

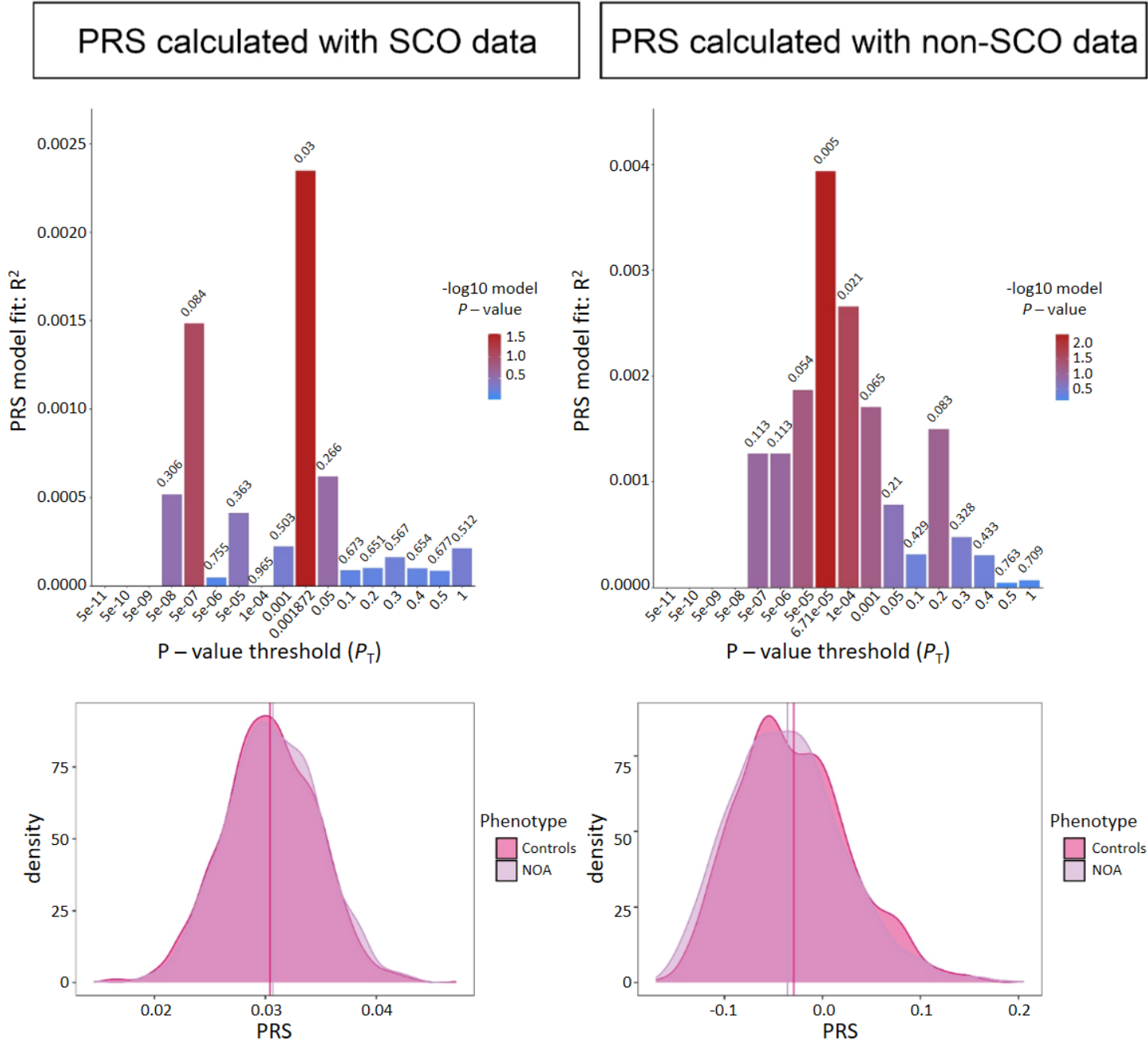
Communications Biology

Supplementary Figures and Tables

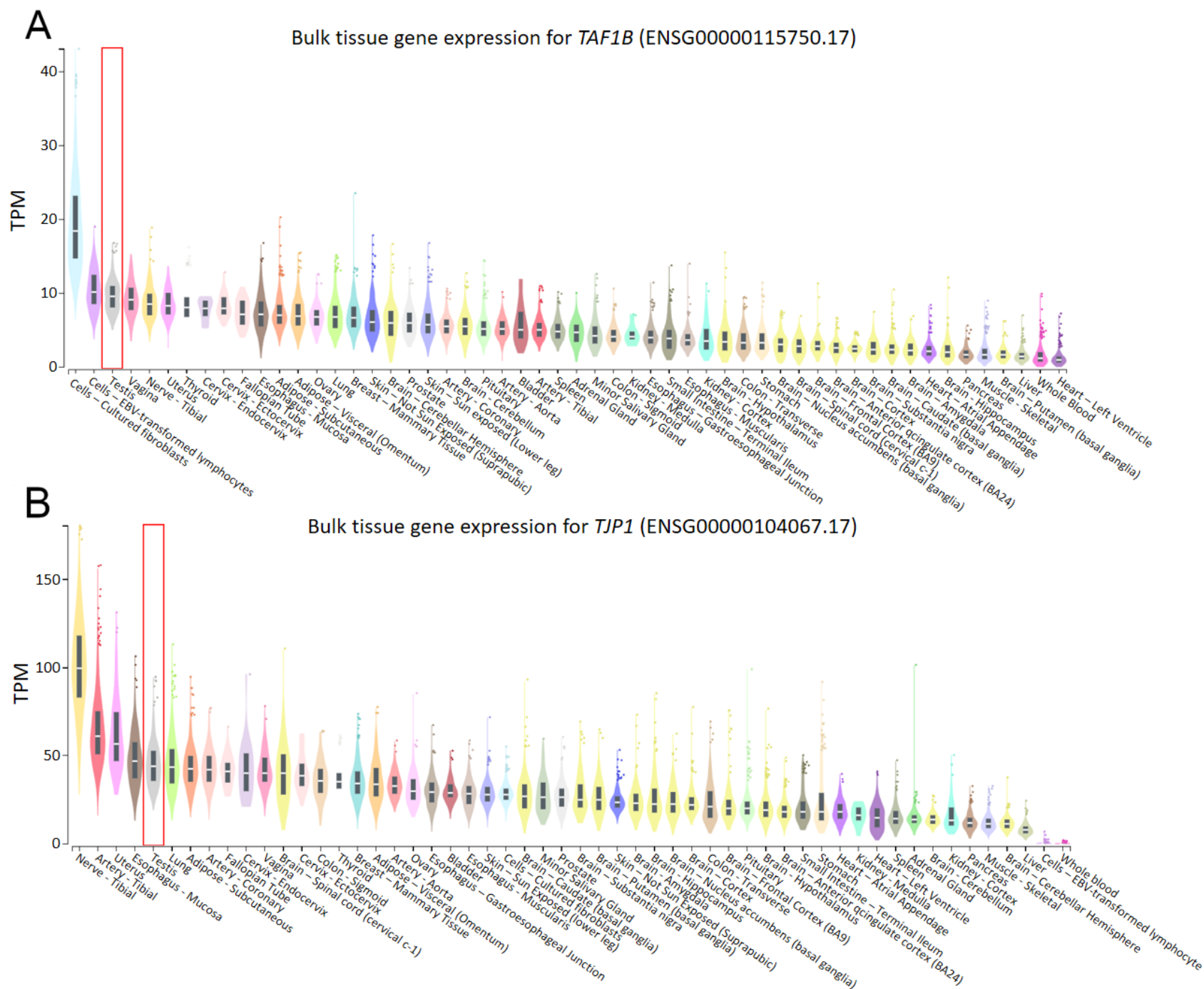
Trans-ethnic GWAS meta-analysis of idiopathic spermatogenic failure highlights the immune-mediated nature of Sertoli cell-only syndrome

