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# Ancestry-enriched and shared polygenic signals associated with high IQ in a Japanese extreme-phenotype cohort

**Jun Kawasaki**
Gftd DAO
**Shun Nogawa**
Genequest Inc.
**Kazuki Tainaka**
kztainaka@bri.niigata-u.ac.jp

Niigata University

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## Abstract

Genome-wide association studies (GWAS) of cognitive traits remain concentrated in European-ancestry cohorts, limiting discovery of ancestry-enriched alleles and transfer of polygenic findings across populations. We conducted a case-control GWAS of 91 Japanese individuals meeting a prespecified high-range cognitive criterion (score ≥ 140 on the Cognitive Ability Measurement Scale [CAMS]) and 41,528 unphenotyped Japanese commercial genetic-testing controls, testing 362,797 directly genotyped autosomal variants. rs146572333, a 5'-untranslated-region variant in *PPP2R1A*, reached genome-wide significance ($P = 1.17 \times 10^{-8}$), was 5.1-fold more frequent in cases than in controls, and was 38.7-fold more frequent in gnomAD East Asian genomes than in a pooled European proxy. The 26 retained $P < 1 \times 10^{-5}$ variants resolved to 17 East Asian linkage disequilibrium (LD)-defined loci. An LD-aware comparison with a European intelligence GWAS showed excess directional concordance among the top 500–2,000 European-ranked variants and a positive weighted signal ($Z = 3.01$; $P = 1.32 \times 10^{-3}$). European-derived polygenic scores were associated with case status at six prespecified thresholds; the secondary optimized score yielded an OR of 1.51 per SD (95% CI, 1.23–1.85; $P = 9.60 \times 10^{-5}$). These findings support ancestry-enriched and shared polygenic components of high IQ and warrant independent replication.


## Introduction

Genome-wide association studies (GWAS) have established that cognitive performance is highly polygenic, and large meta-analyses of directly assessed intelligence have identified many associated loci; however, individual common-variant effects are small and require substantial sample sizes for discovery [1, 2]. The scale of related behavioral-genetic studies continues to grow; for example, a recent genome-wide analysis of educational attainment enrolled approximately three million participants [3]. Educational attainment is a socially embedded outcome genetically correlated with cognitive performance; nonetheless, it is not interchangeable with intelligence or the extremely high-IQ phenotype studied here.

However, the ancestry distribution of these resources remains heavily skewed. European-derived association results and polygenic scores often suffer reduced accuracy when transferred to populations with greater genetic distance from the discovery cohorts [4, 5], whereas multi-ancestry analyses can reveal signals that are rare or poorly tagged in European datasets [6]. Empirical studies across diverse populations have consistently demonstrated both shared biological mechanisms and ancestry-dependent predictive capabilities [5–7]. Chen et al. reported an East Asian educational-attainment GWAS and cross-ancestry meta-analysis showing substantial shared genetic architecture and cross-population polygenic transfer [7], supporting the relevance of cross-ancestry comparisons while reinforcing that educational attainment is not equivalent to intelligence.

Extreme phenotype sampling offers a complementary design when precise phenotyping is available for a small number of individuals in the distributional tail. Human genetic studies and design analyses have shown that this strategy can enrich trait-associated alleles and improve efficiency under specified models [8], though it requires careful handling of the winner's curse [9], unselected controls, and sample ascertainment. A previous genome-wide study of extremely high intelligence in European-ancestry participants demonstrated the feasibility of a case-control extreme-trait design [10].

Large Japanese genomic resources have enabled large-scale studies across many complex traits [11, 12], and a recent population-based Japanese GWAS identified loci associated with cognitive function in older adults [13]. Nevertheless, genetic studies focusing specifically on the extremely high-IQ tail in non-European cohorts remain scarce [10, 13]. Japanese reference panels and cross-population atlases further highlight why ancestry-matched allele frequencies and linkage disequilibrium (LD) information matter: an allele that is uncommon in one ancestry may be sufficiently frequent for discovery in another, while LD differences can alter locus definition and score transferability [5, 7, 12, 14, 15].

We therefore conducted a case-control GWAS of 91 Japanese individuals meeting a prespecified high-range cognitive criterion (Cognitive Ability Measurement Scale [CAMS] score ≥ 140) and 41,528 unphenotyped Japanese commercial genetic-testing controls. The study was designed to test two complementary propositions: first, that a Japanese extreme-

phenotype cohort can identify an ancestry-enriched association, and second, that aggregate polygenic effects show measurable sharing with European intelligence GWAS results. We combined single-variant association, population-frequency comparison, East Asian LD-aware cross-population analysis, and European-derived polygenic scores, while separating prespecified score thresholds from a secondary optimized threshold analysis.

## Materials and Methods

# Ethics approval

This study was approved by the Ethics Committee of the NPO National Clinical Research Council (Reference No. 521; April 12, 2024). All participants provided written informed consent before enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

## Study design and participants

Cases comprised 91 Japanese individuals who were recruited through the Japan High IQ Certification Support Organization (HIQA), which administered the Cognitive Ability Measurement Scale (CAMS) and coordinated participant recruitment. Recruitment was conducted within a high-cognitive-ability community coordinated by HIQA, including many members of Mensa. Mensa membership generally requires a qualifying performance within the upper 2% of the general population on an approved, supervised intelligence test. Individual Mensa membership status was not systematically recorded and was neither an eligibility criterion nor an analytical variable in this study; all cases independently met the prespecified study eligibility criterion of a CAMS score ≥ 140. The CAMS is a high-range matrix-reasoning assessment designed to evaluate fluid reasoning in the upper ability range. Scores are expressed on an IQ-type scale (mean = 100, SD = 15). CAMS is not a comprehensive clinical IQ battery; instrument-construction and calibration details are provided in the "Ascertainment instrument" section of the **Supplementary Note**. Recruitment was conducted between August 2024 and December 2025. The case group comprised 85 men and 6 women.

