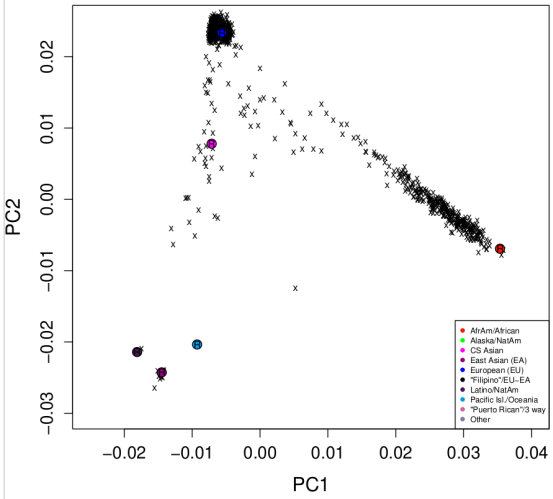
Figure S1

a

Disorders	Sample Size
Affective Disorders	8
Autism Spectrum Disorder	20
Bipolar Disorder	195
Control	687
Schizophrenia	514

b



c

EA	(0.9, 1.0]
	1041

AA	0	(0, 0.1]
	935	106

d

AA	(0.6, 0.7]		(0.7, 0.8]		(0.8, 0.9]			(0.9, 1.0]	
	54		89		111			29	
EU	(0.2, 0.3]	(0.3, 0.4]	(0.1, 0.2]	(0.2, 0.3]	0	(0, 0.1]	(0.1, 0.2]	0	(0, 0.1]
	26	28	50	39	1	37	73	2	27

e

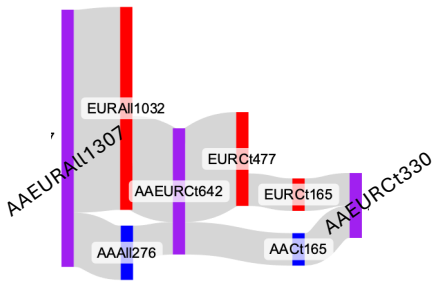
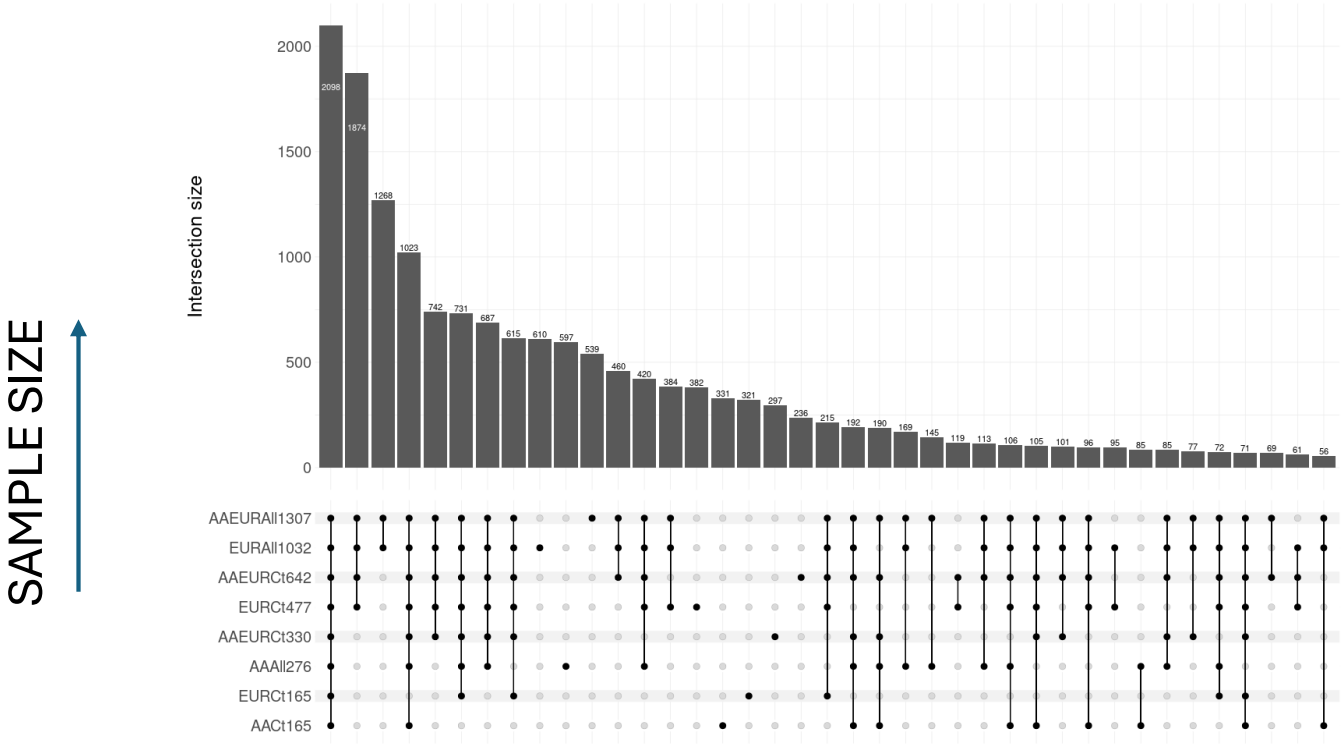


Figure S1:

a) Distribution of disorders across the study cohort, including Affective Disorders (Affe Dis), Autism Spectrum Disorder (ASD), Bipolar Disorder (Bip Dis), controls, and schizophrenia (SCZ). **b)** genotype data projected on ancestry marker PC plot using global ancestry pipeline **c)** Ancestry assignment for EUR (European Ancestry) individuals, with the table showing the proportion of other ancestry in the subjects.

d) Ancestry assignment for AA (African Ancestry) individuals, with the table showing the proportion of other ancestry in the subjects across specified ranges. **e)** Sankey plot illustrating the containment relationship between the 8 GReX DLPFC training datasets. The height of the flows represents the size of the training datasets, while the labels indicate specific dataset combinations, including ancestry-specific (EUR, AA) and bi-ancestry (AAEUR) sets.

Figure S2



Upset plot of gene predicted by 8 GreX models

Figure s3

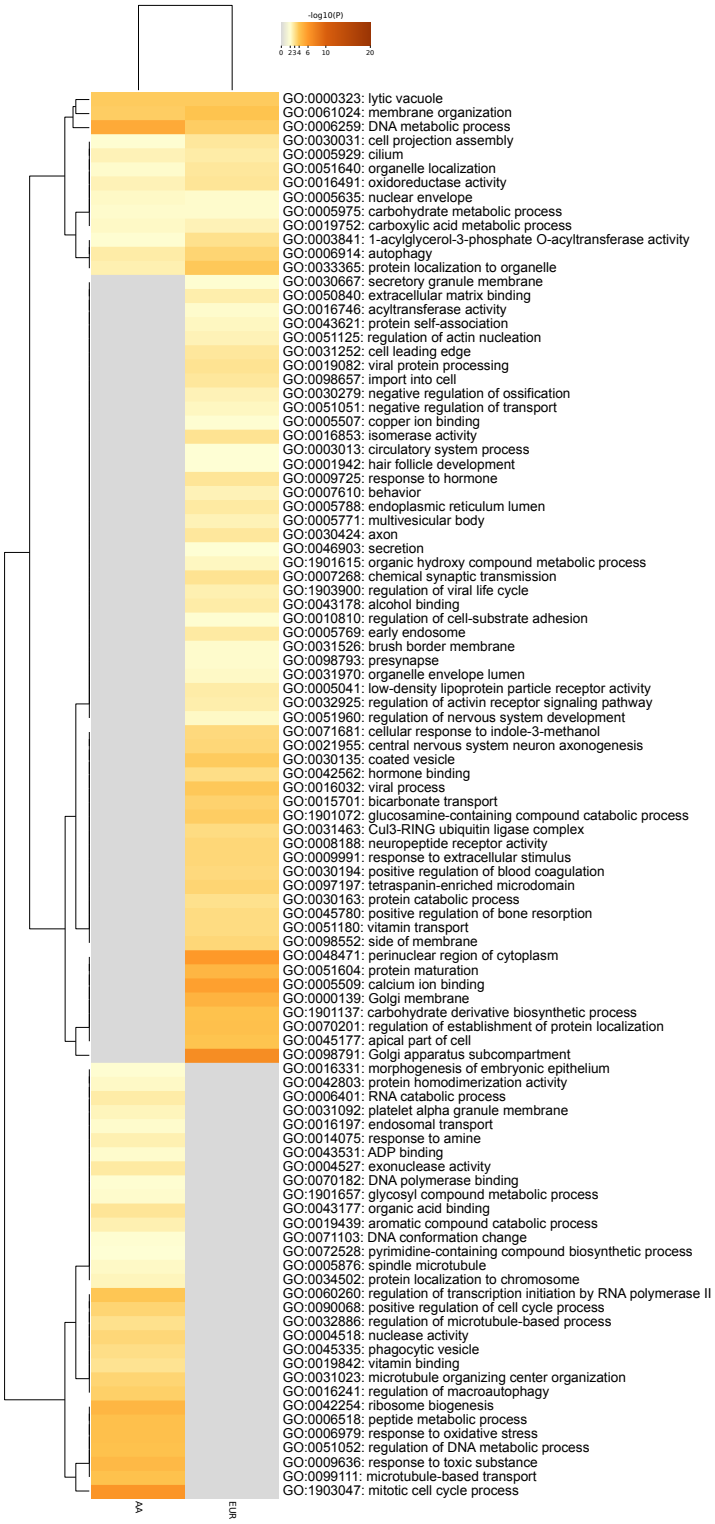


Figure S3: **AA and EUR gene Metascape Gene Ontology Enrichment**. enriched Gene Ontology (GO) terms for AA gene (predicted by AACt165 and higher order AA models but not by EURCt165) and EUR genes (predicted in EURCt165 and higher order EUR models but not by AACt165).

Figure s4

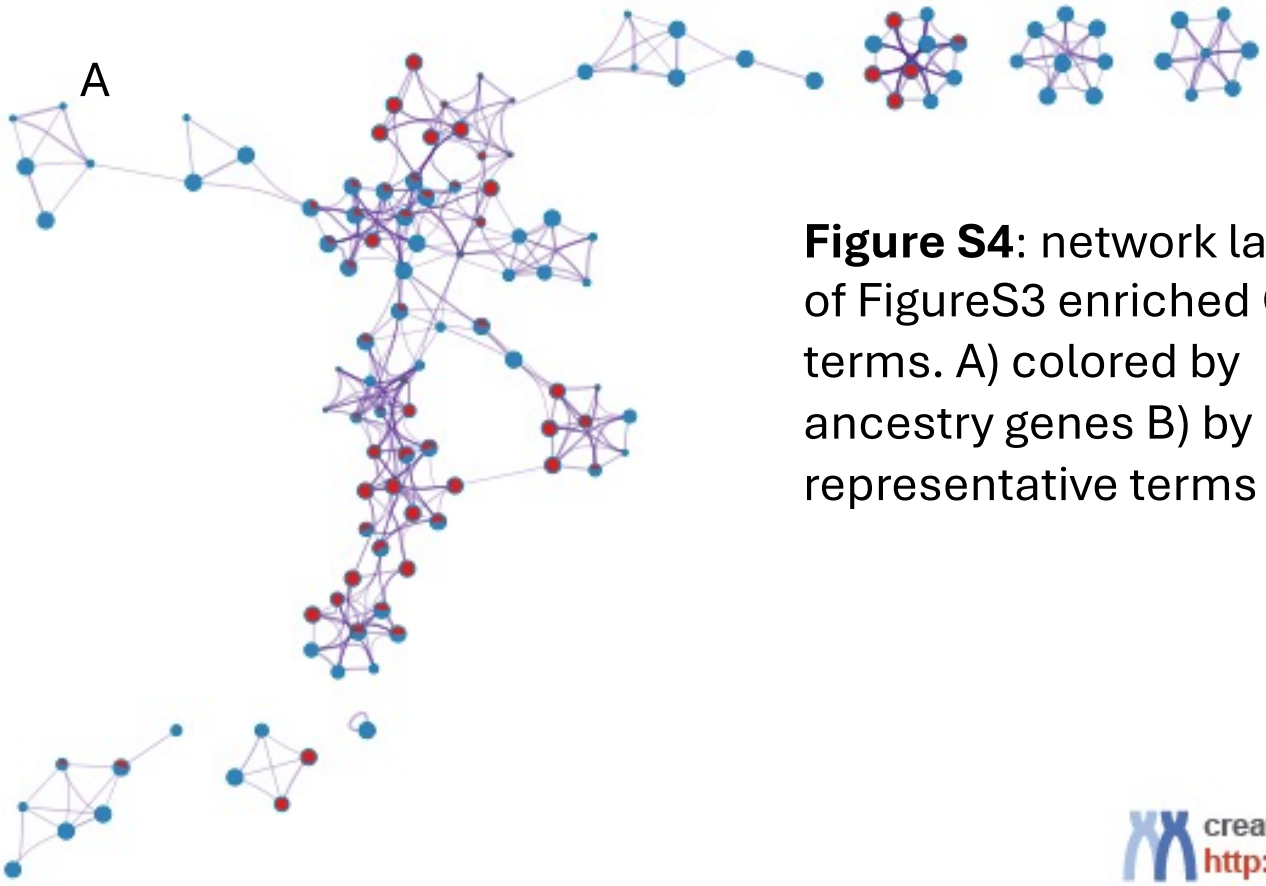


Figure S4: network layout of FigureS3 enriched GO terms. A) colored by ancestry genes B) by representative terms

