (SNPs)⁷. Interestingly, these SNPs show pleiotropic effects on myopia, neurodegenerative diseases, cancer, and metabolic traits, indicating that the macula can reflect systemic conditions. The fovea is responsible for our sharpest vision owing to its unique anatomy, which includes the highest density of cone photoreceptor cells and an avascular structure that allows light to be directly focused onto the cones. Considering the unique anatomy and role of the fovea, the genetic determinants of foveal thickness differ from those of macular thickness.

In the current study, we perform a GWAS of foveal thickness (i.e., 1 mm-wide macular thickness) followed by two replication studies to identify a foveal thickness-susceptibility SNP. In addition, we perform a phenotypic association analysis using the Nagahama study to reveal the association between foveal thickness and non-ocular disease related to the foveal thickness susceptibility SNP.

Methods

The ethics committee of Kyoto University Graduate School of Medicine and Nagahama Municipal Review Board approved the protocols of this study (G278). All participants were fully informed of the purpose and procedures of this study, and written informed consent was obtained from all participants. All procedures of our study followed the tenets of the Declaration of Helsinki.

Study participants and genotyping

In the present study, we examined the first follow-up participants of the Nagahama Prospective Cohort for Comprehensive Human Bioscience (Nagahama study), conducted between 2013 and 2016. The first follow-up of participants in the Nagahama Study included 9850 individuals. Details of this study and the genotyping method have been described elsewhere^{8–12}, but are summarized in the Supplementary Note. A total of 5730 and 3673 samples were included in this study as discovery and first replication datasets, respectively.

The second replication dataset was the data from the Hisayama Study, which is a population-based study on cardiovascular disease and its risk factors in the town of Hisayama, a city in Fukuoka Prefecture. In addition, an epidemiologic study of eye disease among residents aged 40 years or older has been underway since 1998. We used data from cross-sectional surveys conducted between 2012 and 2013. A total of 3108 individuals who were ≥40 years of age consented to participate and underwent an ophthalmic examination. OCT was performed using a 3D OCT-1 Maestro (Topcon Corporation, Tokyo, Japan). Patients without DNA samples, OCT data, unclear OCT images (OCT image quality < 30), refractive error data, and eyes with intraocular lenses were excluded. Ultimately, 935 individuals were included in this study. Further details of the Hisayama Study are summarized elsewhere^{13,14}. Genotyping methods are summarized in the Supplementary Note.

Evaluation of foveal thickness

Images of horizontal and vertical line OCT scans centered on the fovea in the right eye were used to measure macular thickness. The scan width was 6 mm before February 2015 and 9 mm thereafter. The segment of each layer of the macula was lined automatically using the OCT software and manually collected by two ophthalmologists (Y. H. and E. N.). Macular thickness was defined as the distance between the inner border of the inner limiting membrane and the outer border of the retinal pigment epithelium (Supplementary Fig. 1). Macular thickness was automatically measured along each line scan. We used the average macular thickness of the right eye, which was calculated in a 1 mm-wide area centered at the fovea.

Genome-wide association study

Among the 5730 individuals in the discovery stage, 1295 were excluded due to a lack of retinal thickness data. Among the remaining participants, 625 were estimated to have first-degree kinship within this population (Pihat > 0.35, PLINK ver. 1.90 [<https://www.cog-genomics.org/plink/1.9/>]) and were excluded from the analysis. In addition, 359 participants without

refractive error data were excluded from the study. Finally, 3451 individuals were included in the discovery stage analysis. Genome-wide QTL analysis of foveal thickness was performed using multivariate linear regression assuming an additive model. This regression framework allowed us to adjust for covariates such as age, sex, refractive error (spherical equivalent), and the first to third principal components. The genome-wide significance threshold was set at $P < 5.0 \times 10^{-8}$.

Replication studies and meta-analysis

We conducted two replication studies using Japanese datasets to confirm the genetic associations between candidate susceptibility SNP and foveal thickness. Of the 3673 samples from the first replication dataset in the Nagahama Study, 2618 samples were analyzed because they had ocular biometric data and no history of intraocular surgery. These individuals had not undergone whole-genome genotyping, and only the genotypes of the top SNPs were determined using the TaqMan method. Linear regression analysis was used to determine the association between the candidate susceptibility SNP and foveal thickness after adjusting for age, sex, and refractive errors in the right eye.