The controls consisted of 41,528 unphenotyped Japanese commercial genetic-testing users drawn from the Genequest Inc. and Euglena MyHealth databases. They consented to the use of their anonymized genetic data but were not cognitively phenotyped. The combined post-QC sample comprised 41,619 individuals.

## Genotyping and quality control

Saliva samples were collected using Oragene kits, and genomic DNA was extracted following standard protocols. Cases and controls were genotyped at Genequest Inc. using the Illumina Infinium Global Screening Array-24 v3.0. Variant-level QC criteria included a call rate > 95%, a minor-allele frequency > 1%, and control Hardy-Weinberg equilibrium $P > 1 \times 10^{-6}$. The analysis was restricted to directly genotyped autosomal variants. Sample-level QC included a call rate > 95%, concordance between reported and genetically inferred sex, relatedness filtering at $PI_{HAT}$ >0.1875, and ancestry assessment. Following these procedures, 362,797 variants, 91 cases, and 41,528 controls were retained (see **Supplementary Note** section "Quality-control procedures"). Principal component analysis (PCA) was performed using PLINK v1.9 [16].

A post hoc technical review excluded the variant rs376128944 because its array-derived frequency was markedly discordant with Japanese reference data, and its signal was highly redundant with a neighboring marker. Consequently, it was not retained as a lead or top variant.

## Genome-wide association testing

Association was tested using logistic regression with case status as the outcome, adjusting for sex and principal components 1–10 (PC1–PC10). Genome-wide significance was set at $P < 5 \times 10^{-8}$, and suggestive significance was defined as $P < 1 \times 10^{-5}$. Genomic inflation was summarized using the genomic inflation factor ($\lambda_{GC}$). Firth-penalized logistic regression [17] was performed as a sensitivity analysis for the 200 top-ranked variants; 199 yielded results that were unchanged at the reported precision, and one small numerical difference did not alter its significance classification. For the lead variant rs146572333, the Firth sensitivity analysis yielded $\beta = 1.66589$, SE = 0.292035, and $P = 1.1673 \times 10^{-8}$, identical to the primary model values at this precision.

Given the unbalanced case-control design, the conventional effective sample size was calculated as $N_{\text{eff}} = \frac{4N_{\text{case}}N_{\text{control}}}{N_{\text{case}}+N_{\text{control}}}$, which yielded approximately 363. The observed sample sizes, rather than an assumed extreme-sampling multiplier, defined all primary inferences (see **Supplementary Note** section “Effective sample size and qualitative power interpretation”).

## Cross-population comparison

The cross-population direction-of-effect comparison used summary statistics from the Coleman et al. European intelligence GWAS [2]. Summary-level variants were harmonized to GRCh37 coordinates and reconciled by chromosome and position, and effect alleles were aligned between the Japanese analysis and the Coleman findings before signed-*Z* reconstruction. Japanese signed *Z*-statistics were calculated directly as $Z_{\text{JP}} = \frac{\beta_{\text{JP}}}{\text{SE}_{\text{JP}}}$. European signed *Z*-statistics were reconstructed from the Coleman et al. two-sided *P* values and reported $\beta$ directions as $Z_{\text{EUR}} = \text{sign}(\beta_{\text{EUR}}) \times \Phi^{-1}\left(1 - \frac{P_{\text{EUR}}}{2}\right)$. Here, the European $\beta$ supplies direction information only, and its magnitude is reconstructed from the two-sided *P* value. LD clumping was performed using PLINK v2.0.0-a.7.1 [18] with a 1000 Genomes Phase 3 East Asian reference panel [19] of *N* = 504, ranking candidate variants by European *P*-value with no *P*-value ceiling and merging correlated variants at $r^2 \geq 0.10$ within a 500 kb window under the primary specification; only variants with allele information compatible with the reference were retained. After clumping, 86,681 LD-clumped lead variants were available for the primary analysis. The final Japanese-Coleman harmonized clumping input comprised 307,822 variants meeting signed-*Z* eligibility, LD eligibility, and finite European-*P* criteria before East Asian LD clumping.

For each European *P*-value rank threshold *K* in {100, 500, 1,000, 2,000}, we computed the proportion of top-*K* European lead variants whose Japanese and European effect directions agreed, and tested the excess over 50% with a one-sided exact binomial test and a Clopper-Pearson 95% confidence interval. For the four prespecified *K* thresholds, $P < 0.0125$ (0.05/4) was used as a conservative family-wise benchmark; the exact one-sided P values remain the reported inferential results. Signed *Z*-statistics were summarized across LD-clumped lead variants using Spearman’s rank correlation (bootstrap 95% percentile interval; master seed 42; 1,000 resamples), with Pearson’s correlation as a complementary measure.

The European-association-weighted directional *Z* statistic was defined as

$$Z = \frac{\sum_{i=1}^{m} s_i w_i}{\sqrt{\sum_{i=1}^{m} w_i^2}}$$

where $s_i \in \{+1, -1\}$ indicates per-lead directional concordance, $w_i = -\log_{10}\left[\max\left(P_{\text{EUR},i}, 10^{-300}\right)\right]$ is the European-association weight for lead variant *i*, and *m* is the number of LD-clumped lead variants. The statistic was evaluated using a one-sided normal test; it summarizes weighted directional sharing and is not a conventional effect-size meta-analysis or a formal estimate of trans-ancestry genetic correlation. Sensitivity analyses evaluated $r^2$ thresholds of 0.05 and 0.20 within 500 kb, and $r^2 = 0.10$ within 250 kb and 1 Mb. The signed-*Z* Spearman rank correlation was unweighted across LD-clumped leads, whereas the European-association-weighted directional *Z* statistic weighted each lead's concordance sign by $-\log_{10}$(European *P*).