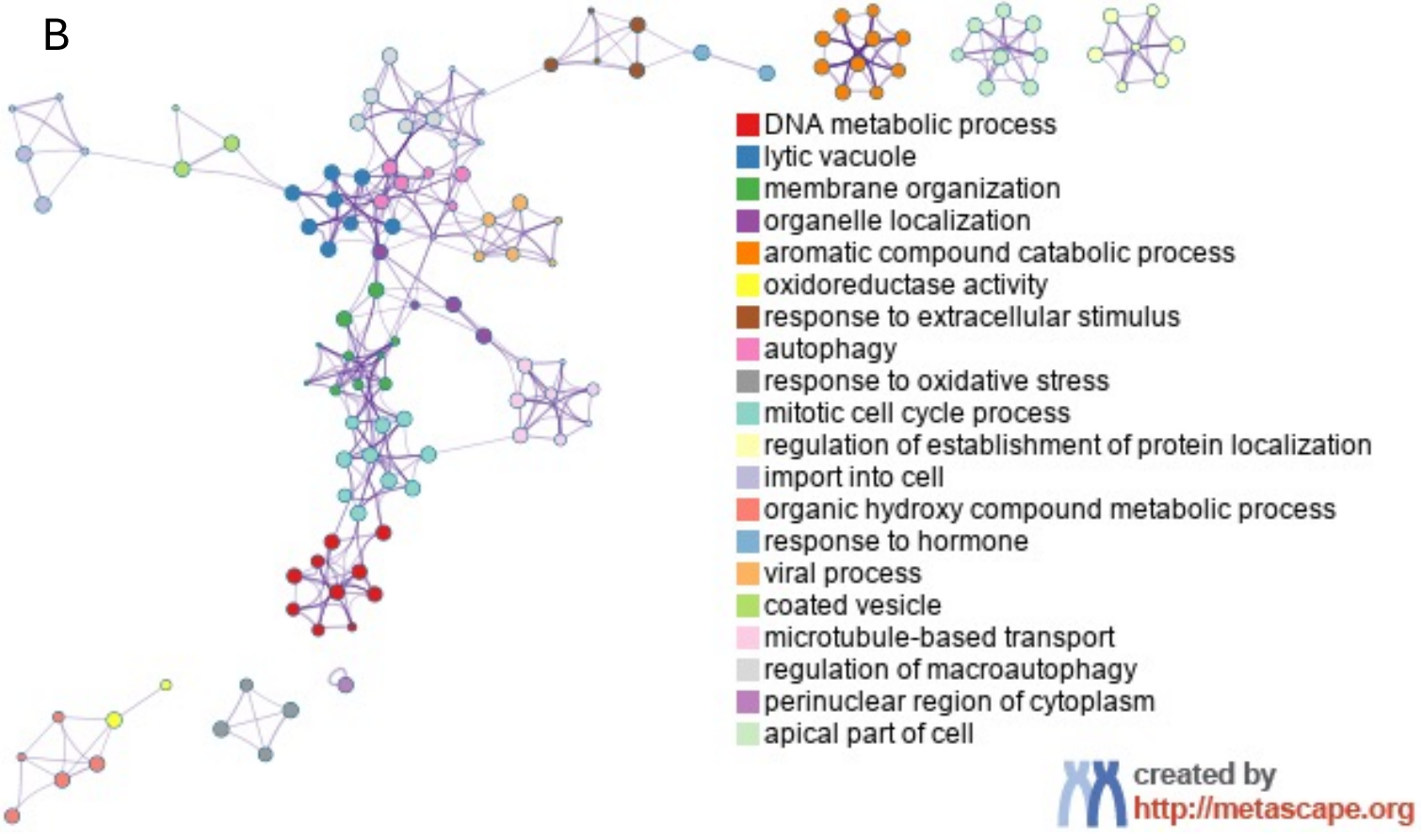


Figure 5

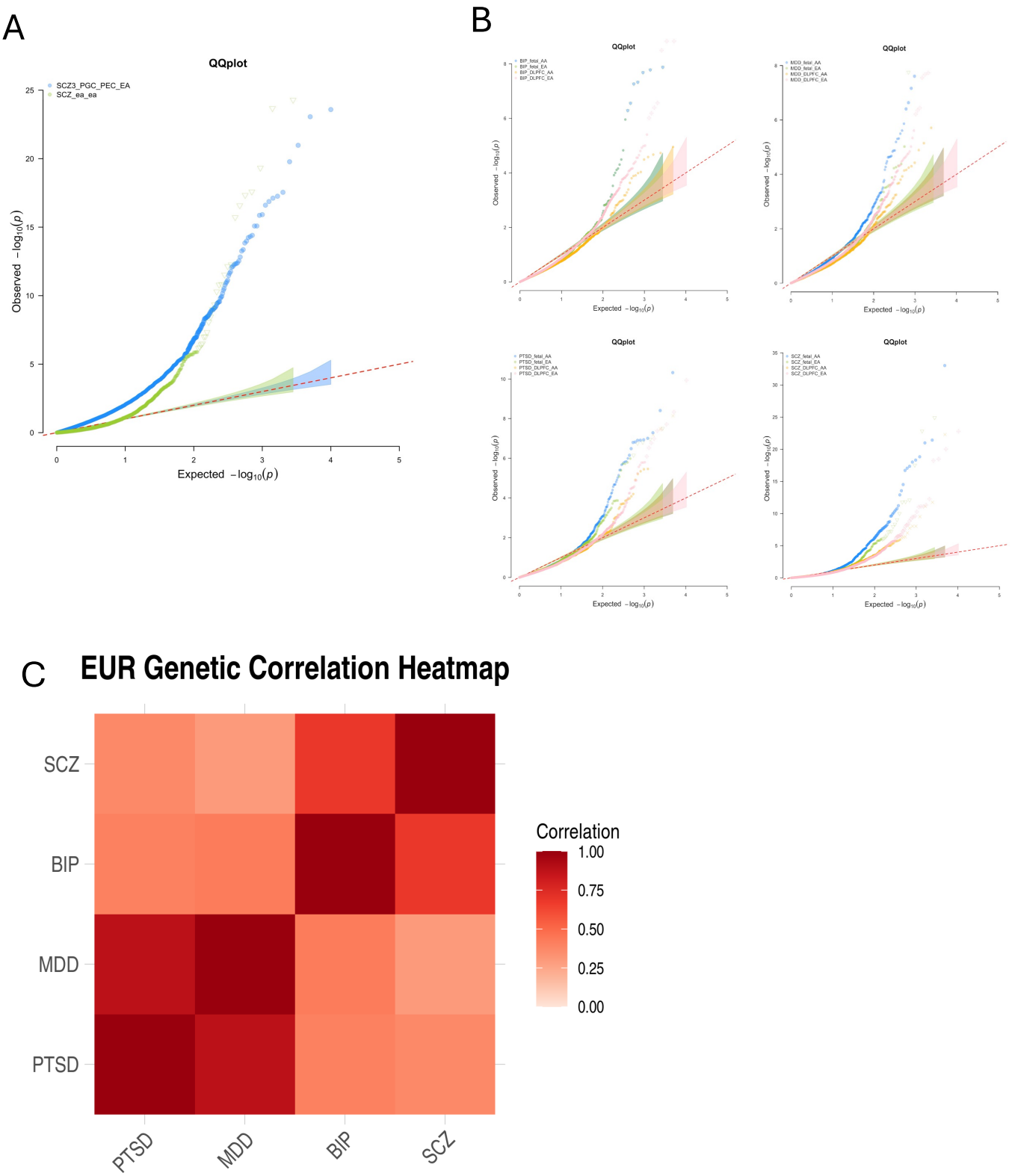


Figure S5: A. QQ plot of TWAS results across tissues and ancestry models by trait. B. QQ plot comparing JEPEGMiX and metaXcan SCZ TWAS results for EURCt477(EUR). C. genetic correlation of EUR GWAS (used in the paper) for each pair of trait.

Figure 6

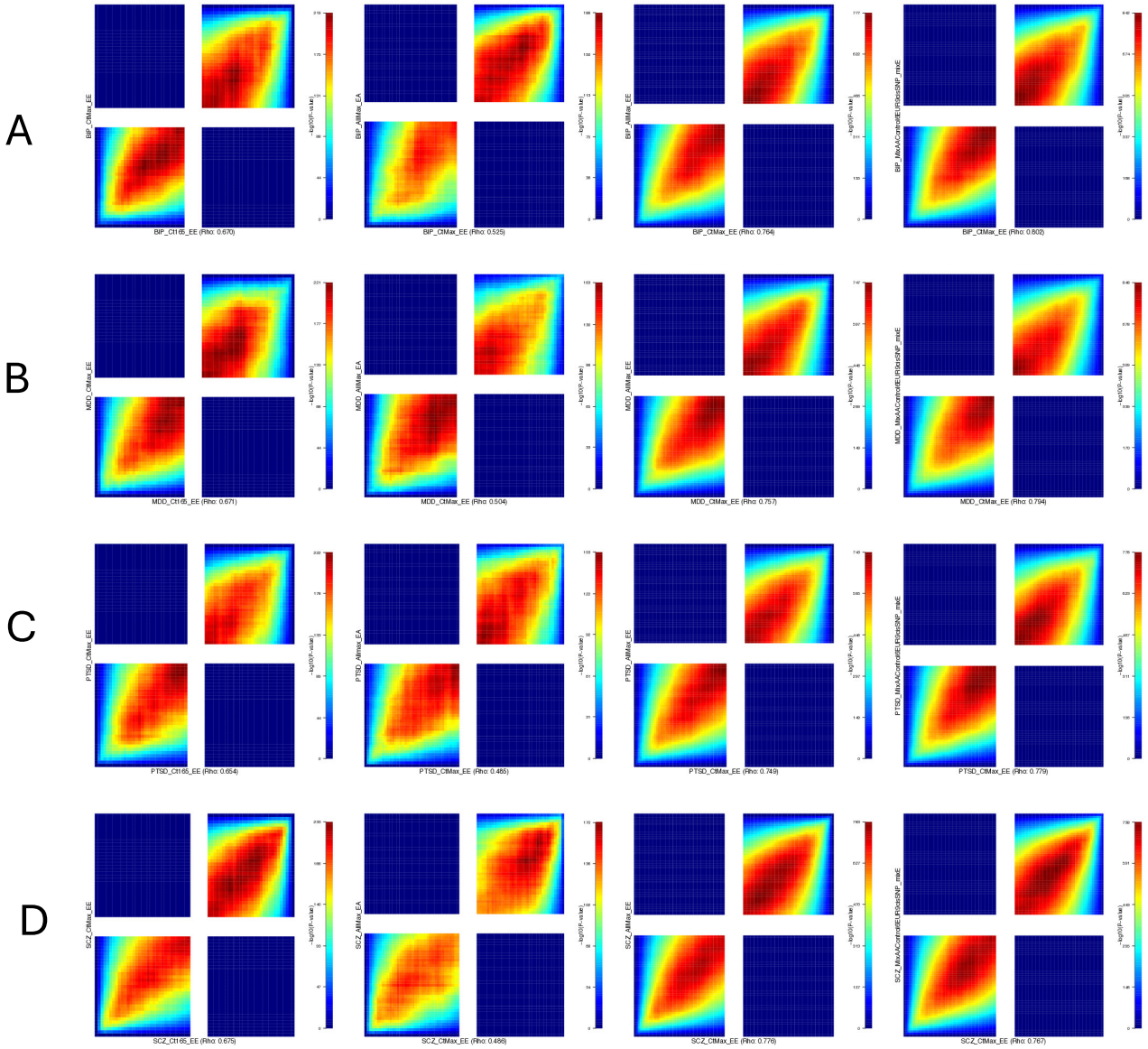


Figure S6: RRHO plots between pairs of TWAS of EUR GWAS across GReX models. Each row corresponds to a specific trait: BIP, MDD, PTSD, and SCZ (from top to bottom). Within each row, from left to right, the columns represent comparisons of EURCt165 vs EURCt477, EURCt477 vs AAAll276, EURCt477 vs EURAll1032, and EURCt477 vs AAEURCt642.

Figure 7

A

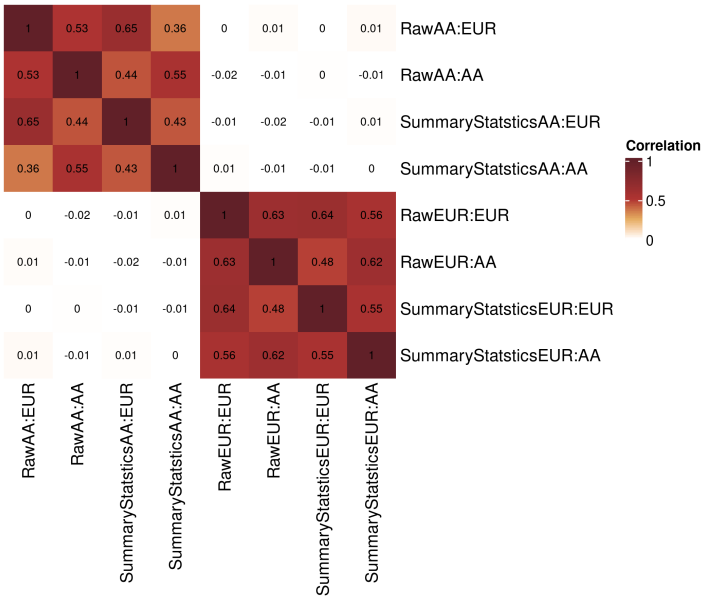


Figure S7: GTP cohort TWAS (Ct165 GReX pair) comparision A) Heatmap of pairwise z-score correlations for raw and summary statistics across EUR and AA cohorts. B) RRHO plots, where the top row represents raw associations and the bottom row represents summary statistics associations. The first column compares the Ct165 pair on EUR subjects, while the second column compares the Ct165 pair on AA subjects.