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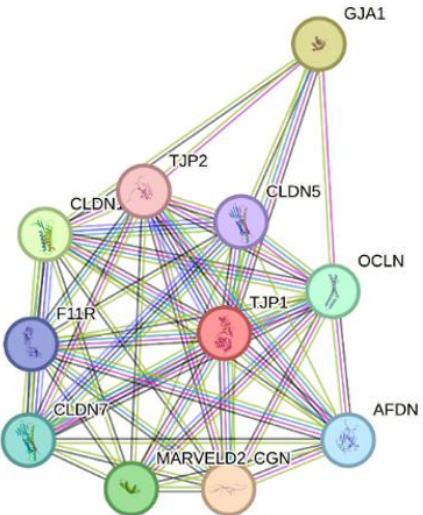
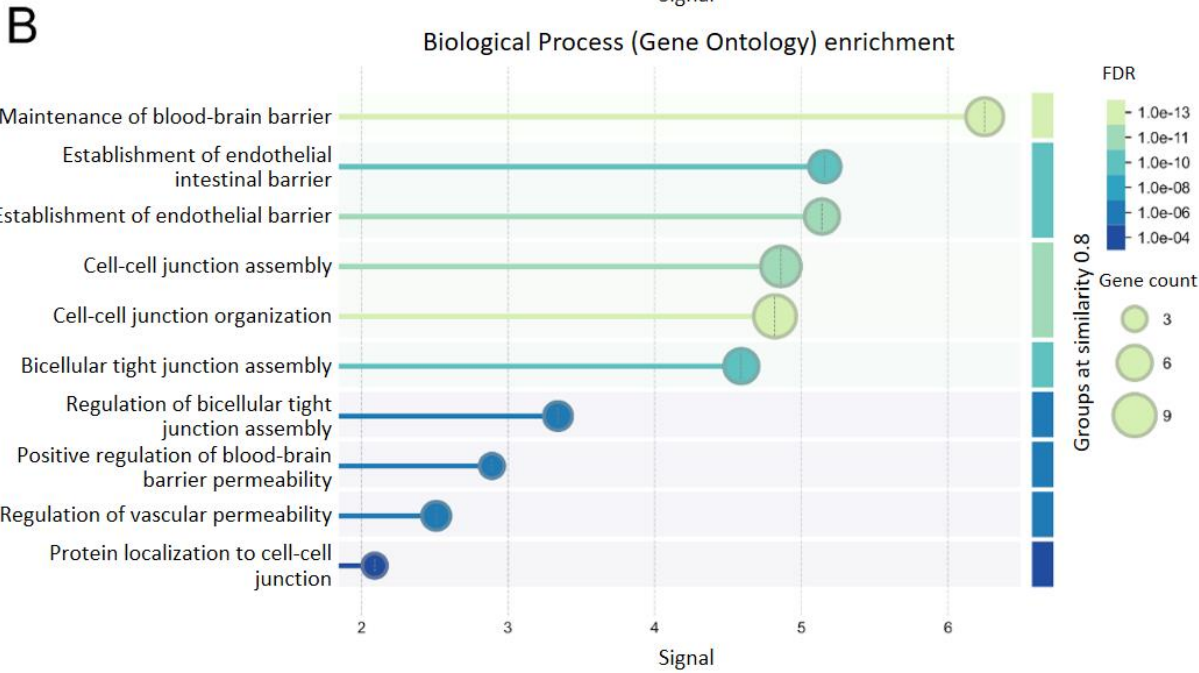
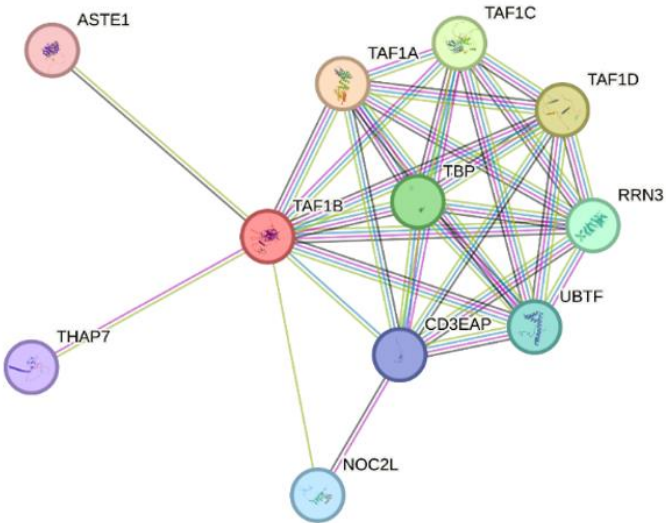
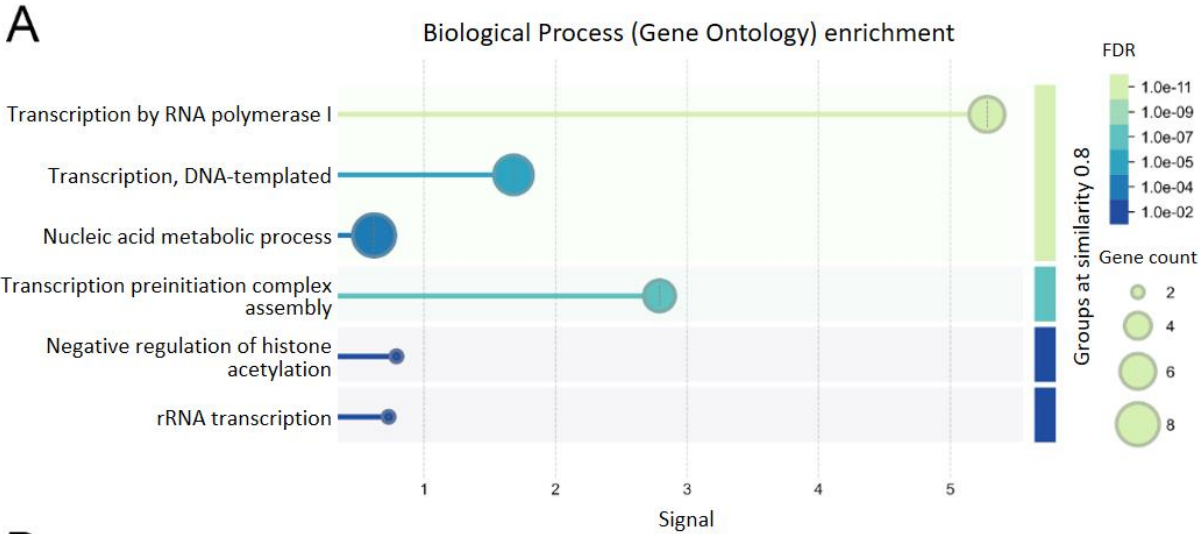
Supplementary Figure 1. Polygenic risk score (PRS) models assessed in the Asian cohort of this study. The weighted allelic effects for calculating the scores were based on the results from the comparisons between non-obstructive azoospermia (NOA) patients with the Sertoli cell-only (SCO) phenotype vs controls (SCO data) and between NOA patients without SCO vs controls (non-SCO data) from the European cohort (displayed on the right and left, respectively). The top panels illustrate the identification of the best-fitting PRS model for each comparison, while the distribution of PRS values for NOA cases and controls in the Asian cohort is depicted at the bottom.