# Population-frequency comparison

Effect-allele frequencies for the retained top variants were compared with the ToMMo 38KJPN-SNV/INDEL Allele Frequency Panel [15] and gnomAD v4 genome populations [20]. A European proxy was created by pooling the non-Finnish European and Finnish groups, summing their respective allele counts (AC) and allele numbers (AN). Frequency ratios were calculated from unrounded AC/AN-derived frequencies prior to display rounding. Loci were defined using the East Asian LD analysis described above, yielding 17 primary loci. Frequency ratios are descriptive of the directly genotyped variant set and do not serve as estimates of genome-wide ancestry-enrichment prevalence. Categories were defined as East Asian-enriched for EAS/EUR > 2.0, European-enriched for EAS/EUR < 0.5, and similar frequency for 0.5 ≤ EAS/EUR ≤ 2.0.

## Polygenic score analysis

Polygenic scores were calculated using PRSice-2 [21] with the European intelligence GWAS by Savage *et al.* [1] as the base study. Base variants were restricted to the directly genotyped sites available in the target dataset. Scores were clumped at $r^2 < 0.1$ within 250 kb and standardized using the control mean and standard deviation. Logistic regression models included sex and principal components 1–10 (PC1–PC10) as covariates. Six prespecified *P*-value thresholds ($5 \times 10^{-8}$, $5 \times 10^{-5}$, $1 \times 10^{-4}$, $1 \times 10^{-3}$, $1 \times 10^{-2}$, and $5 \times 10^{-2}$) formed the primary analysis. Because the six scores were nested and strongly correlated, nominal covariate-adjusted *P* values were reported for the prespecified grid, with $P < 0.0083$ (0.05/6) used strictly as a conservative Bonferroni benchmark, rather than treating the thresholds as six independent discoveries. The threshold selected by PRSice-2 within the study sample was reported separately as a secondary analysis.

## Variant annotation

Variants were annotated against GRCh37 using the Ensembl Variant Effect Predictor (VEP) [22]. Gene expression and prior trait associations were reviewed using the GTEx Portal [23] and the NHGRI-EBI GWAS Catalog [24].

# AI-assisted tools

Claude (Anthropic) and OpenAI ChatGPT/Codex assisted with manuscript drafting and editing, code review, provenance organization, and literature reference management. The authors verified all AI-assisted outputs against primary sources and designated aggregate analysis records, made all scientific decisions, and accept full responsibility for the accuracy and integrity of this manuscript.

## Results

# Study overview and association results

This analysis compared 91 Japanese high-IQ cases with 41,528 unphenotyped Japanese commercial genetic-testing controls. After quality control (QC), 362,797 autosomal variants were tested. The genomic inflation factor was $\lambda_{GC} = 1.054$. One variant exceeded the genome-wide significance threshold (Fig. 1).

The single-nucleotide polymorphism (SNP) rs146572333 at chr19:52,703,635 (GRCh37) was associated with the high-IQ phenotype ($P = 1.17 \times 10^{-8}$; $\beta = 1.666$; SE = 0.292). The effect allele frequency was 0.061 in cases and 0.012 in controls, representing a 5.1-fold enrichment; the corresponding odds ratio (OR) was 5.29 (95% CI 2.98–9.38). The variant is located in the 5'-untranslated region (5'-UTR) of *PPP2R1A*. Twenty-five additional retained variants met the suggestive significance threshold after the technical exclusion described in the Methods section. The top-variant results are summarized in Table 1. The ten rows in Table 1 include correlated variants and, therefore, do not represent ten independent loci. The full set of 26

retained variants, including East Asian LD lead/non-lead status and population-frequency annotations, is provided in **Supplementary Table S1**. The complete sample and variant quality-control flow is provided in **Supplementary Table S2**.

Table 1
Top variants associated with the high-IQ phenotype.

| SNP | Chr:position | Effect allele | Other allele | *P* value | *β* | SE | Case AF | Control AF | Case AC | Significance |
|---|---|---|---|---|---|---|---|---|---|---|
| rs146572333 | 19:52703635 | A | C | $1.17 \times 10^{-8}$ | 1.666 | 0.292 | 0.061 | 0.012 | 11 | Genome-wide |
| rs139129152 | 16:77880365 | T | C | $8.86 \times 10^{-8}$ | 1.523 | 0.285 | 0.071 | 0.018 | 13 | Suggestive |
| rs78137899 | 7:232179 | T | C | $1.55 \times 10^{-7}$ | 1.431 | 0.273 | 0.077 | 0.021 | 14 | Suggestive |
| rs4396508 | 15:26457523 | C | T | $2.34 \times 10^{-7}$ | 0.762 | 0.147 | 0.396 | 0.237 | 72 | Suggestive |
| rs17135001 | 10:3327931 | A | C | $2.44 \times 10^{-7}$ | 1.145 | 0.222 | 0.115 | 0.040 | 21 | Suggestive |
| rs7653468 | 3:61046955 | C | T | $3.15 \times 10^{-7}$ | 1.566 | 0.306 | 0.060 | 0.014 | 11 | Suggestive |
| rs60409151 | 15:26455100 | T | C | $6.45 \times 10^{-7}$ | 0.748 | 0.150 | 0.357 | 0.211 | 65 | Suggestive |
| rs28478647 | 2:110382715 | A | G | $8.09 \times 10^{-7}$ | 1.360 | 0.276 | 0.071 | 0.020 | 13 | Suggestive |
| rs17675581 | 4:5080187 | G | A | $8.57 \times 10^{-7}$ | 1.162 | 0.236 | 0.106 | 0.036 | 19 | Suggestive |
| rs28729447 | 4:5064533 | C | A | $9.13 \times 10^{-7}$ | 1.253 | 0.255 | 0.091 | 0.027 | 16 | Suggestive |

# Population-frequency context and LD-dependent locus definition

In gnomAD v4.1.1 genomes, the rs146572333 effect allele was observed in 84 of the 5,180 called East Asian alleles (AF = 0.0162) and 33 of the 78,656 called alleles in the pooled European proxy (AF = 0.0004), corresponding to a 38.7-fold enrichment calculated from unrounded AC/AN-derived frequencies. This combination of case enrichment and marked ancestry-frequency divergence constitutes the principal ancestry-enriched finding of this study. The SNP rs139129152 was also nearly absent in the European reference data.