B

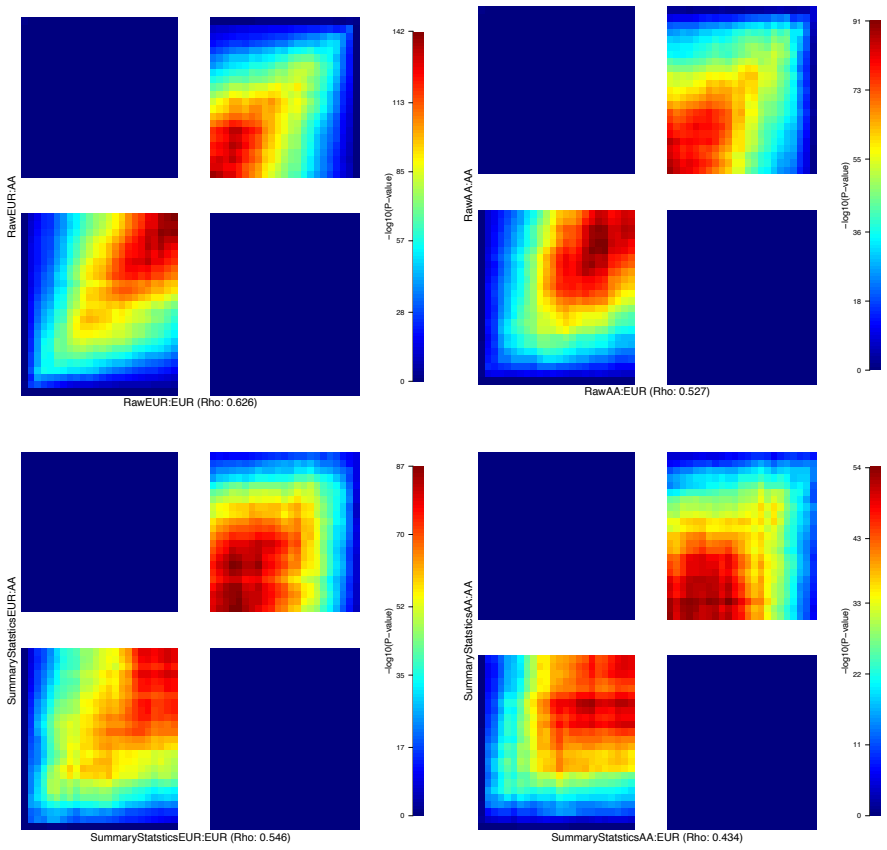


Figure 8

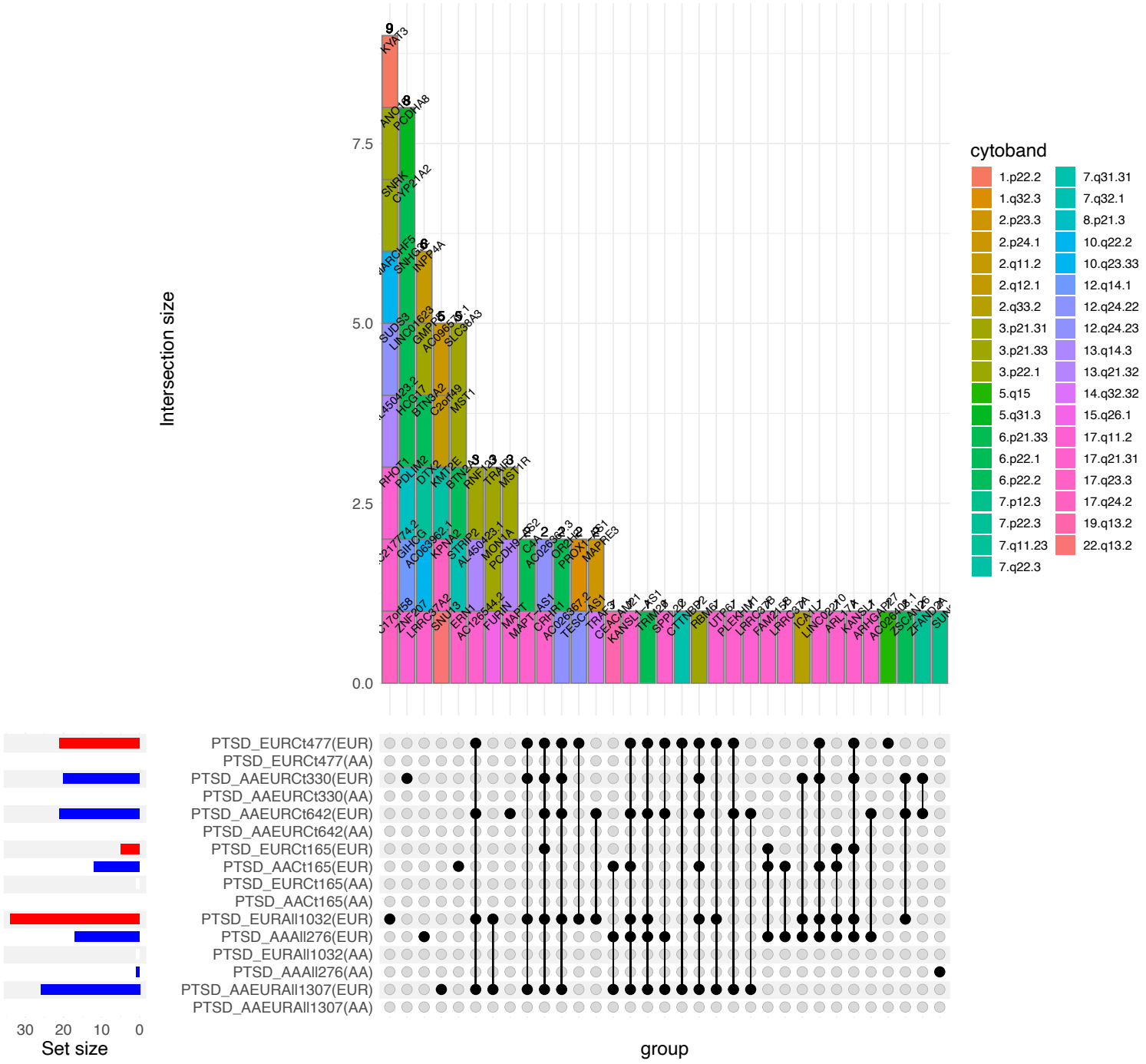


Figure S8. UpSet plots visualizing the intersection of FDR-GTAs within PTSD for all possible single ancestry asscoaited TWAS

Figure 9

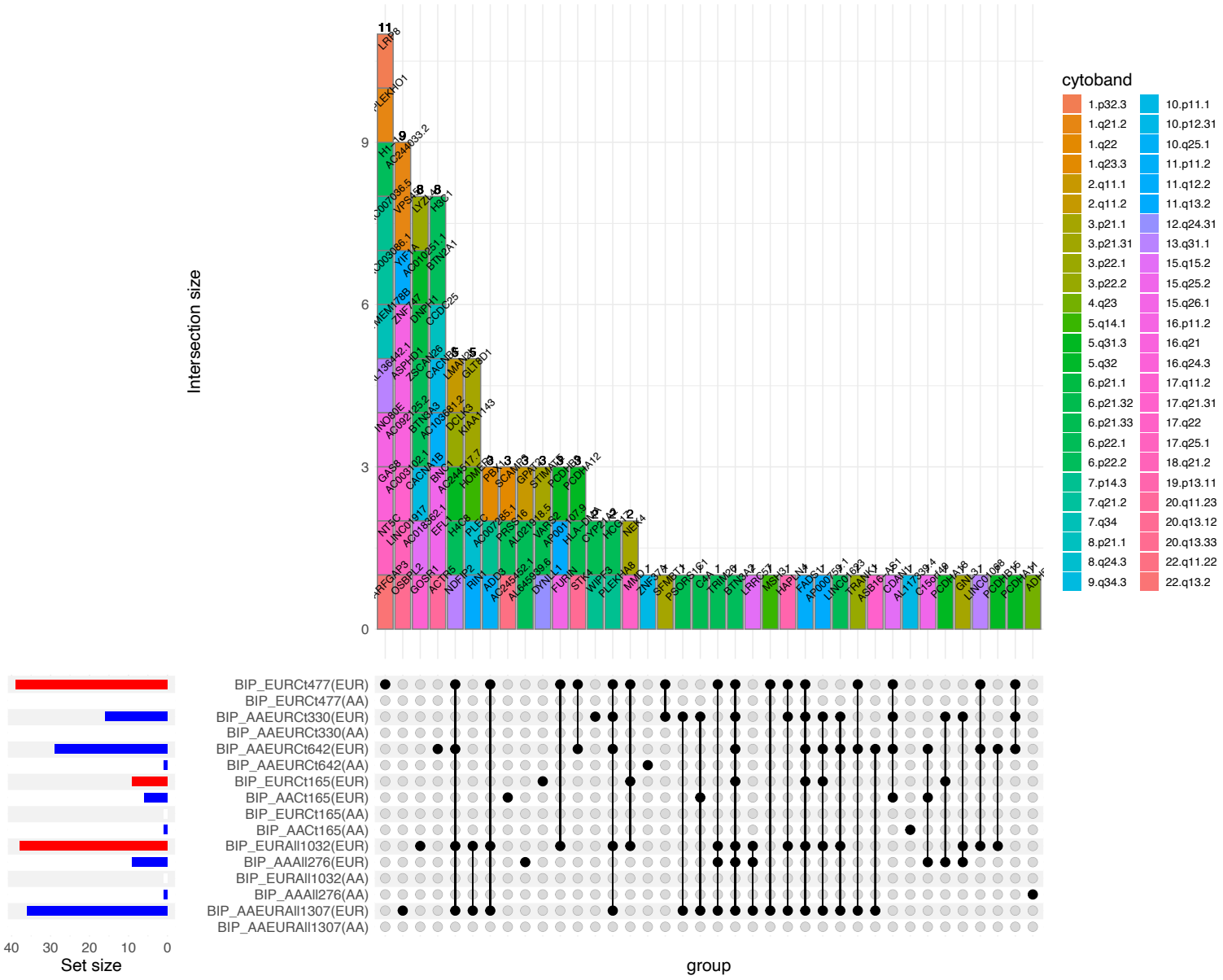


Figure S9. UpSet plots visualizing the intersection of FDR-GTAs within BIP for all possible single ancestry asscoaited TWAS

Figure 10

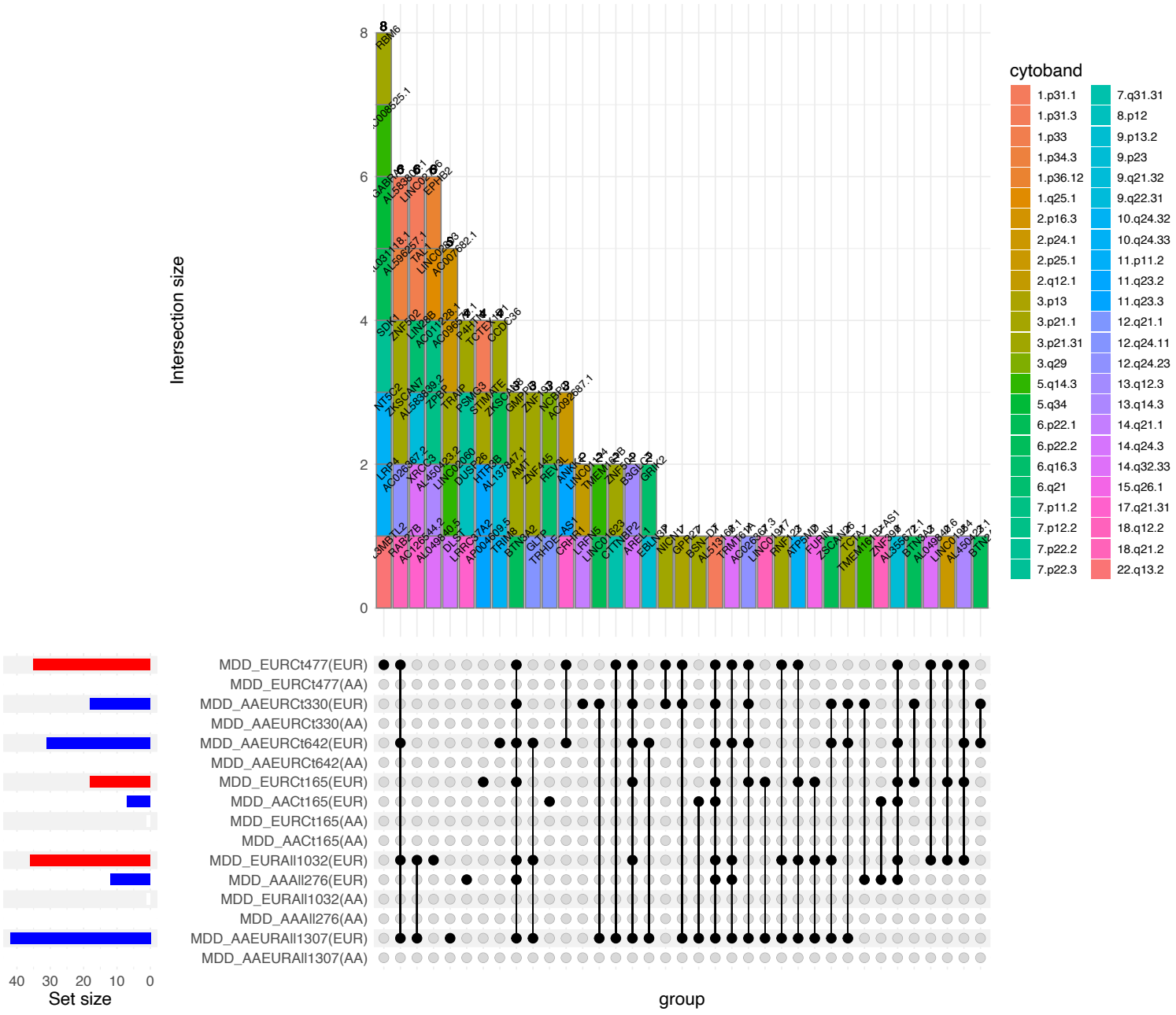


Figure S10. UpSet plots visualizing the intersection of FDR-GTAs within MDD for all possible single ancestry asscoaited TWAS