Supplementary Figure 2. Gene expression for *TAF1B* (A) and *TJP1* (B). Linear representations of transcripts per million (TPM) values are shown. Testis expression is highlighted with red boxes. Data Source: GTEx Analysis Release V8.



Supplementary Figure 3. Gene Ontology (GO) biological process enrichment analysis of the most relevant protein-protein interaction networks for TAF1B (A) and TJP1 (B), as determined by the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING).



Supplementary Table 1. Summary data of the best-fit polygenic risk score (PRS) model for the Asian cohort calculated using the results from the comparative analyses between "Sertoli cell-only (SCO) vs controls" (SCO data) and "spermatogenic failure (SPGF) patients without SCO vs controls" (non SCO data) within the European cohort. CI, confidence interval; df, degrees of freedom; SNP, single-nucleotide polymorphism; t, Student's t-statistic.

	SCO data	Non SCO data
P-value model	0.0303053	0.00516039
Coefficient (beta)	21.0646	-2.03019
Standard error	9.72479	0.725886
Threshold	0.001872	6.71E-05
PRS R2	0.00246278	0.00413235
Full R2	0.0492754	0.0508667
Null R2	0.0469282	0.0469282
Number independent SNPs	1077	12
Mean Controls	0.03042721	-0.02913667
Mean Cases	0.03070343	-0.03566535
t	-1.626	2.8348
df	2066.1	2055.2
P-value T-test	0.1041	0.004631
95% CI	[-6.09E-04 - 5.69E-05]	[2.01E-3 - 1.10E-2]

Supplementary Table 2. Results of MAGMA gene-set analysis for the grey zones ($P < 1E-05$) in the trans-ethnic genome-wide association (GWAS) meta-analyses. Significantly enriched gene ontology (GO) terms within the grey zone of the GWASs of overall spermatogenic failure (SPGF), non-obstructive azoospermia (NOA), and Sertoli cell-only syndrome (SCO) are shown. For each gene set, the number of genes (N genes), beta values (Beta and Beta STD), standard error (SE), and P-values (P) are reported.