In the second replication dataset from the Hisayama Study, 935 individuals were analyzed. In this study, we performed a genome-wide association analysis and looked up only the top SNPs. Linear regression analysis was used to assess the association between the candidate susceptibility SNP and foveal thickness after adjusting for age, sex, refractive error (spherical equivalent), and the first to third principal components. Details of replication studies are described in the Supplementary Note.

We performed a meta-analysis of three datasets, namely, the Nagahama discovery set, Nagahama Taqman dataset, and Hisayama dataset, using an inverse variance weighted fixed effect model.

Expression in human tissue

To explore the association between the genotypes of the novel foveal thickness susceptibility SNPs and the expression levels of various genes in multiple human tissues, we performed eQTL analysis. We searched a publicly available eQTL database (Genotype-Tissue Expression (GTEx)¹⁵ Portal version 8; <https://gtexportal.org/home/>).

Phenome-wide association study

We performed a phenome-wide association study (PheWAS) using BBJ data to investigate the pleiotropic effects of the identified SNPs. The BBJ is one of the largest biobanks with 200,000 individuals, with at least one of the 47 target common diseases collected from 12 Japanese medical facilities, investigated mainly by RIKEN¹⁶. The BBJ contains information and genomic data on 47 common diseases, including heart disease, cancer, and in the field of ophthalmology, glaucoma, and cataracts^{17,18}. They conducted 220 deep phenotype GWASs and QTLs analyses¹⁹. We performed PheWAS using the summary statistics from these results (<http://jenger.riken.jp>). For PheWAS, we considered a P -value (Bonferroni correction applied) of $<0.05/220$ phenotypes = 2.3×10^{-4} to indicate statistical significance.

Association between foveal thickness and arrhythmia

As PheWAS identified a shared genetic susceptibility between foveal thickness and arrhythmia, we conducted phenotypic association analysis using the Nagahama Study cohort. We divided the population into four groups according to foveal thickness quartiles and evaluated the prevalence of arrhythmia. For types of arrhythmia with a prevalence greater than 2%, the association between arrhythmia and foveal thickness was statistically assessed using logistic regression, both nominally and adjusted for age and sex. A total of 8486 individuals from the Nagahama Study with ECG and retinal thickness data were analyzed.

Statistical analysis

P -values of less than 0.05 were considered to indicate statistical significance, while P -values between 0.05 and 0.1 were considered to indicate marginal significance. Statistical analyses were performed using R software (version

4.2.1; R Foundation for Statistical Computing) and PLINK (version 1.9; <https://www.cog-genomics.org/plink2>).

Results

Background

The clinical characteristics of the study participants are summarized in Table 1. The mean ages in the discovery, Nagahama Taqman, and Hisayama datasets were 58.5 ± 12.4 , 58.4 ± 12.2 , and 64.5 ± 7.9 years, respectively, and the average foveal thicknesses were 254.0 ± 17.6 , 254.0 ± 17.8 , and 236.3 ± 27.2 μm .

Genome-wide association study and the replication study

A Manhattan plot of the discovery stage of the GWAS is shown in Fig. 1. We identified a locus with a genome-wide significant P -value of $<5.0 \times 10^{-8}$ for rs4903064 ($\beta = 2.62$, $\text{SE} = 0.41$, $P = 1.33 \times 10^{-10}$), located in the *double PHD Fingers 3* gene (*DPF3*). The T allele (allele frequency [AF] = 0.47) was associated with an increase in foveal thickness (Table 2). Figure 2 shows a regional plot of rs4903064. Quantile-quantile plots for the association between all analyzed SNPs and foveal thickness at the discovery stage are shown in Supplementary Fig. 2. The genomic inflation factor lambda (λ_{GC}) was 1.02.

The results of the replication and meta-analysis are shown in Table 2. We observed a statistically significant association between rs4903064 and foveal thickness in the Nagahama Taqman dataset ($\beta = 1.61$, $\text{SE} = 0.47$, $P = 5.64 \times 10^{-4}$). In another replication dataset (the Hisayama Study), there was marginally significant association ($\beta = 2.18$, $\text{SE} = 1.2$, $P = 0.08$). The meta-analysis of all three datasets revealed a genome-wide significant association ($\beta = 2.18$, $\text{SE} = 0.59$, $P = 2.93 \times 10^{-13}$).

eQTL analysis

A multi-tissue expression quantitative trait locus (eQTL) plot of rs4903064 and *DPF3* is shown in Supplementary Fig. 3. The effect size of rs4903064 on *DPF3* expression was strongest in the tibial artery (normalized effect size = 0.444, $P = 2.0 \times 10^{-34}$), followed by the aorta (normalized effect size = 0.395, $P = 6.4 \times 10^{-16}$) and coronary artery (normalized effect size = 0.356, $P = 5.9 \times 10^{-6}$). In the original GTEx project, eQTLs were Bonferroni-corrected with the assumption that each of the 20,000 genes was tested⁸, leading to a significance threshold of $P = 0.05/20,000 = 2.5 \times 10^{-6}$. Applying the same Bonferroni correction, only the P -value for *DPF3* met the threshold for significance.