Figure 11

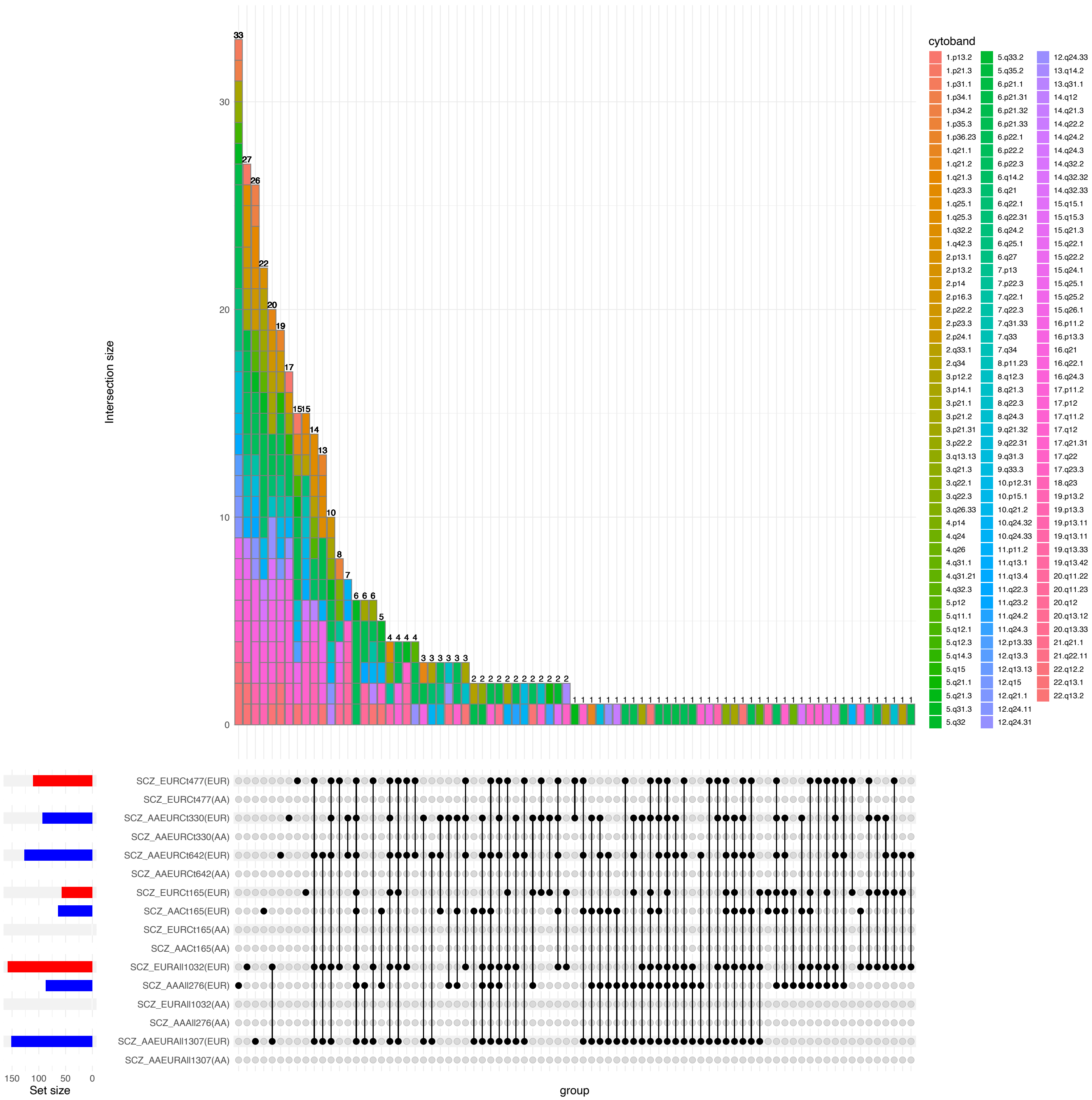


Figure S11. UpSet plots visualizing the intersection of FDR-GTAs within PTSD for all possible single ancestry asscoaited TWAS

Figure 12

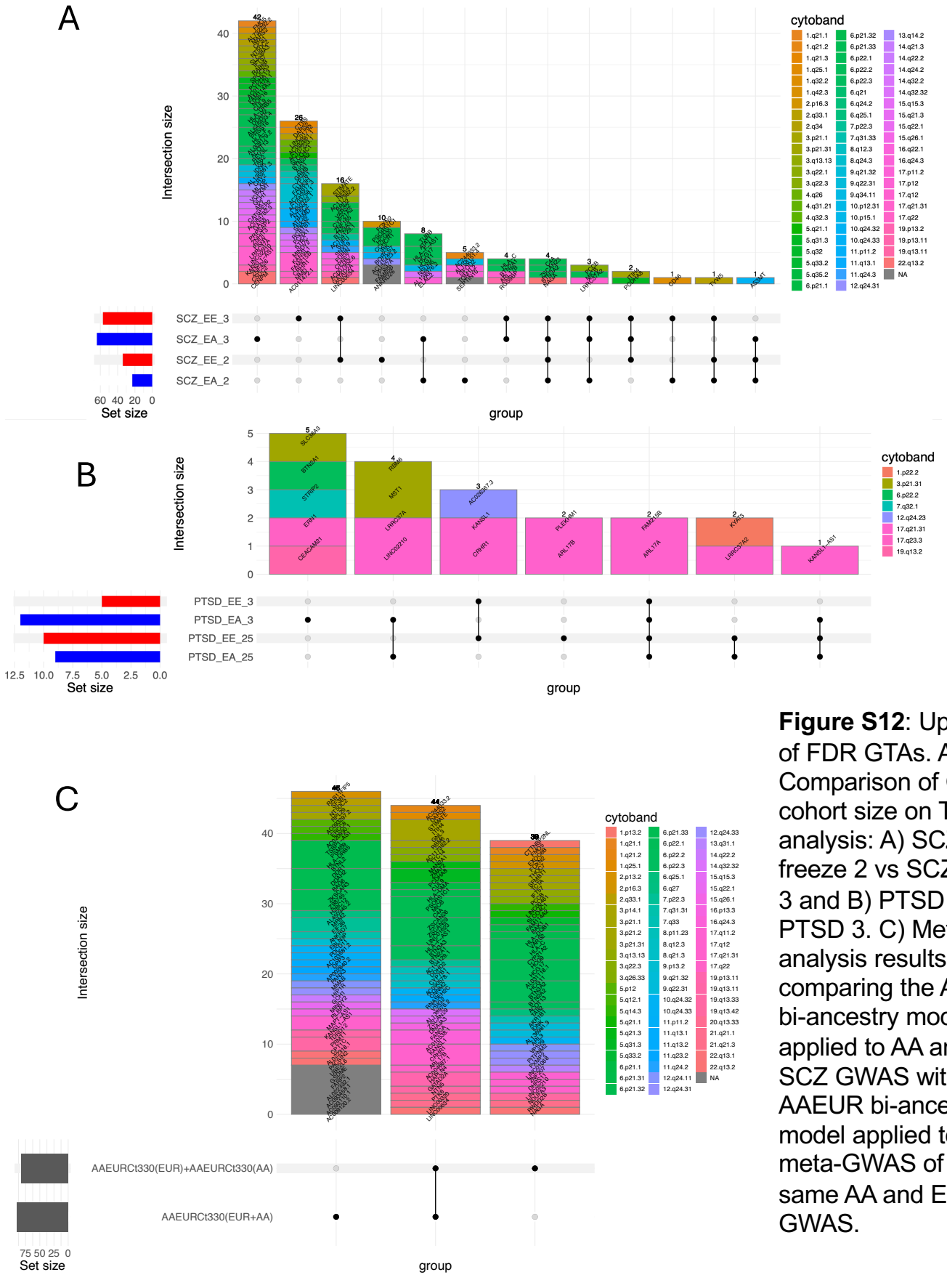


Figure S12: UpSet plot of FDR GTAs. A–B) Comparison of GWAS cohort size on TWAS analysis: A) SCZ freeze 2 vs SCZ freeze 3 and B) PTSD 2.5 vs PTSD 3. C) Meta-analysis results comparing the AAEUR bi-ancestry model applied to AA and EUR SCZ GWAS with the AAEUR bi-ancestry model applied to the meta-GWAS of the same AA and EUR GWAS.

Figure 13

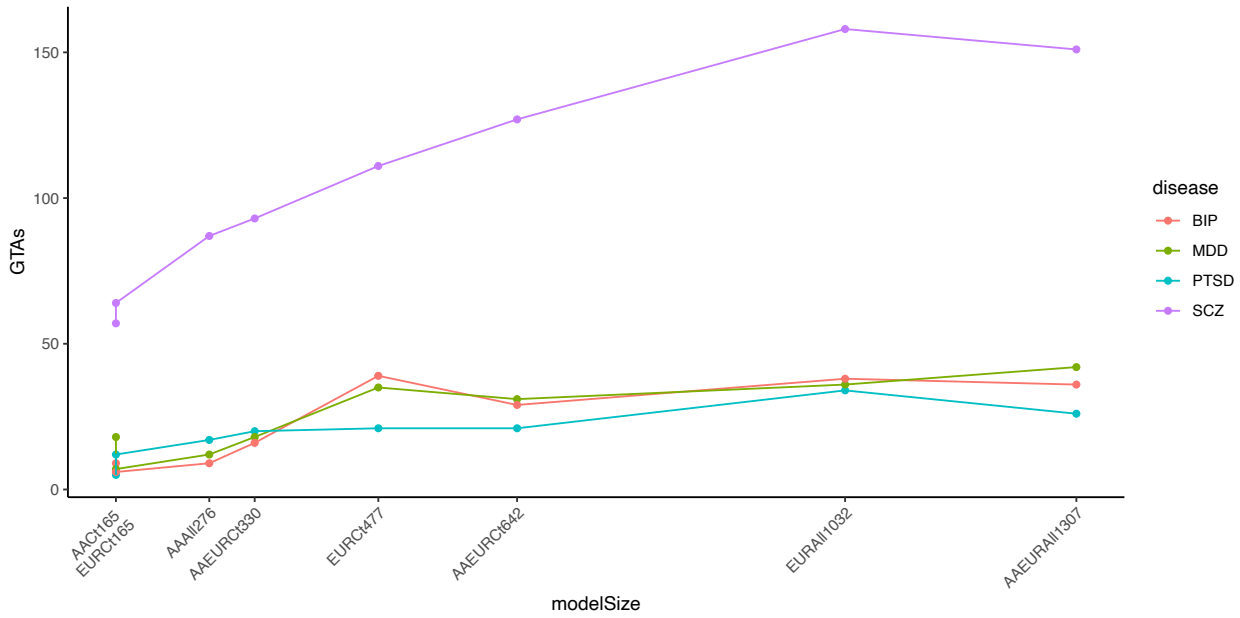


Figure S13: Number of **gene-trait associations (GTAs)** identified across increasing model sizes for BIP, MDD, PTSD, and SCZ. The x-axis represents the model sizes (AACt165, EURCt165, AAAll276, AAEURCt330, EURCt477, AAEURCt642, EURAll1032, and AAEURAll1307), while the y-axis shows the number of GTAs. SCZ consistently identifies the highest number of GTAs across all model sizes.

Figure 14

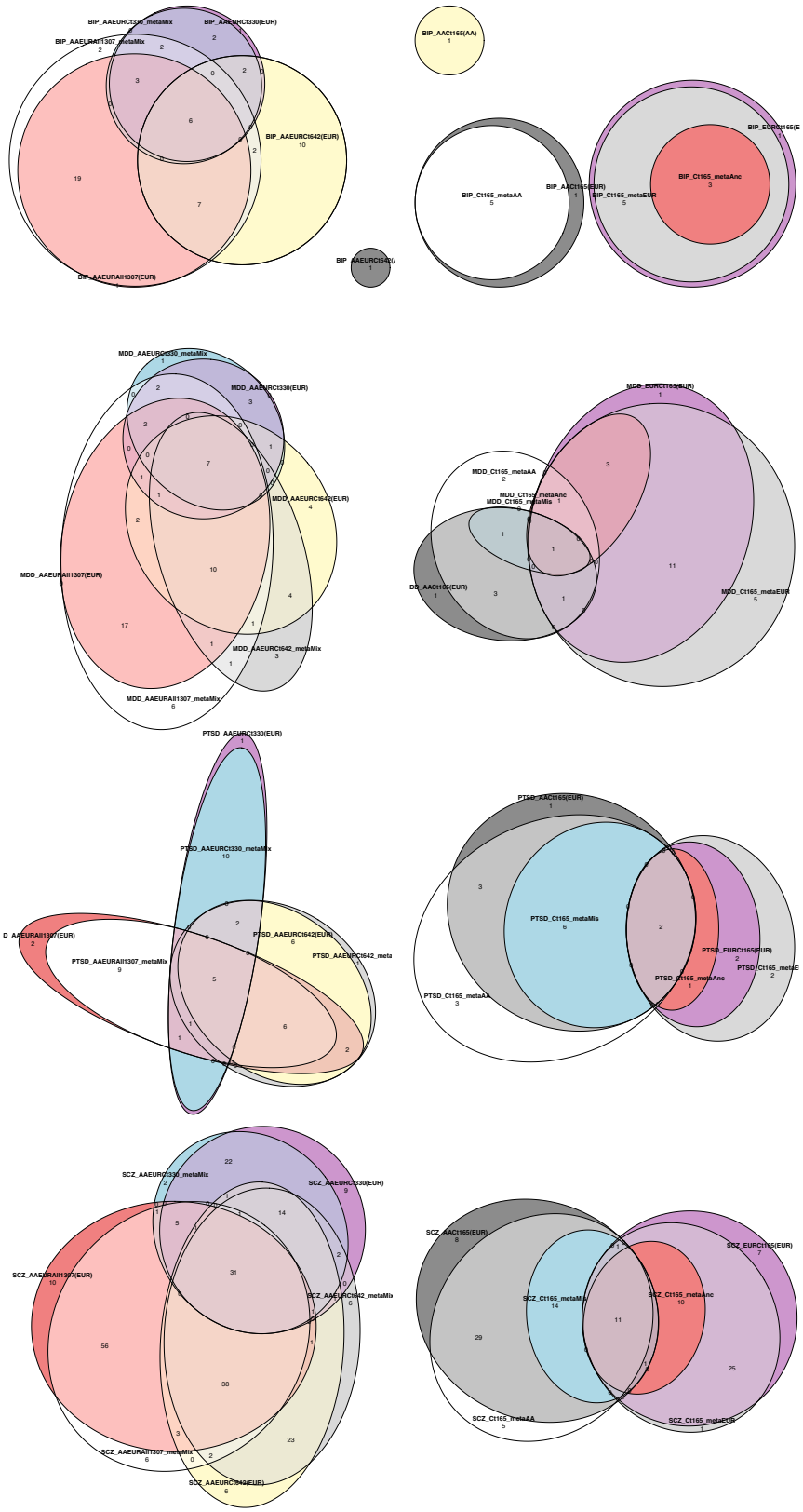


Figure **S14** Euler Plots of showing overlap of FDR GTAs across TWAS results with single-ancestry and meta TWAS results. Each row is a trait. Right ones are across Ct165 models and right across bigger EUR models

