PGCa-1 Paper Revisions

10.28.2024

General Overview

- Redid all of the analyses to address the comments, results are attached here
  - Majorly just cleaned up the analyses (performed needed exclusions and restricted to *EUR* genetic ancestry)
- No major results changed, everything still holds as it once did in UKBB but with slightly different OR/SE
- Also performed basic analysis for *pLOF* variants within PPARGAMA as per what was suggested to see if anything pops up

Heart-Failure-Phenotype Definition

Field	Coding	Exclude
20002	1076 1079	0
41202	I11.0 I13.0 I13.2 I25.5 I42.0 I42.5 I42.8 I42.9 I50 I50.0	0
41202	I50.1 I50.9	0
41204	I11.0 I13.0 I13.2 I25.5 I42.0 I42.5 I42.8 I42.9 I50 I50.0	0
41204	I50.1 I50.9	0
40001	I11.0 I13.0 I13.2 I25.5 I42.0 I42.5 I42.8 I42.9 I50 I50.0	0
40001	I50.1 I50.9	0
40002	I11.0 I13.0 I13.2 I25.5 I42.0 I42.5 I42.8 I42.9 I50 I50.0	0
40002	I50.1 I50.9	0
41203	4254 4280 4281 4280	0
41205	4254 4280 4281 4280	0
20002	1588	1
41202	I42.1 I42.2	1
41204	I42.1 I42.2	1
40001	I42.1 I42.2	1
40002	I42.1 I42.2	1

Missense Variants Mask Results

Counts of PPARGAMA Missense Variants within UKBB

N PPARGAMA missense Carriers among UKBB	N EUR
91 (0.023%)	395187

UKBB Heart-Failure Analysis

- Firth's Logistic Regression adjusting for enrollment age, genotyping array, sex, and the first ten principal components of ancestry
- HF ~ PPARGAMA_MISS + age + sex + genotyping_array + PC1 + PC2 + PC3 + PC4 + PC5 + PC6 + PC& + PC8 + PC9 + PC10

N PPARGAMA missense Carriers among HF Cases	N EUR	OR for All-Cause-Heart Failure	p-value
8	395187	3.235 (1.414, 6.45)	0.002119

UKBB Heart-Failure Analysis

- Firth's Logistic Regression adjusting for enrollment age, genotyping array, sex, and the first ten principal components of ancestry using the *R-Packaage* **logistf**

HF ~ PPARGAMA_MISS + age + sex + genotyping_array + PC1 + PC2 + PC3 + PC4 + PC5 + PC6 + PC& + PC8 + PC9 + PC10

N PPARGAMA missense Carriers among HF Cases	N EUR	OR for All-Cause-Heart Failure	p-value
8	395187	3.406 (0, 6.687)	0.004392815

UKBB Carrier Characteristics

Average Age	Sex Breakdown	Race	Atrial Fibrillation	Hypertension	Type II Diabetes	CAD (All)
63.3 years	4 Males 4 Females	8 EUR	3 (37.5%)	5 (62.5%)	1 (12.5%)	3 (37.5%)

Variant Characteristics

Locus	N	AFIB	Hypertension	Diabetes	CAD
chr4:23801856:G:A_G	2	1	1	0	1
chr4:23802266:A:G_A	1	0	1	0	0
chr4:23831568:C:T_C	1	0	1	0	1
chr4:23831660:A:G_A	1	1	0	1	0
chr4:23831667:G:T_G	1	1	1	0	0
chr4:23831703:T:C_T	1	0	1	0	1
chr4:23884822:A:T_A	1	0	0	0	0
Total	8	3	5	1	3

Loss of Function Variants

Section Overview

- A couple of basic analyses to show that any association is not seen when we pool together rare-predicted loss of function variants within PPARGAMA

Counts of PPARGAMA Loss-of-Function Variants within UKBB

N PPARGAMA Loss of Function Carriers among UKBB	N EUR
35 (0.009%)	395187

UKBB Heart-Failure Analysis

- Logistic Regression adjusting for enrollment age, genotyping array, sex, and the first ten principal components of ancestry
- HF ~ PPARGAMA_pLOF + age + sex + genotyping_array + PC1 + PC2 + PC3 + PC4 + PC5 + PC6 + PC& + PC8 + PC9 + PC10

N PPARGAMA missense Carriers among HF Cases	N EUR	OR for All-Cause-Heart Failure	p-value
0	395187	1.251e-5	0.864708