SPGF Gene Set	N genes	Beta	Beta STD	SE	P
WP_SARSCOV2_B117_VARIANT_ANTAGONISES_INNATE_IMMUNE_ACTIVATION	8	1.3232	0.0271	0.2809	1.25E-06
GOBP_SERTOLI_CELL_DEVELOPMENT	12	0.9729	0.0244	0.2504	5.14E-05
GOBP_POSITIVE_REGULATION_OF_SEQUESTERING_OF_TRIGLYCERIDE	9	1.0303	0.0224	0.2683	6.17E-05
REACTOME_ACTIVATION_OF_IRF3_IRF7_MEDIATED_BY_TBK1_IKK_EPSILON	16	0.8820	0.0255	0.2340	8.21E-05
REACTOME_TRAF3_DEPENDENT_IRF_ACTIVATION_PATHWAY	14	0.7762	0.0210	0.2074	9.11E-05
REACTOME_LIPOPHAGY	9	0.8628	0.0187	0.2318	9.90E-05
GOMF_TYPE_I_TRANSFORMING_GROWTH_FACTOR_BETA_RECEPTOR_BINDING	11	1.0738	0.0258	0.3005	1.77E-04
GOMF ESTRADIOL_17_BETA_DEHYDROGENASE_ACTIVITY	16	0.8049	0.0233	0.2254	1.79E-04
REACTOME_MYD88_INDEPENDENT_TLR4_CASCADE	102	0.2959	0.0216	0.0842	2.23E-04
WP_MIRNA_REGULATION_OF_P53_PATHWAY_IN_PROSTATE_CANCER	24	0.6320	0.0224	0.1824	2.65E-04
NOA Gene Set	N genes	Beta	Beta STD	SE	P
WP_SARSCOV2_B117_VARIANT_ANTAGONISES_INNATE_IMMUNE_ACTIVATION	8	1.1819	0.0242	0.2811	1.31E-05
GOBP_POSITIVE_REGULATION_OF_SEQUESTERING_OF_TRIGLYCERIDE	9	1.0729	0.0233	0.2684	3.22E-05
REACTOME_TRAF3_DEPENDENT_IRF_ACTIVATION_PATHWAY	14	0.7527	0.0204	0.2074	1.43E-04
WP_MIRNA_REGULATION_OF_P53_PATHWAY_IN_PROSTATE_CANCER	24	0.6610	0.0234	0.1824	1.46E-04
REACTOME_ACTIVATION_OF_IRF3_IRF7_MEDIATED_BY_TBK1_IKK_EPSILON	16	0.8479	0.0246	0.2341	1.46E-04
GOMF_SINGLE_STRANDED_RNA_BINDING	77	0.3479	0.0221	0.1006	2.73E-04
GOBP_LIPID_DROPLET_DISASSEMBLY	6	0.9789	0.0174	0.2841	2.86E-04
GOMF_TYPE_I_TRANSFORMING_GROWTH_FACTOR_BETA_RECEPTOR_BINDING	11	1.0280	0.0247	0.3006	3.14E-04
WP_INTERACTIONS_BETWEEN_IMMUNE_CELLS_AND_MICRORNAS_IN_TUMOR_MICROENVIRONMENT	23	0.6152	0.0214	0.1812	3.45E-04
GOBP_REGULATION_OF_SEQUESTERING_OF_TRIGLYCERIDE	15	0.7122	0.0200	0.2157	4.83E-04
SCO Gene Set	N genes	Beta	Beta STD	SE	P
WP_SARSCOV2_B117_VARIANT_ANTAGONISES_INNATE_IMMUNE_ACTIVATION	8	1.2145	0.0249	0.2853	1.05E-05
WP_PATHOGENESIS_OF_SARSCOV2_MEDIATED_BY_NSP9NSP10_COMPLEX	20	0.8353	0.0270	0.2006	1.58E-05
WP_SMALL_LIGAND_GPCRS	18	0.8031	0.0247	0.2088	6.02E-05
GOBP_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_EXOGENOUS_PEPTIDE_ANTIGEN_VIA_MHC_CLASS_II	28	0.7250	0.0278	0.1895	6.55E-05
GOBP_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_EXOGENOUS_ANTIGEN	45	0.5190	0.0252	0.1375	8.02E-05
GOCC_NLRP3_INFLAMMASOME_COMPLEX	7	1.6072	0.0308	0.4269	8.36E-05
WP_STING_PATHWAY_IN_KAWASAKILIKE_DISEASE_AND_COVID19	19	0.6739	0.0213	0.1790	8.38E-05
GOBP_MATERNAL_PROCESS_INVOLVED_IN_PARTURITION	5	1.2295	0.0199	0.3267	8.43E-05
GOMF_ANKYRIN_BINDING	19	0.7381	0.0233	0.1965	8.66E-05
GOBP_SENSORY_ORGAN_DEVELOPMENT	557	0.1411	0.0238	0.0382	1.12E-04