Figure 15

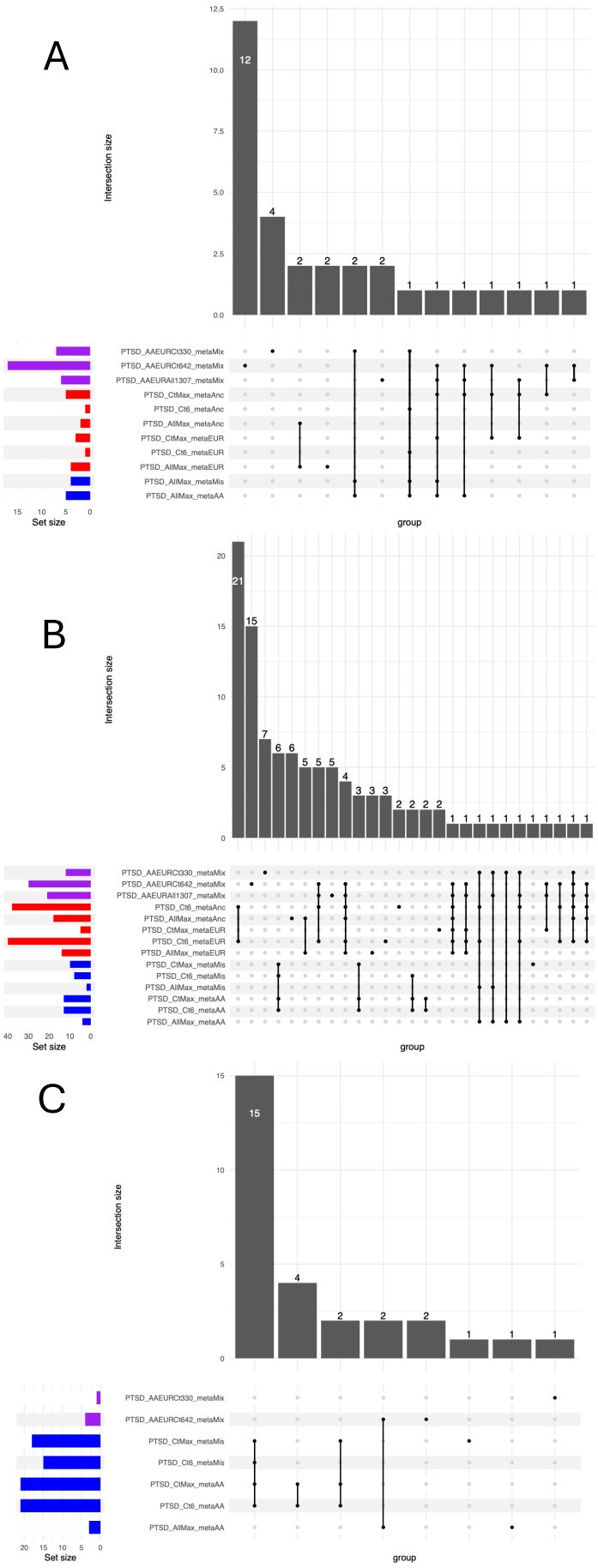


Figure S15: **PTSD FDR TWAS pathways**. UpSet plots showing PTSD FDR TWAS-pathway intersections across GReX models for three Gene Ontology (GO) categories: **A)** Biological Process (BP), **B)** Cellular Component (CC), and **C)** Molecular Function (MF).

Figure 16

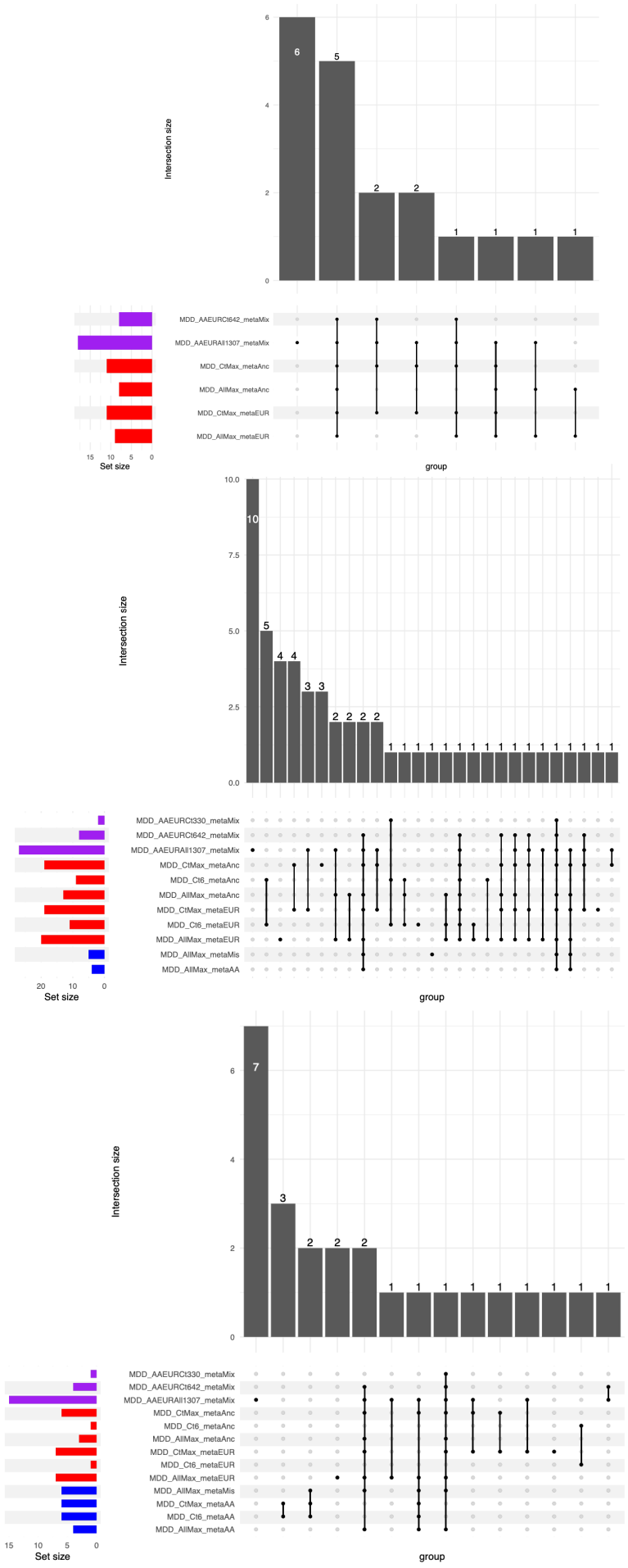
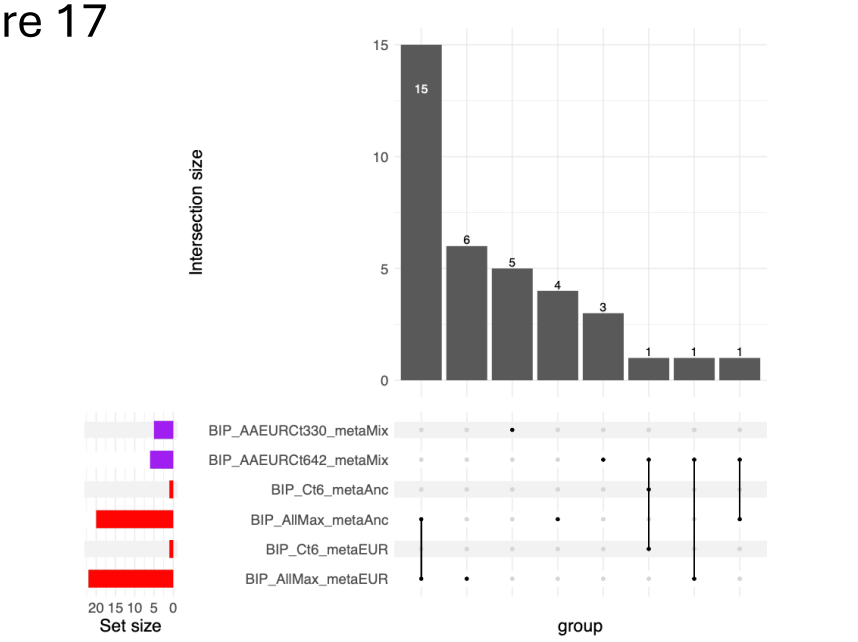
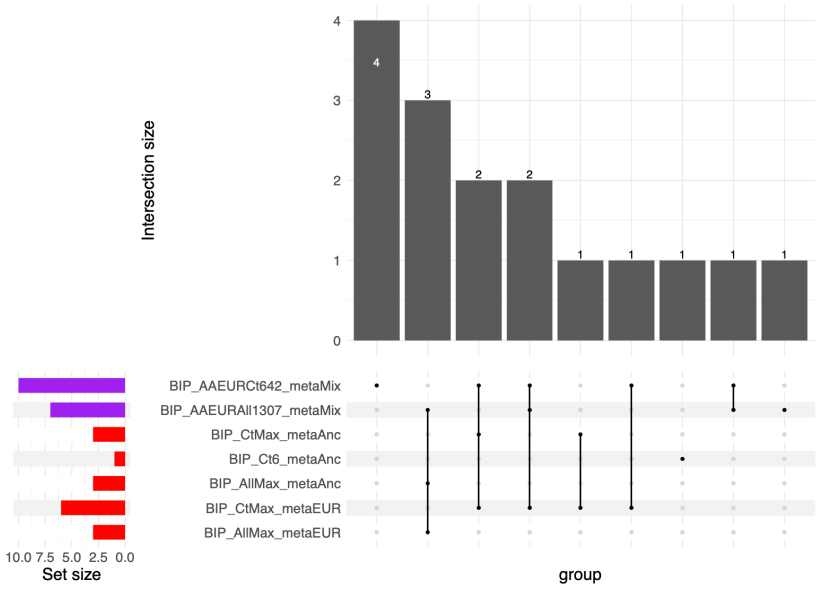


Figure S16: **MDD FDR TWAS pathways**. UpSet plots showing MDD FDR TWAS-pathway intersections across GReX models for three Gene Ontology (GO) categories: **A)** Biological Process (BP), **B)** Cellular Component (CC), and **C)** Molecular Function (MF).

Figure 17





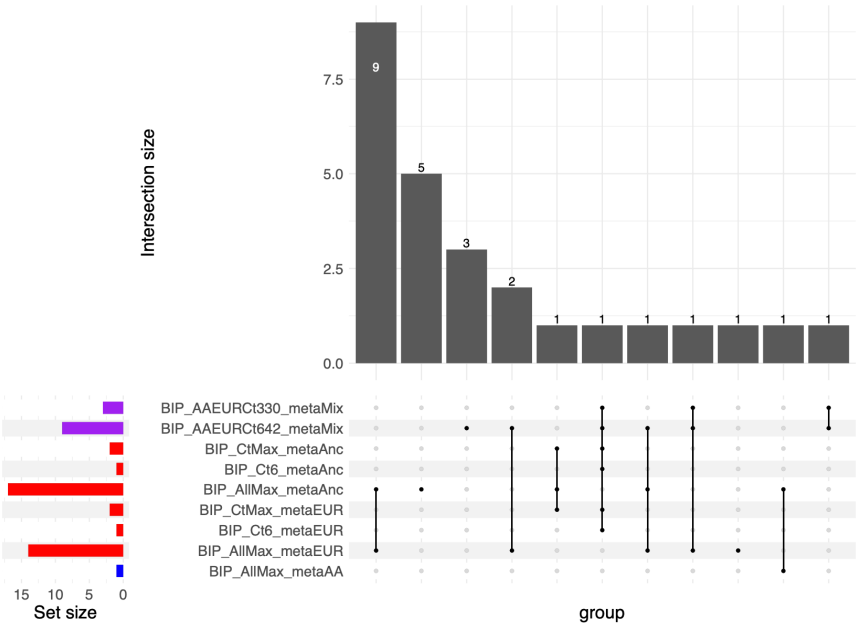


Figure S17: **BIP FDR TWAS pathways**. UpSet plots showing BIP FDR TWAS-pathway intersections across GReX models for three Gene Ontology (GO) categories: **A)** Biological Process (BP), **B)** Cellular Component (CC), and **C)** Molecular Function (MF).