Phenome-wide association study

The associations between rs4903064 and multiple human phenotypes in the BioBank Japan (BBJ) project are shown in Fig. 3 and Supplementary Table 1. The SNP was phenome-wide and significantly associated with arrhythmia in the BBJ dataset ($\beta = -0.049$, $\text{SE} = 0.012$, $P = 2.50 \times 10^{-5}$, for arrhythmia-stratified meta; $\beta = -0.047$, $\text{SE} = 0.012$, $P = 3.90 \times 10^{-5}$, for arrhythmia). The T allele of rs4903064, which is associated with a thicker fovea, is associated with a lower risk of arrhythmia.

Associations between the arrhythmia and foveal thickness

The results are summarized in Table 3. There was no statistically significant association between the whole arrhythmia and foveal thickness (odds ratio [OR], 0.98, 95% confidence interval [CI], 0.92 to 1.04, P -value, 0.42, adjusting for age and sex). However, by subdividing the arrhythmia, we revealed a significant association between the prevalence of premature cardiac complex, namely premature atrial contraction (PAC) and premature ventricular contraction (PVC), and foveal thickness; the prevalence of premature cardiac complex decreased with increasing foveal thickness (OR, 0.86, 95% CI, 0.75 to 0.98, P -value, 0.022, adjusting for age and sex).

Discussion

We performed a GWAS on foveal thickness and identified rs4903064 in *DPF3* as a robust SNP associated with this phenotype. Interestingly, a subsequent phenome-wide association study revealed that the SNP was also associated with arrhythmia, among which the premature cardiac complex was found to be associated with foveal thickness through comorbidity analysis using the Nagahama Study data. To our knowledge, this is the first study to suggest the association between these two conditions.

The fovea, situated at the center of the macula, has a unique structure characterized by the highest density of cone photoreceptor cells and an avascular configuration. As such, the fovea exhibited distinct associations with systemic parameters compared with the peripheral macular area. Studies have reported that the relationship between retinal thickness and factors such as age, sex, and refraction is dissimilar between the central and peripheral regions of the macula²⁰. This discrepancy may account for the failure to identify rs4903064 in *DPF3* in previous large-scale association studies of 6 mm-wide macular thickness^{7,20}. Given the critical role of the fovea in enabling high-precision visual acuity, investigating its genetic underpinnings is crucial for comprehending variability in visual function.

DPF3, also known as *Cerd4*, is a gene whose expression has been confirmed in the retina of mice²¹. We searched publicly available single-cell RNA sequencing (scRNA-seq) database (Spectacle, <https://singlecell-eye.org>)²² and found that *DPF3* is highly expressed in cone cells, which are most densely located in the fovea and are largely responsible for visual functions such as distinguishing the color and shape of objects. The spectacle provided regional gene expression patterns across six independent retinal scRNA-seq studies, allowing for the evaluation *DPF3* expression patterns in different macular regions. Our analysis indicated that there may be differences in *DPF3* gene expression between the central and peripheral areas of the retina, with the largest log-fold change of the six studies being 3.3 (Supplementary Fig. 4)²³. These findings strongly suggest that *DPF3* plays a direct role in influencing foveal thickness.

From a systemic perspective, eQTL analysis demonstrated a correlation between the rs4903064 mutation and the expression level of the *DPF3* gene in arterial tissues (tibial artery, aorta, and coronary arteries). Notably, these three arteries are the only arterial tissues evaluated in the GTEx dataset, and the genotype of rs4903064 was consistently associated with *DPF3* expression across all three tissues. This observation raises the possibility that

Table 1 | Characteristics of study participants

	Discovery	Replication datasets		P
	Nagahama GWAS	Nagahama Taqman	Hisayama study	
n	3451	2618	935	
Age (years)	58.5 ± 12.4	58.4 ± 12.2	64.5 ± 7.9	9.2×10^{-4}
Number of females (%)	2298 (66.6)	1810 (69.1)	562 (60.1)	3.2×10^{-6}
Spherical equivalent (Diopter)	-1.2 ± 2.8	-1.2 ± 2.8	-0.5 ± 2.6	3.5×10^{-2}
Foveal thickness (μm)	254.0 ± 17.6	254.0 ± 17.8	236.3 ± 27.2	1.3×10^{-3}

mean $\pm$ standard error.