After primary East Asian LD clumping ($r^2$ = 0.10, 500-kb window), the 26 retained $P < 1 \times 10^{-5}$ variants resolved to 17 LD-defined lead loci. Under the primary specification, these loci were divided into five East Asian-enriched, five similar-frequency, and seven European-enriched loci (Fig. 2); specifically, rs8177374 (*TIRAP*) was merged with rs601580 (*DCPS*) into a single clump on chromosome 11 (28.2 kb apart). Sensitivity settings retained 17 loci at $r^2$ = 0.05 (500 kb), 17 at $r^2$ =

0.10 (250 kb), 17 at $r^2$ = 0.10 (1 Mb), and 18 at $r^2$ = 0.20 (500 kb), owing to the splitting of the *FAM230I* cluster on chromosome 22.

# Cross-population aggregate sharing

After LD clumping with the 1000 Genomes Phase 3 East Asian reference panel ($r^2$ = 0.10, 500-kb window), directional concordance exceeded 50% across all tested European GWAS rank thresholds. Concordance was statistically significant for the top 500 variants (56.0%, 280/500; one-sided $P = 4.13 \times 10^{-3}$), the top 1,000 variants (54.5%, 545/1,000; $P = 2.43 \times 10^{-3}$), and the top 2,000 variants (53.2%, 1,064/2,000; $P = 2.25 \times 10^{-3}$), whereas the top-100 threshold was not significant (56.0%, 56/100; $P$ = 0.136). The results for the top-500, top-1,000, and top-2,000 thresholds remained below the conservative Bonferroni benchmark of $P < 0.0125$ for the four tested $K$ thresholds (Fig. 3a).

The European-association-weighted directional $Z$ statistic was positive ($Z$ = 3.01; one-sided $P = 1.32 \times 10^{-3}$), and all four alternative LD specifications preserved this positive direction. Figure 3b shows that this statistic remained above the one-sided $\alpha$ = 0.05 threshold under all four sensitivity LD specifications ($r^2$ = 0.05 at 500 kb, $r^2$ = 0.20 at 500 kb, $r^2$ = 0.10 at 250 kb, and $r^2$ = 0.10 at 1 Mb). Numerical results for the primary and sensitivity LD specifications are provided in **Supplementary Table S3**.

Across all 86,681 LD-clumped lead variants, the signed-$Z$ rank correlation was positive but small (Spearman $\rho$ = 0.0058; two-sided $P$ = 0.0899; bootstrap 95% CI, − 0.0013 to 0.0120). Taken together, these analyses support modest aggregate directional sharing without providing a formal estimate of genetic correlation.

# European-derived polygenic scores

All six prespecified fixed thresholds showed nominal covariate-adjusted associations with case status. Because the six scores were nested and strongly correlated, these threshold results were interpreted as a prespecified pattern rather than six independent discoveries. Four of the six thresholds met the conservative Bonferroni benchmark ($P < 0.0083$). Incremental Nagelkerke $R^2$ ranged from 0.0047 to 0.0082, and nominal covariate-adjusted $P$ values ranged from $1.23 \times 10^{-3}$ to $1.36 \times 10^{-2}$. The fixed-threshold results are summarized in Table 2 and Fig. 4b.

Table 2
Prespecified fixed-threshold polygenic score results (primary analysis).

| Threshold | *N* SNPs | Incremental Nagelkerke $R^2$ | Covariate-adjusted *P* |
|---|---|---|---|
| $5 \times 10^{-8}$ | 167 | 0.0047 | $1.36 \times 10^{-2}$ |
| $5 \times 10^{-5}$ | 960 | 0.0076 | $1.77 \times 10^{-3}$ |
| $1 \times 10^{-4}$ | 1,204 | 0.0071 | $2.63 \times 10^{-3}$ |
| $1 \times 10^{-3}$ | 2,787 | 0.0069 | $2.94 \times 10^{-3}$ |
| $1 \times 10^{-2}$ | 8,093 | 0.0082 | $1.23 \times 10^{-3}$ |
| $5 \times 10^{-2}$ | 18,914 | 0.0052 | $9.92 \times 10^{-3}$ |

In the secondary optimized analysis, PRSice-2 selected $P$ = 0.0064 (6,518 SNPs). The adjusted OR was 1.51 per SD (95% CI, 1.23–1.85; $P = 9.60 \times 10^{-5}$), with an incremental Nagelkerke $R^2$ = 0.0119. The polygenic score (PGS)-only, covariates-only, and full-model area under the curve (AUC) values were 0.612, 0.758, and 0.793, respectively (**Supplementary Fig. S1**); the likelihood-ratio test yielded $P = 9.38 \times 10^{-5}$. The optimized threshold results are summarized in Table 3 and Fig. 4a.

Table 3
Optimized-threshold model metrics (secondary analysis).

| Threshold | *N* SNPs | Incremental Nagelkerke $R^2$ | OR per SD | 95% CI | Covariate-adjusted *P* | PGS-only AUC | Covariates-only AUC | Full AUC | LRT *P* |
|---|---|---|---|---|---|---|---|---|---|
| 0.0064 | 6,518 | 0.0119 | 1.51 | 1.23–1.85 | $9.60 \times 10^{-5}$ | 0.612 | 0.758 | 0.793 | $9.38 \times 10^{-5}$ |

In a male-only sensitivity analysis applying the full-sample optimized threshold (85 cases and 20,300 controls), the association remained significant ($\beta = 0.380$; SE = 0.109; $P = 5.06 \times 10^{-4}$; OR per SD = 1.46, 95% CI 1.18–1.81; AUC = 0.634 for the PGS + PC1–PC10 model).