Figure 18

Figure S18: **SCZ FDR TWAS pathways**. UpSet plots showing BIP FDR TWAS-pathway intersections across GReX models for three Gene Ontology (GO) categories: **A)** Biological Process (BP), **B)** Cellular Component (CC), and **C)** Molecular Function (MF).

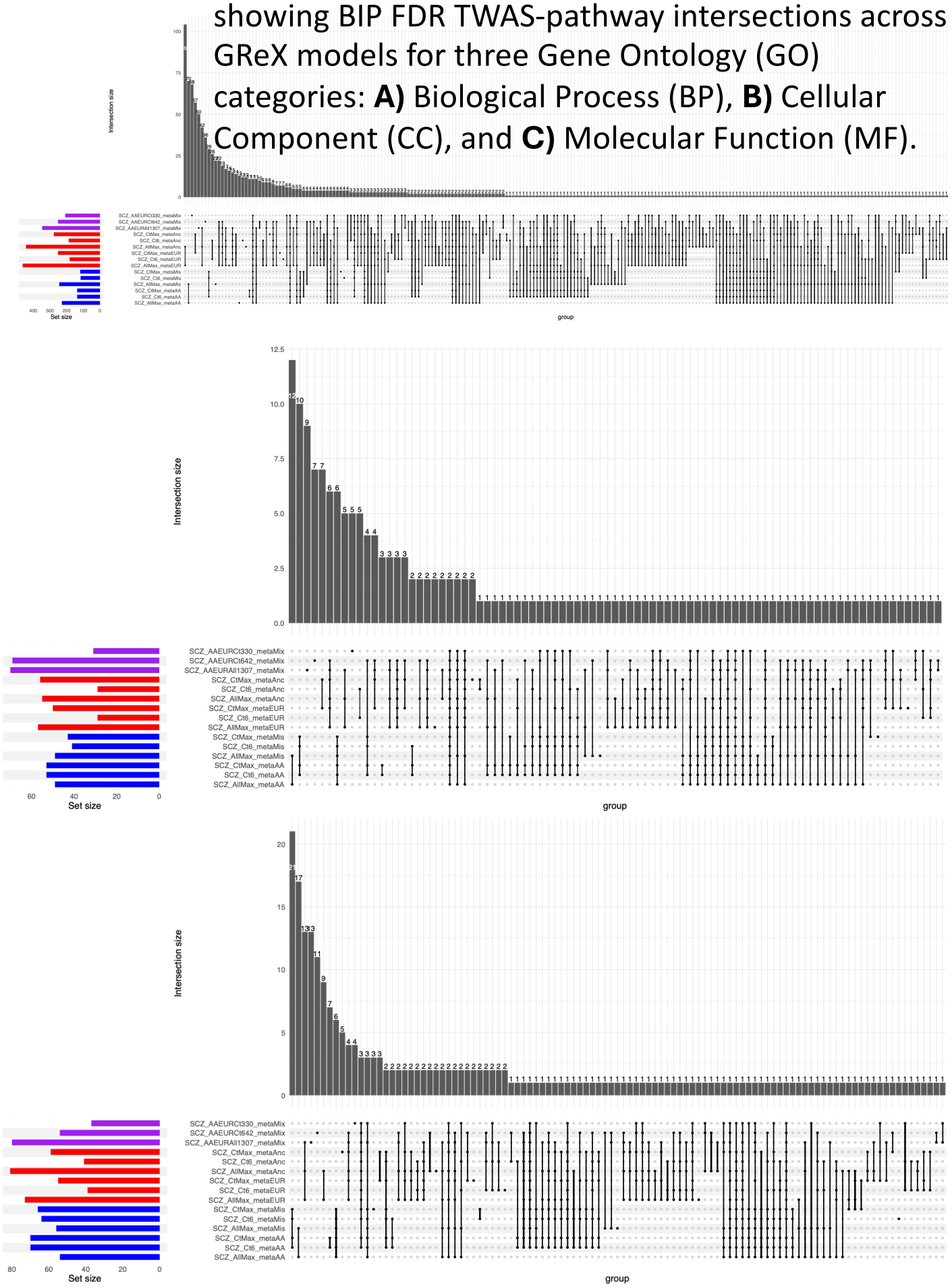


Figure 19

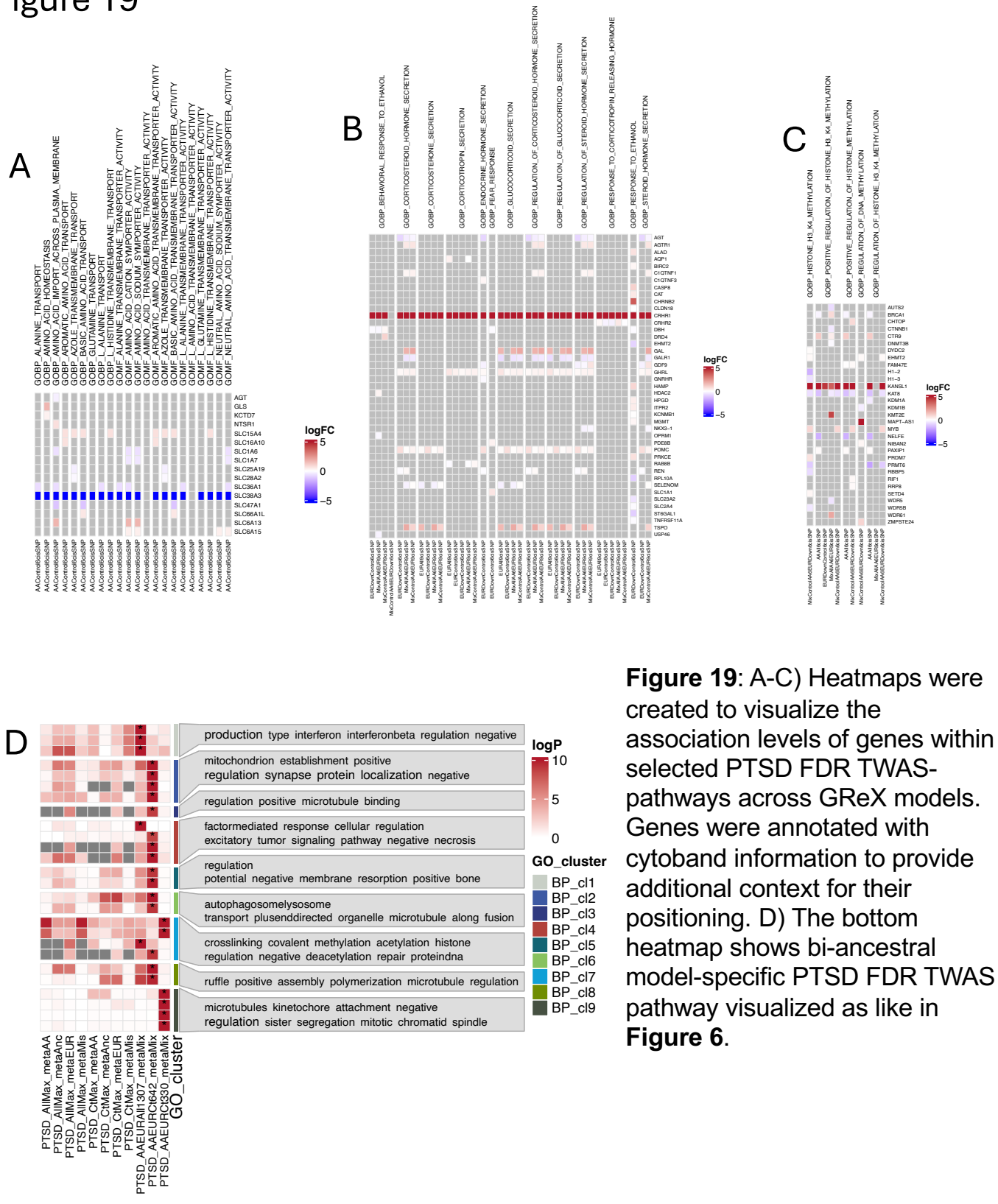


Figure 19: A-C) Heatmaps were created to visualize the association levels of genes within selected PTSD FDR TWAS-pathways across GReX models. Genes were annotated with cytoband information to provide additional context for their positioning. D) The bottom heatmap shows bi-ancestral model-specific PTSD FDR TWAS pathway visualized as like in **Figure 6**.

Figure 20

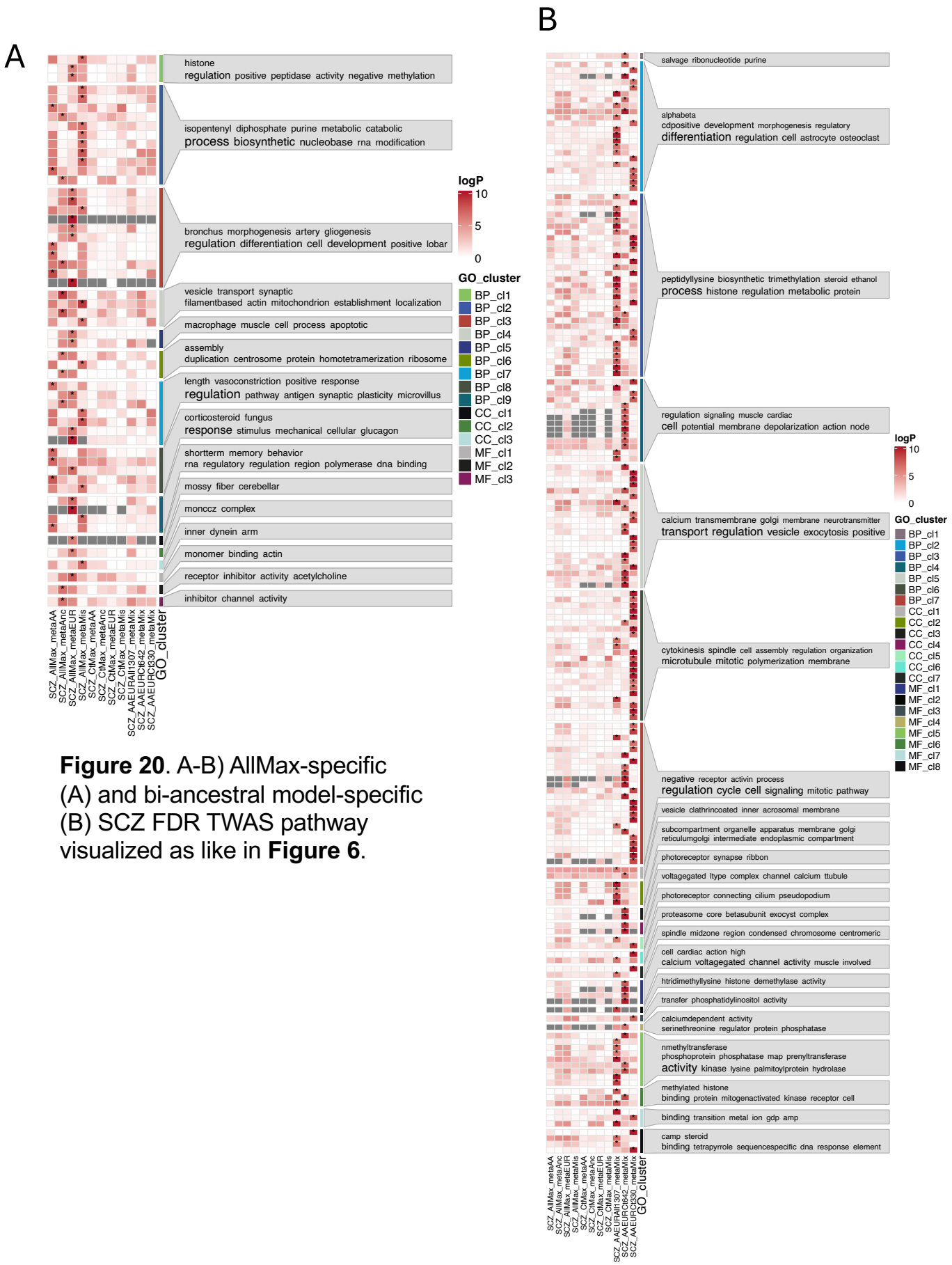


Figure 20. A-B) AllMax-specific (A) and bi-ancestral model-specific (B) SCZ FDR TWAS pathway visualized as like in **Figure 6**.