GWAS: genome-wide association study.

P -values of age, spherical equivalent, and foveal thickness were analyzed by One-way ANOVA.

P -value of number of females was analyzed by Chi-squared test.

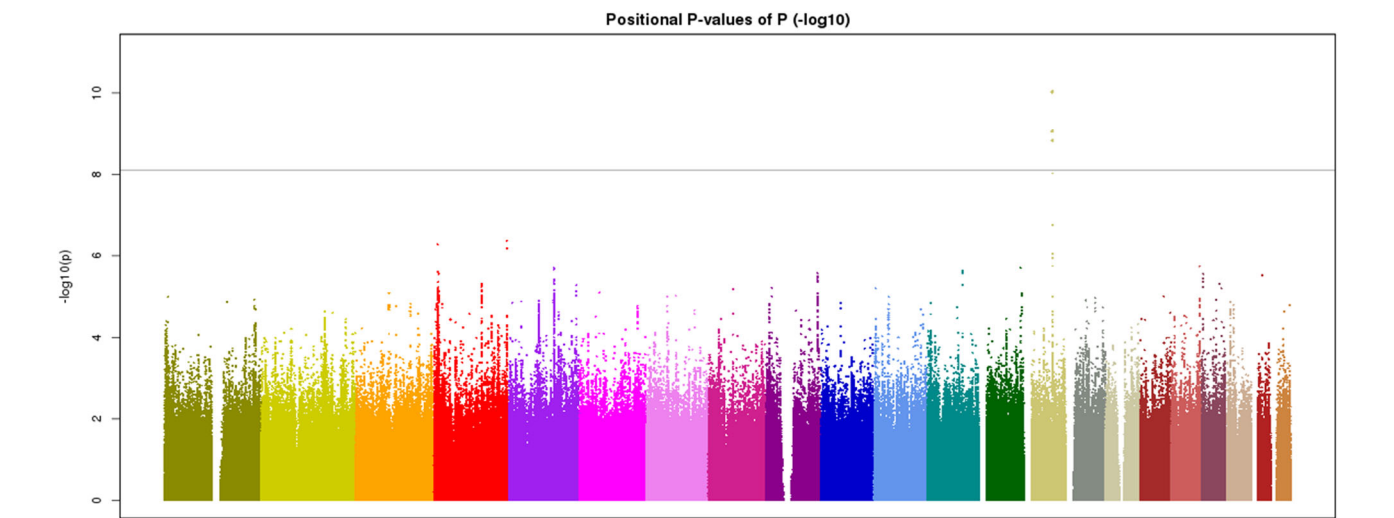


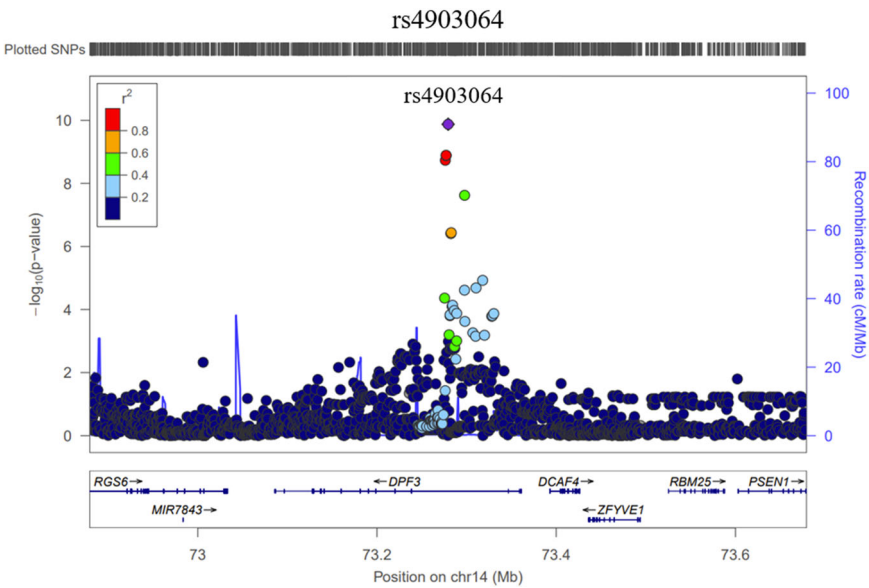
Fig. 1 | Manhattan plots of the discovery-stage GWAS for foveal thickness. Each plot shows $-\log_{10}$ (transformed P values) for all SNPs. The horizontal line is the genome-wide significance threshold ($P = 5.0 \times 10^{-8}$). GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