# Biological annotation of the leading regions

The genome-wide significant variant rs146572333 lies in the 5'-UTR of *PPP2R1A*, which encodes the structural A-subunit of protein phosphatase 2A (PP2A). Pathogenic *PPP2R1A* variants cause a spectrum of neurodevelopmental disorders [25], and dysfunction of PP2A subunits or PP2A-dependent phosphorylation homeostasis has been implicated in neurodevelopmental and neuronal phenotypes [26, 27]. These gene-level observations provide biologically plausible context for further investigation, but do not establish that rs146572333 is causal or functionally active.

Several highly ranked, directly genotyped variants mapped to the vicinity of *GABRB3*, including intronic variants rs4396508 and rs60409151. *GABRB3* encodes the $\beta$-3 subunit of the GABA-A receptor [28]. In the primary East Asian LD analysis, these variants formed a single five-member clump led by rs4396508 (**Supplementary Table S1**).

## Discussion

This study yielded two principal positive findings. First, rs146572333 in the 5'-UTR of *PPP2R1A* showed genome-wide significance and marked East Asian enrichment. Second, aggregate cross-population and polygenic score analyses supported the sharing of many small intelligence-associated genetic effects between European discovery data and the Japanese high-IQ phenotype. These ancestry-enriched and shared components are complementary rather than mutually exclusive.

This lead association illustrates the value of studying underrepresented populations in which an allele is sufficiently frequent to be informative. Its frequency in the gnomAD East Asian genome panel was 38.7 times higher than in the pooled European proxy, while the effect allele was 5.1 times more frequent in cases than in controls. A European-centered discovery strategy would have limited power to detect such an allele, even with a large total sample size. Conversely, the presence of ancestry-enriched alleles does not imply that the broader genetic architecture is population-exclusive [6, 7, 12].

Cross-population LD-aware analysis provided a second aggregate signal. Directional concordance with the European intelligence GWAS was significantly greater than 50% at the top 500, 1,000, and 2,000 European-ranked LD-clumped lead variants, and the European association-weighted directional *Z* statistic was positive under the primary East Asian LD specification ($Z = 3.01$; one-sided $P = 1.32 \times 10^{-3}$). This positive direction was preserved across all four alternative LD specifications, indicating that the observed excess was not an artifact of a single parameter choice. The signed-*Z* rank correlation across 86,681 LD-clumped lead variants was positive but small (Spearman $\rho = 0.0058$; two-sided $P = 0.0899$) with a bootstrap 95% CI that included zero; additional details are provided in the “Cross-population LD analysis” section of the **Supplementary Note**. Together, the top-*K*, weighted-*Z*, and rank-correlation results were interpreted as evidence of directional sharing between differently ascertained cross-population GWAS phenotypes, rather than a formal estimate of trans-ancestry genetic correlation.

The fixed-threshold PGS results provide the clearest prespecified evidence of aggregate sharing. Associations were observed across all six thresholds, with the largest fixed-threshold incremental $R^2$ at P = $1 \times 10^{-2}$. This pattern is consistent with a highly polygenic trait, for which restricting the score to genome-wide significant European variants discards informative subthreshold signals [1]. The optimized threshold produced stronger model metrics; however, because it was selected within the same sample, it was considered secondary to the fixed grid. The male-only analysis indicated that the optimized threshold association was not solely driven by marked sex imbalance, although sex and ancestry covariates accounted for much of the full model's predictive discrimination.

*PPP2R1A* provides a plausible neurodevelopmental candidate because PP2A signaling is critical for neuronal function, and pathogenic *PPP2R1A* variants cause a spectrum of developmental disorders [25]. Nevertheless, the associated 5'-UTR allele has no established molecular function, and public expression quantitative trait loci (eQTL) resources such as GTEx have limited statistical power for alleles rare in their donor populations [23]. The observed effect estimate is also vulnerable to the winner's curse [9]. Gene-level plausibility, therefore, motivates further functional investigation but does not identify a definitive causal mechanism.

The main limitations of this study are as follows: the case group was small and predominantly male, whereas controls lacked cognitive phenotyping. Although cases and controls were genotyped in the same facility on the same array platform, different recruitment sources leave potential for residual technical confounding. Reliance on directly assayed Global Screening Array (GSA) v3.0 content without East Asian-matched imputation may have influenced the observed ancestry-category distribution and limited fine-mapping resolution. Furthermore, the cross-population comparison contrasted a quantitative European intelligence GWAS with a Japanese extreme case-control design. These features limit effect-size precision, generalizability to females, and clinical interpretation. Consequently, this study does not support causal claims or individual trait predictions.

In conclusion, a Japanese high-IQ extreme-phenotype study identified a genome-wide significant East Asian-enriched association and an aggregate polygenic signal shared with European intelligence results. Larger, sex-balanced Japanese cohorts with ancestry-matched imputation or sequencing and independent replication are needed to establish the magnitude, locus structure, and biological significance of these findings.

# Data availability

Privacy-filtered Japanese GWAS summary statistics generated for this study, East Asian LD-defined locus definitions, cross-population aggregate outputs, source data underlying the figures and tables, **Supplementary Table S1**, accompanying data dictionaries, and the public reproducibility package are available on GitHub (https://github.com/Kazuki-Tainaka/japanese-high-iq-gwas) and archived in Zenodo (https://doi.org/10.5281/zenodo.21711574). The public package contains only aggregate or privacy-filtered data. Individual-level case genotypes, phenotypes, principal components, and polygenic score data are not publicly available due to participant consent, privacy, and ethical restrictions. Requests for controlled access to eligible case-level data may be directed to the corresponding authors and will be evaluated on a case-by-case basis under applicable ethical guidelines, data governance procedures, and the execution of a formal data use agreement. Individual-level control genotypes, control-level polygenic score values, and array signal intensity/cluster data are managed by Genequest Inc. and were not transferred to the academic repository; access to these data for verification is subject to Genequest Inc.'s authorization and governance. External reference datasets are available from the original sources cited in the manuscript.