Figure 21

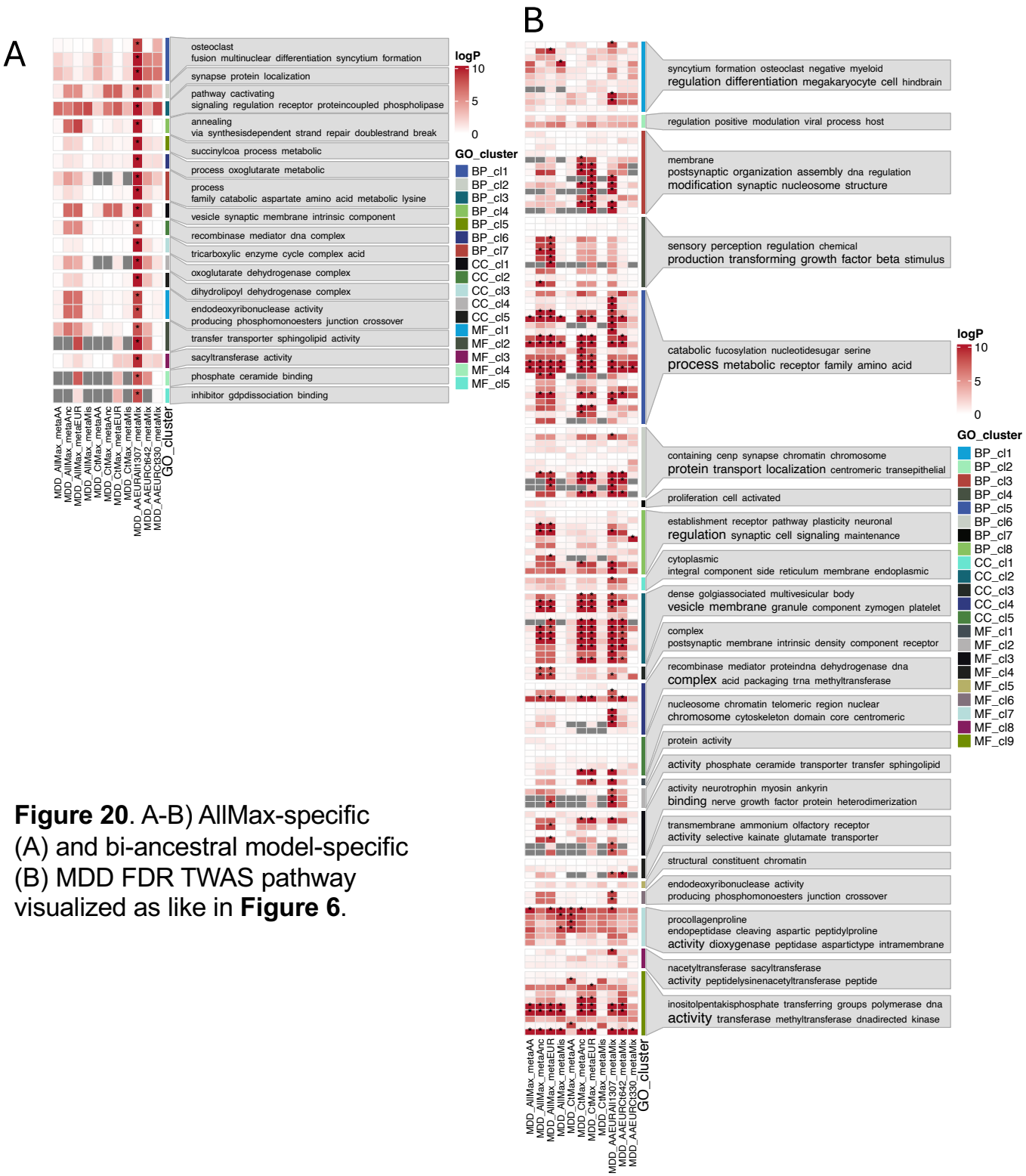


Figure 20. A-B) AllMax-specific (A) and bi-ancestral model-specific (B) MDD FDR TWAS pathway visualized as like in **Figure 6**.

Figure 22

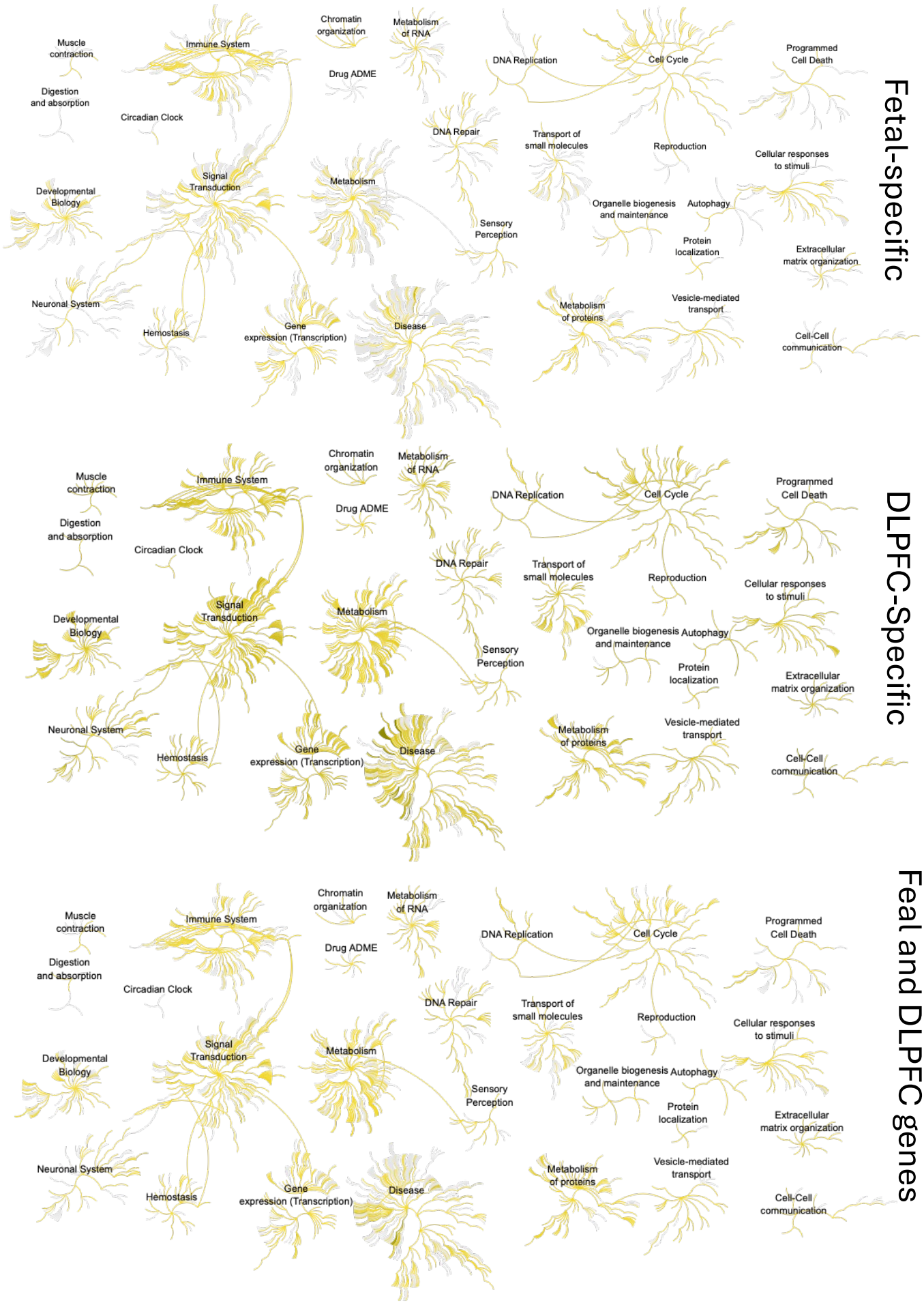
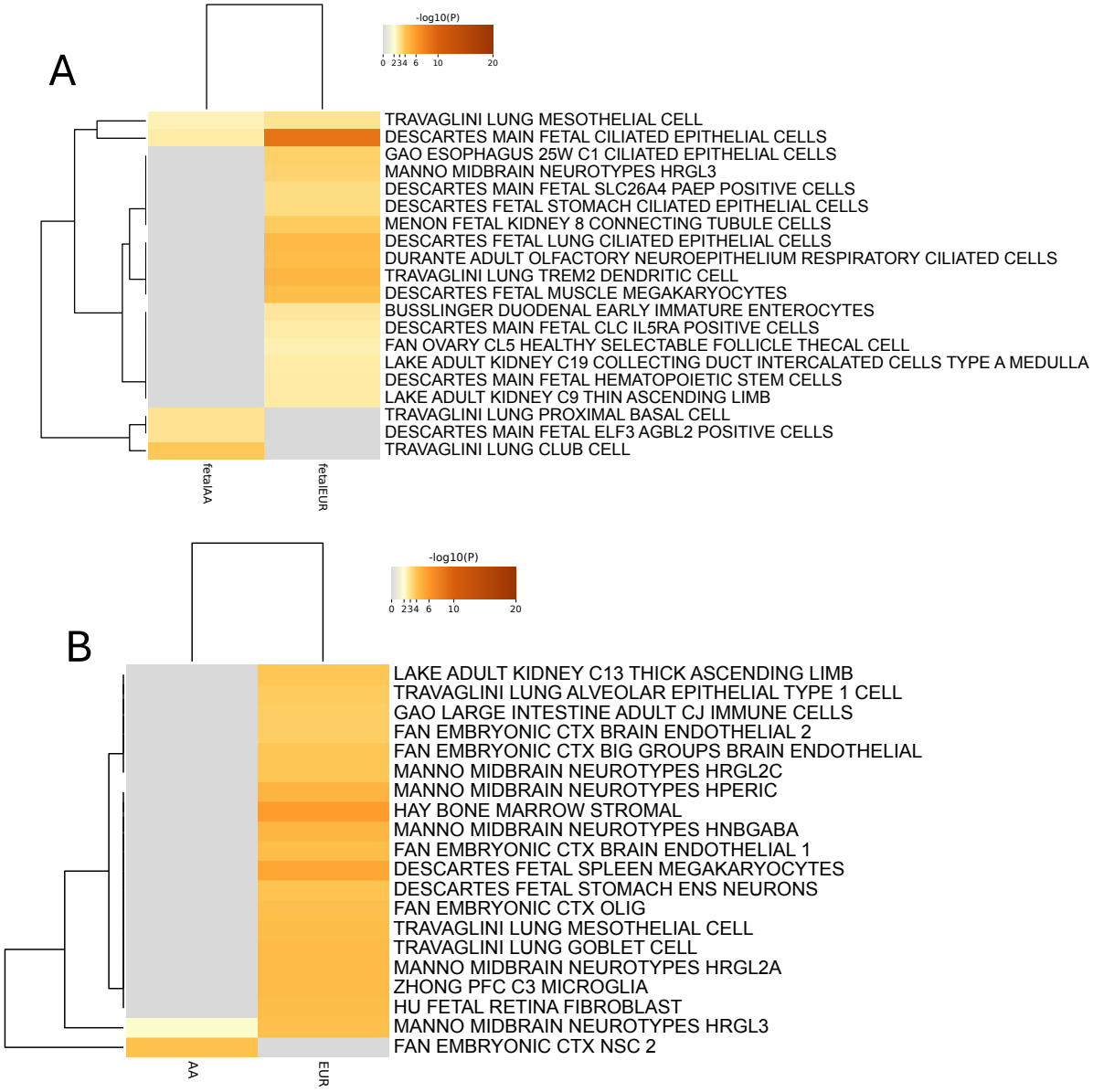

Fetal-specific
DLPFC-Specific
Feal and DLPFC genes
Muscle contraction
Immune System
Chromatin organization
Metabolism of RNA
Digestion and absorption
Drug ADME
DNA Replication
Cell Cycle
Programmed Cell Death
Circadian Clock
DNA Repair
Transport of small molecules
Reproduction
Cellular responses to stimuli
Developmental Biology
Signal Transduction
Metabolism
Organelle biogenesis and maintenance
Autophagy
Sensory Perception
Protein localization
Extracellular matrix organization
Neuronal System
Hemostasis
Gene expression (Transcription)
Disease
Metabolism of proteins
Vesicle-mediated transport
Cell-Cell communication

Figure 22: **Reactome over-representation analysis**. GReX model predicted genes are grouped into three categories: Fetal-specific (top), DLPFC-specific (middle), and genes shared between Fetal and DLPFC (bottom).

Figure 23



Cell type enrichment using online metascape software. A. DLPFC predicted gens B. fetal predicted genes

Figure 24

Figure 4: fetal FDR-GTA overlaps within trait UpSet plots visualizing the intersection of FDR-GTAs within each trait for matched and mismatched ancestry TWAS associated with fetal pair. Bars represent the intersection sizes and the bar colors represent cytobands of GTAs. Horizontal bars indicate the total number of GTAs in each group. (A) BIP, (B) MDD, (C) PTSD, and (D) SCZ.