Table 2 | Summary of the discovery genome-wide association study and replication studies

SNP	Gene	CHR	Position	Effect allele	Dataset	<i>n</i>	EAf	β	SE	<i>P</i>
rs4903064	DPF3	14	73279420	T	Discovery Stage (Nagahama GWAS dataset)	3451	0.47	2.62	0.41	1.33×10^{-10}
					Replication 1 (Nagahama Taqman dataset)	2618	0.47	1.61	0.47	5.64×10^{-4}
					Replication 2 (Hisayama dataset)	935	0.47	2.18	1.2	0.08
					Meta-analysis	7004	0.47	2.18	0.59	2.93×10^{-13}

SNP single nucleotide polymorphism, CHR chromosome, EAF effect allele frequency, SE standard error, GWAS genome-wide association study.

Fig. 2 | Regional plots around rs4903064 in the discovery-stage GWAS. Plots are produced in LocusZoom and show $-\log_{10}$ (P values) in the discovery-stage GWAS. The purple diamond plot is the most significantly associated SNP, rs4903064. GWAS, genome-wide association study; SNP single nucleotide polymorphism.



rs4903064 may also influence *DPF3* expression in other arterial tissues, including retinal arteries. The protein encoded by *DPF3* is involved in cardiovascular development and function. Furthermore, elevated *DPF3* expression has been reported in patients with Tetralogy of Fallot (TOF), a congenital heart defect characterized by muscle hypertrophy²⁴. Consequently, *DPF3* may play a role in cardiovascular development and influence

the occurrence of arrhythmias. Based on these results, it might be possible that *DPF3* affects the cardiac output via arrhythmias and arterial anomalies, and the associated changes in retinal blood flow could result in variations in foveal thickness.

In recent studies, there has been a focus on the relationship between eye health and circulatory factors like hypertension and stroke risk, using

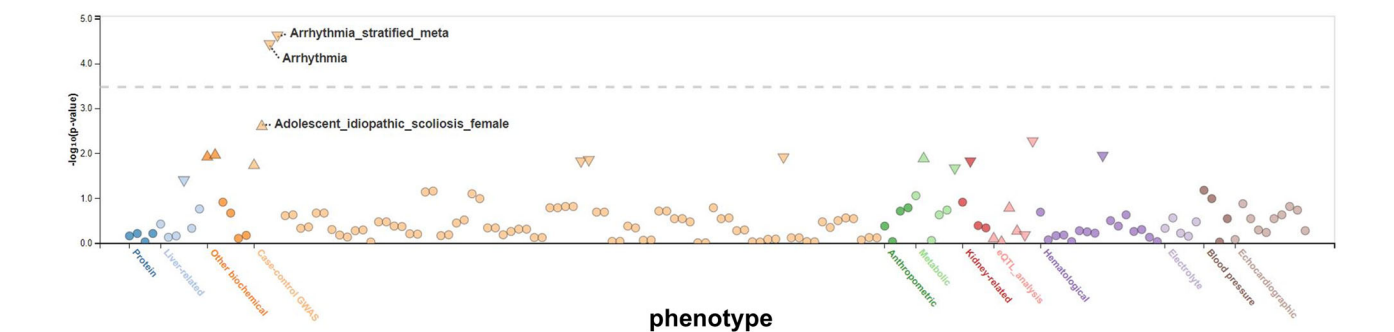


Fig. 3 | Associations between rs4903064 and multiple human phenotypes. We looked up the associations between rs4903064 and multiple human phenotypes using the summary statistics of GWASs and QTLs in the BBJ project (<http://jenger.riken.jp>). Plots show $-\log_{10}(P \text{ values})$ for phenotypes. The horizontal line is the Bonferroni corrected significance threshold ($P = 2.3 \times 10^{-4}$). GWAS, genome-wide association study; BBJ, BioBank Japan.