# Code availability

The custom code used to generate the reported LD-aware analyses, aggregate cross-population results, tables, figures, and quality-assurance outputs, together with environment specifications, command manifests, and data dictionaries, is publicly available on GitHub (https://github.com/Kazuki-Tainaka/japanese-high-iq-gwas) and archived in Zenodo

(https://doi.org/10.5281/zenodo.21711574). Provider-internal scripts executed exclusively by Genequest Inc. and not transferred to the academic team were not included; however, the corresponding aggregate outputs and analytical methods are fully documented in the manuscript and public release package.

## Declarations

**Competing Interests**

The authors declare the following competing interests: J.K. serves as Representative Director of Gftd Japan Co., Ltd., as a Core Contributor to Gftd DAO, and as a Director of HIQA. Gftd DAO and Gftd DeSci provided funding for this study, and HIQA administered the ascertainment assessment. S.N. is employed by Genequest Inc., which provided the control genotype data. K.T. declares no competing interests.

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# Author Contribution

J.K. conceived the study, performed data analysis, and drafted the manuscript. S.N. provided control data, performed quality control, and contributed to data analysis. K.T. supervised the project, contributed to data interpretation, and revised the manuscript. All authors read and approved the final manuscript.

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# Data Availability

Privacy-filtered Japanese GWAS summary statistics generated for this study, East Asian LD-defined locus definitions, cross-population aggregate outputs, source data underlying the figures and tables, Supplementary Table S1, accompanying data dictionaries, and the public reproducibility package are available on GitHub (https://github.com/Kazuki-Tainaka/japanese-high-iq-gwas) and archived in Zenodo (https://doi.org/10.5281/zenodo.21711574). The public package contains only aggregate or privacy-filtered data. Individual-level case genotypes, phenotypes, principal components, and polygenic score data are not publicly available due to participant consent, privacy, and ethical restrictions. Requests for controlled access to eligible case-level data may be directed to the corresponding authors and will be evaluated on a case-by-case basis under applicable ethical guidelines, data governance procedures, and the execution of a formal data use agreement. Individual-level control genotypes, control-level polygenic score values, and array signal intensity/cluster data are managed by Genequest Inc. and were not transferred to the academic repository; access to these data for verification

is subject to Genequest Inc.'s authorization and governance. External reference datasets are available from the original sources cited in the manuscript.

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# Figures

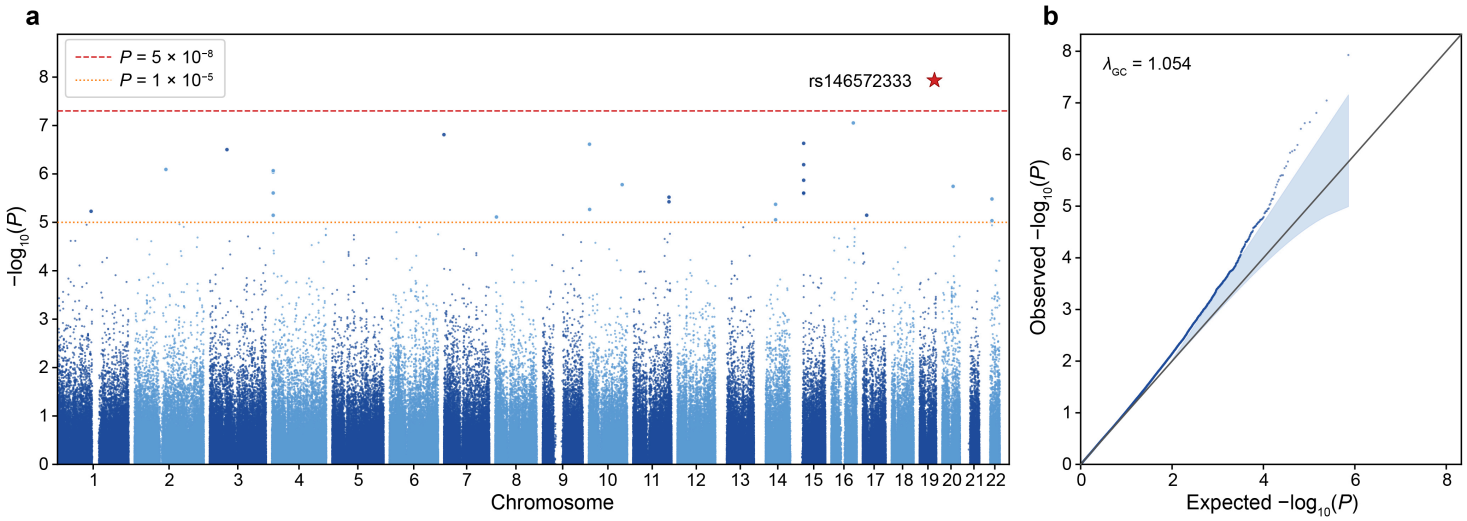



**Figure 1**

**Genome-wide association results for the Japanese high-IQ phenotype.** (**a**) Manhattan plot for 362,797 autosomal variants; horizontal lines denote $P = 5 \times 10^{-8}$ and $P = 1 \times 10^{-5}$. rs146572333 is highlighted. (**b**) Quantile-quantile plot; $\lambda_{GC} = 1.054$.

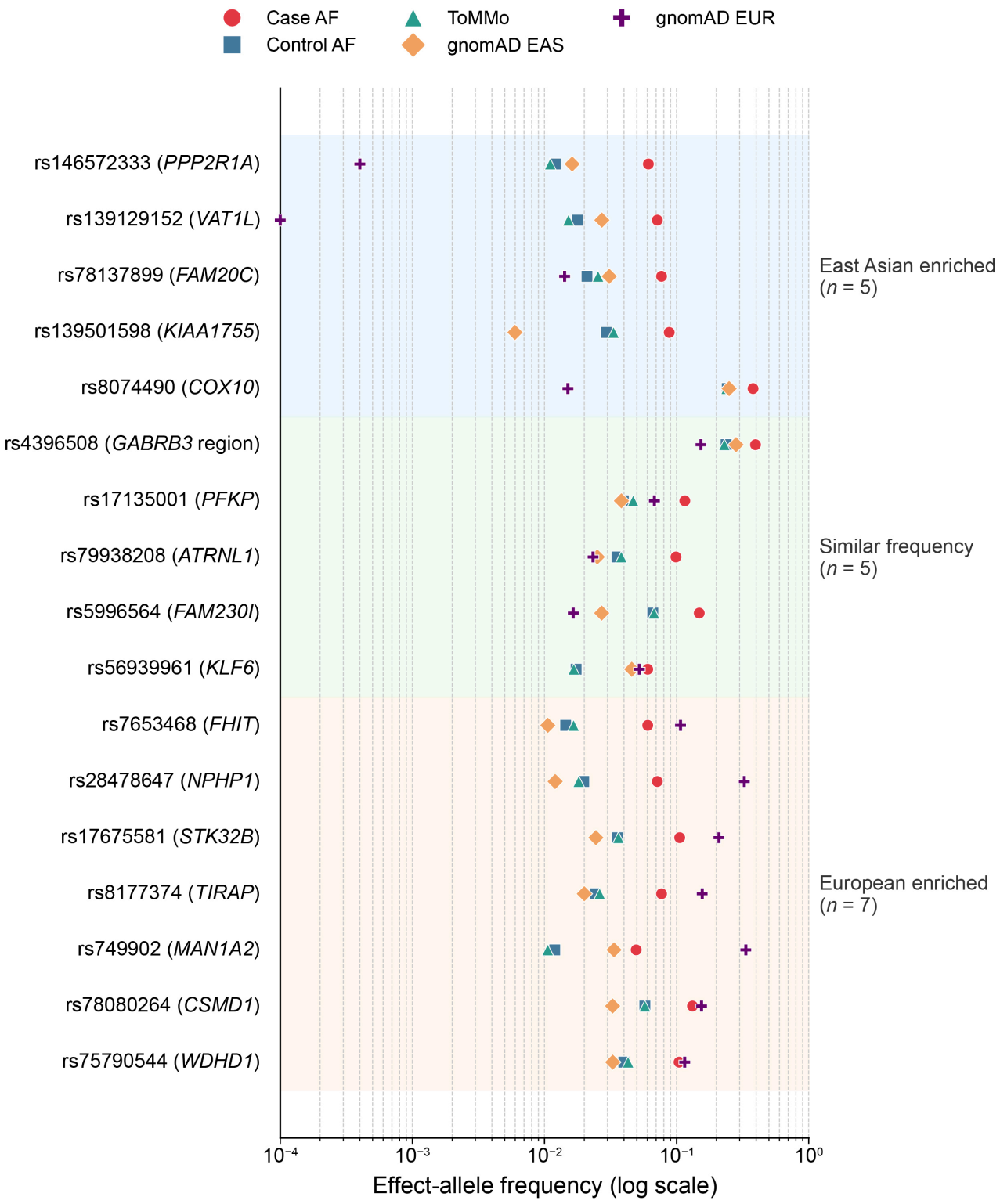



**Figure 2**

**Population-frequency context for 17 linkage disequilibrium (LD)-defined lead loci.** Effect-allele frequencies for the 17 East Asian LD-defined lead loci (primary specification: 1000 Genomes Phase 3 East Asian reference; $r^2$ = 0.10; 500 kb window) are shown as five plotted series: Case AF, Control AF, ToMMo 38KJPN AF, gnomAD v4 EAS AF, and gnomAD v4 European-proxy AF (pooled non-Finnish European and Finnish genome groups). The 17 loci are grouped by ancestry-enrichment category (East Asian enriched, 5; similar frequency, 5; European enriched, 7) and ordered within categories by Japanese association *P* value (ascending). Gene labels reproduce the Gene field in **Supplementary Table S1**.