Table 3 | Associations between the arrhythmia and foveal thickness quartiles in the Nagahama study

	Quartile	+	−	Nominal		Adjusted ^a	
				Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Arrhythmia (total)	Q1	258	1865	1.04 (0.98–1.10)	0.16	0.98 (0.92–1.04)	0.42
	Q2	277	1843				
	Q3	276	1845				
	Q4	291	1831				
	Q1	141	1982				
Sinus bradycardia	Q2	172	1948	1.11 (1.04–1.20)	0.003	0.86 (0.96–1.12)	0.32
	Q3	165	1956				
	Q4	199	1923				
	Q1	56	2067				
	Q2	48	2072				
Premature cardiac complex	Q3	48	2073	0.87 (0.76–0.99)	0.038	0.86 (0.75–0.98)	0.022
	Q4	35	2087				

^aAdjusted for age and sex using logistic regression.
CI confidence interval.

artificial intelligence and other techniques^{25,26}. However, our current research reveals a previously unreported connection between arrhythmia and foveal thickness. It's important to note that a thin retina is a common characteristic of vision-impairing conditions such as retinitis pigmentosa, the atrophic form of age-related macular degeneration (AMD), and high myopia, making it an important clinical biomarker. While PAC/PVC arrhythmias themselves are not life-threatening, the presence of a thin retina alongside them may prompt patients to seek eye examinations for early detection of ocular diseases.

Our study has several limitations. First, despite utilizing a relatively large cohort dataset from the Nagahama study, the ethnicity was restricted to the Japanese population. Several studies have demonstrated ethnic differences in macular thickness^{20,27–29}, necessitating further evaluation of the generalizability to other ethnic groups. Additionally, the three SNPs (rs7503894, rs1042602, and rs1800407) associated with foveal thickness identified in the UK Biobank study³⁰ were absent in our Japanese dataset. Frequency analysis revealed that these SNPs are extremely rare in East Asian populations (minor allele frequencies [MAF] <0.2%) but relatively common in European populations (rs7503894: ~40%, rs1042602: 20–45%, rs1800407: 5–10%). This suggests that their absence reflects genuine genetic differences between populations rather than limitations in our dataset. These findings underscore the importance of population-specific genetic studies to better understand phenotypic variability. Secondly, there is the potential discrepancy in LD patterns between the GWAS data, which is based on the Japanese population, and the GTEx database, primarily derived

from European populations. This discrepancy could result in spurious overlaps in eQTL signals, particularly when the causal variants for the phenotype and transcript differ but are in LD with the same GWAS SNPs.

Third, the OCT device used varied across studies. In the Nagahama study, the RS-3000 Advance was employed, whereas the Hisayama study used the 3D OCT-1 Maestro. The UK Biobank study used a 3D OCT 1000 Mk2 (Topcon Corporation, Tokyo, Japan). There may be discrepancies between devices, such as in the automatic segmentation of blurred OCT images. However, we believe that such bias was minimal because we excluded low-quality OCT images, and all the included images underwent manual autosegmentation by ophthalmologists. Fourth, the nominally significant association between premature cardiac complex and foveal thickness became insignificant after Bonferroni correction. Therefore, future studies with larger sample sizes might lead to a more robust association, which is highly anticipated.

In conclusion, we identified a locus, rs4903064 in *DPF3*, associated with foveal thickness using data from the Nagahama study, followed by replication and meta-analyses. Further analysis of this SNP revealed an association between foveal thickness and premature cardiac complex, a type of arrhythmia. Our study provides an opportunity to investigate the association between foveal thickness and cardiac diseases, including arrhythmia.

Data availability

The essential summary statistics required to reproduce Fig. 1 (Manhattan plot) are accessible from Figshare at <https://doi.org/10.6084/m9.figshare>.

29457722. The full GWAS summary statistics have also been deposited in the NHGRI-EBI GWAS Catalog under accession GCST90624113. Source data underlying Figs. 2–3 are provided as Supplementary Data 1–2. Supplementary Data 2 was reconstructed based on previously published tables and available summary statistics from BBJ, due to the temporary suspension of PheWeb.

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Author contributions

S.N., M.M., E.N., Y.M., and K.M. designed the study. S.N., M.M., K.F., E.N., Y.M., K.M., Y.H., Y.T., and M.A. gathered the clinical data. S.N., M.M., K.F., E.N., Y.M., K.M., Y.H., Y.T., and M.A. generated genetic data. S.N., M.M., K.F., E.N., Y.M., K.M., Y.H., Y.T., M.A., K.Y., H.T., J.H., T.N., F.M., K.-H.S. and A.T. analysed the data. S.N., M.M., E.N., Y.M., and K.M. interpreted the data. S.N., M.M., and E.N. drafted the paper. All the authors contributed towards the revision of the paper.

Competing interests

The authors declare no competing interests.

Additional information

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