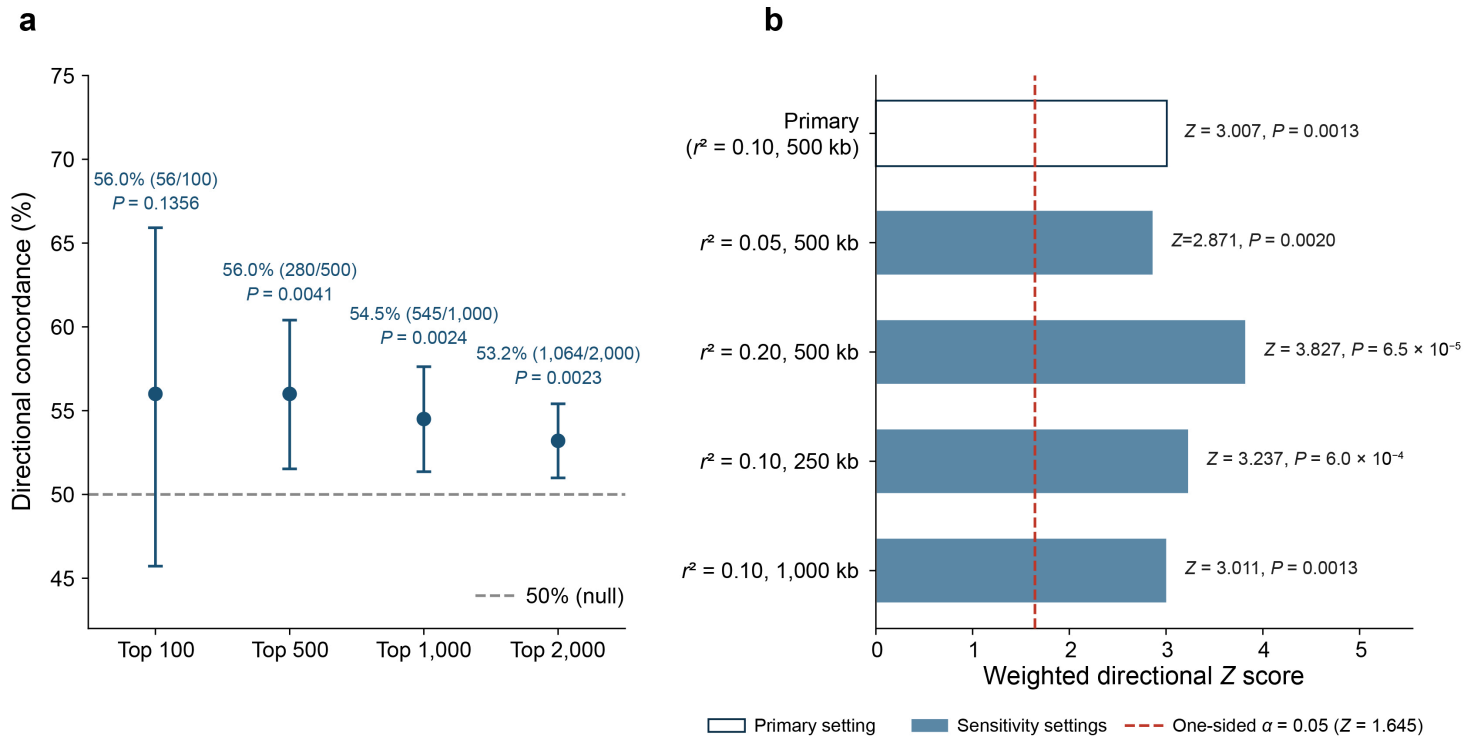



**Figure 3**

**East Asian linkage disequilibrium (LD)-aware cross-population comparison with European intelligence GWAS.** (**a**) Top-*K* directional concordance versus 50% at European *P*-value rank thresholds *K* = 100, 500, 1,000, and 2,000 with Clopper-Pearson 95% confidence intervals under the primary East Asian LD clumping (1000 Genomes Phase 3 EAS, *N* = 504; $r^2$ = 0.10; 500 kb; 86,681 LD-clumped leads). (**b**) Weighted directional *Z* statistic across the primary specification and four sensitivity LD specifications ($r^2$ = 0.05 with 500 kb, $r^2$ = 0.20 with 500 kb, $r^2$ = 0.10 with 250 kb, and $r^2$ = 0.10 with 1 Mb) with the one-sided $\alpha$ = 0.05 reference (*Z* = 1.6449).

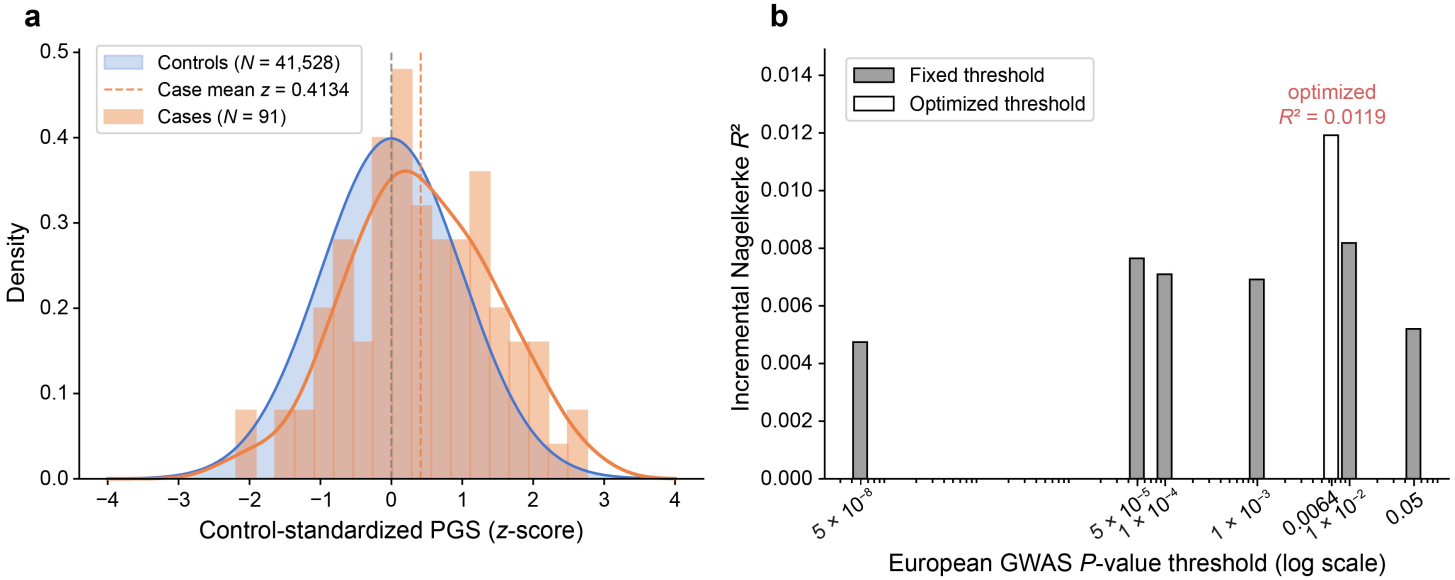



**Figure 4**

**European-derived polygenic scores (PGS) in the Japanese high-IQ study.** (**a**) Control-standardized PGS density at the secondary optimized threshold (*P* = 0.0064; 6,518 SNPs). Controls are represented by a normal approximation based on

41,528 participants, whereas cases are shown as the empirical distribution of 91 individual PGS values; dashed vertical lines indicate group means. (**b**) Incremental Nagelkerke $R^2$ for the six fixed thresholds and the optimized threshold. Fixed-threshold results are primary; the optimized result is secondary.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1.csv
- SI.pdf