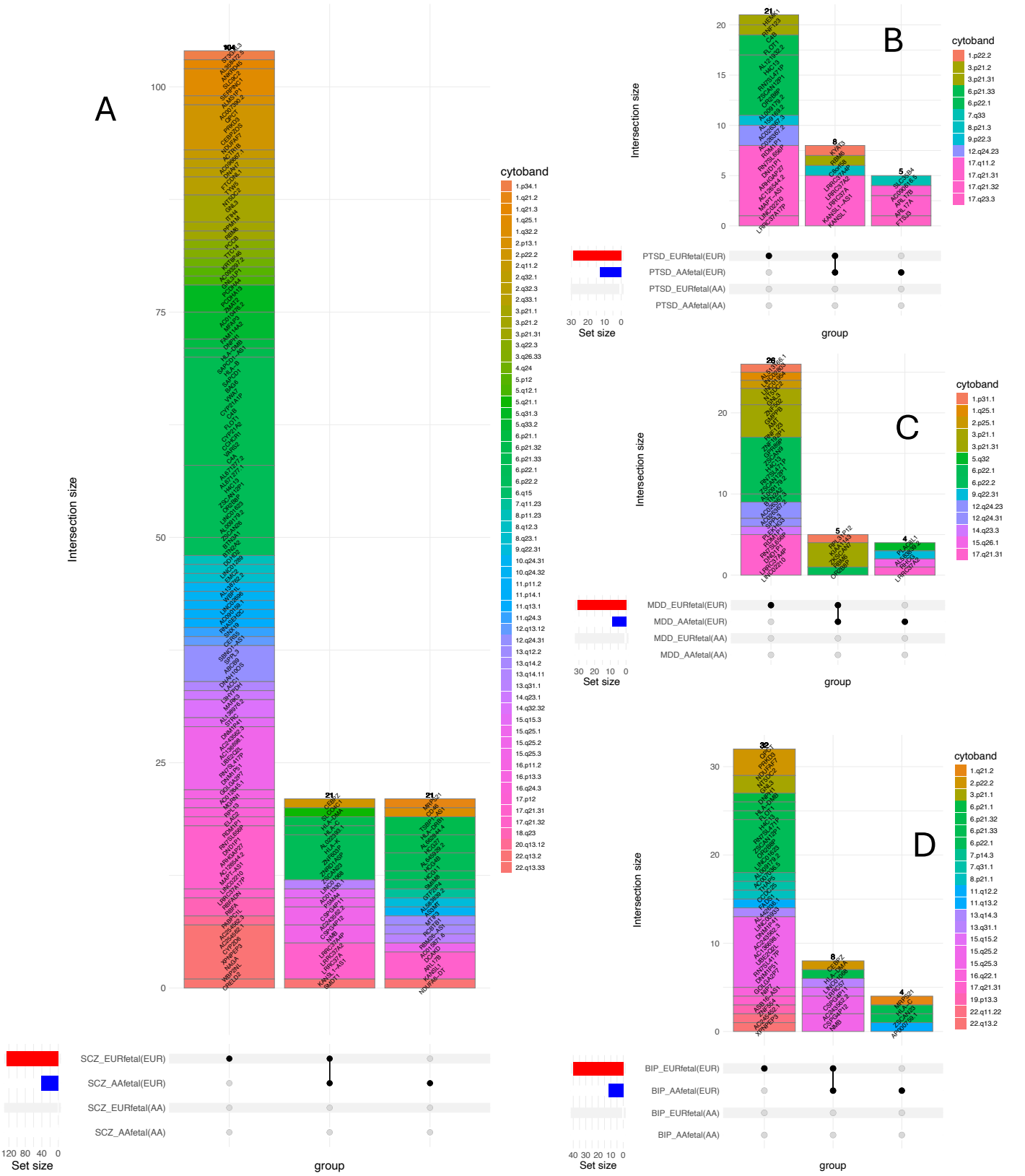


Figure 25

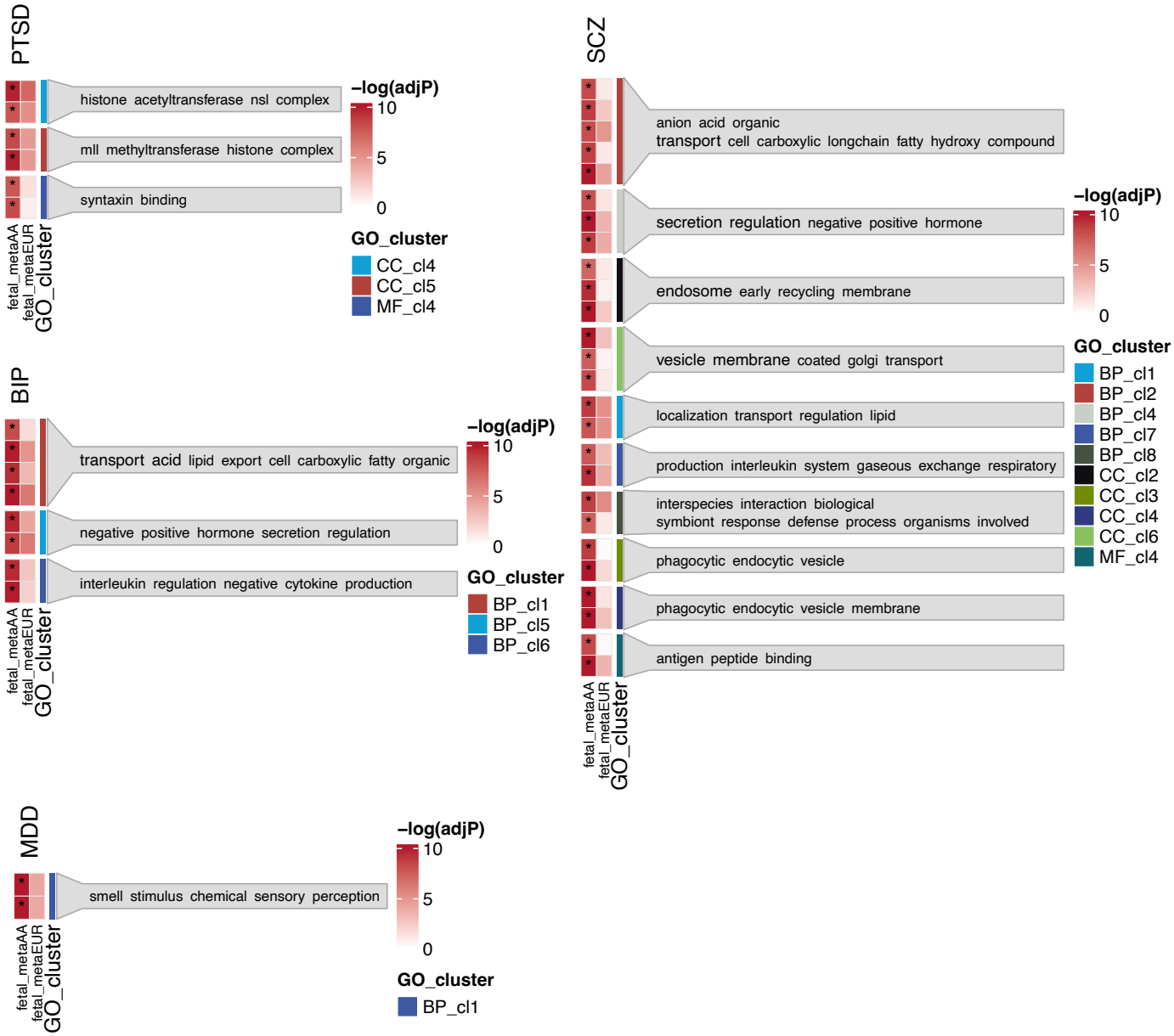


Figure S25: **fetalAA-specific FDR-significant pathways**. Pathways are visualized similarly to **Figure 6**.

Figure 26

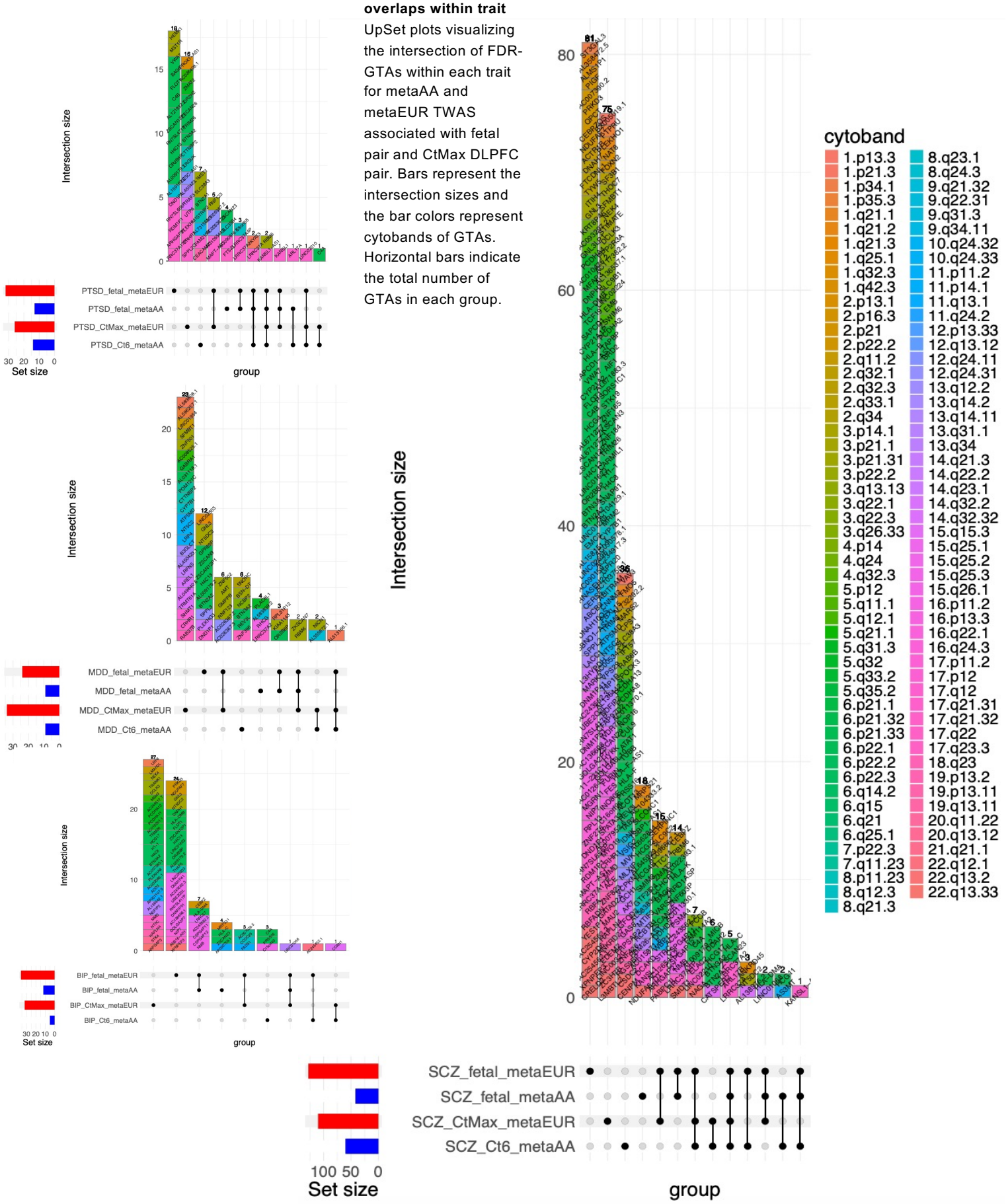


Figure 26: fetaland DLPFC FDR-GTA overlaps within trait
UpSet plots visualizing the intersection of FDR-GTAs within each trait for metaAA and metaEUR TWAS associated with fetal pair and CtMax DLPFC pair. Bars represent the intersection sizes and the bar colors represent cytobands of GTAs. Horizontal bars indicate the total number of GTAs in each group.

Figure 27

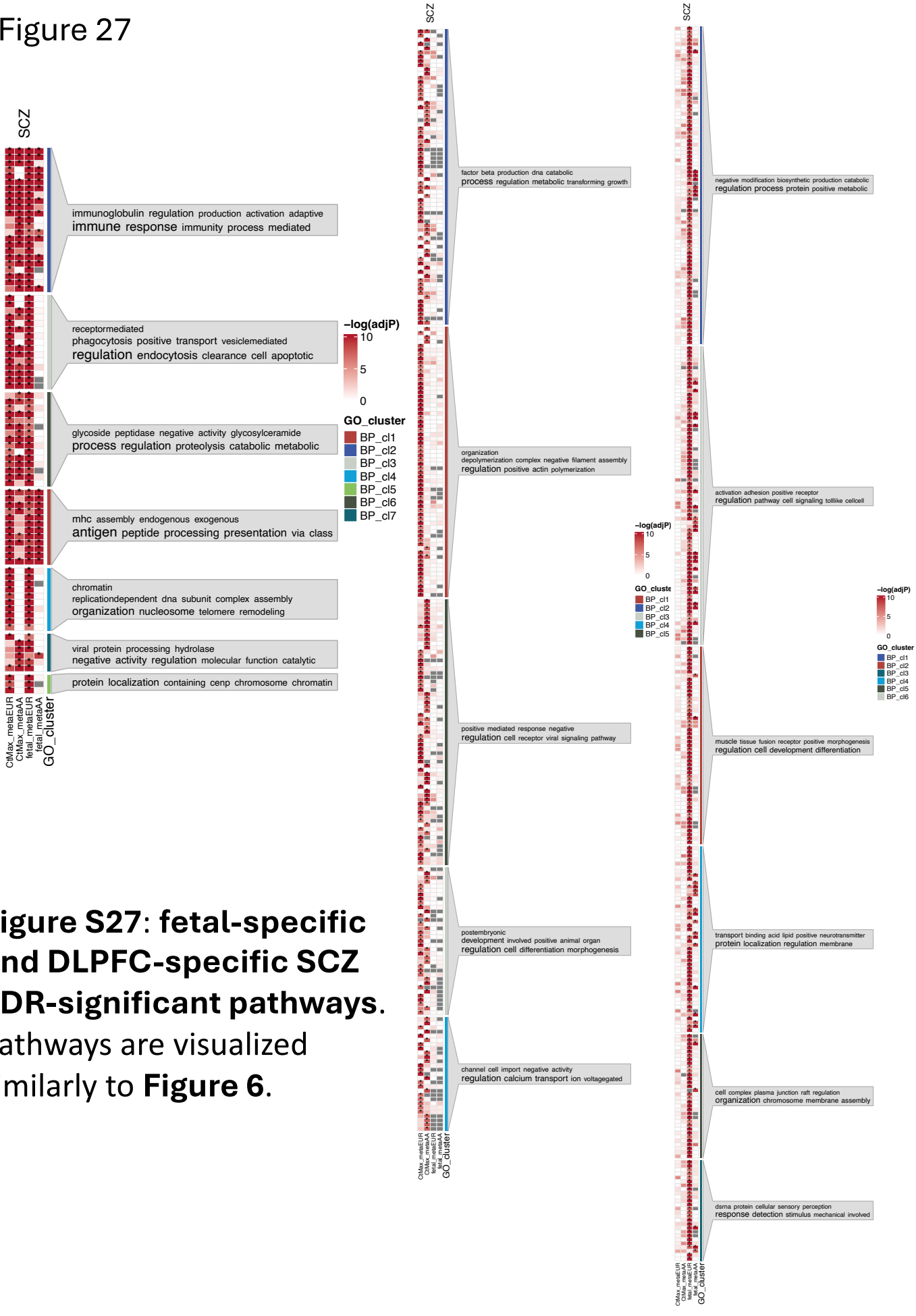


Figure S27: **fetal-specific and DLPFC-specific SCZ FDR-significant pathways**. Pathways are visualized similarly to **Figure 6**.

Figure 28

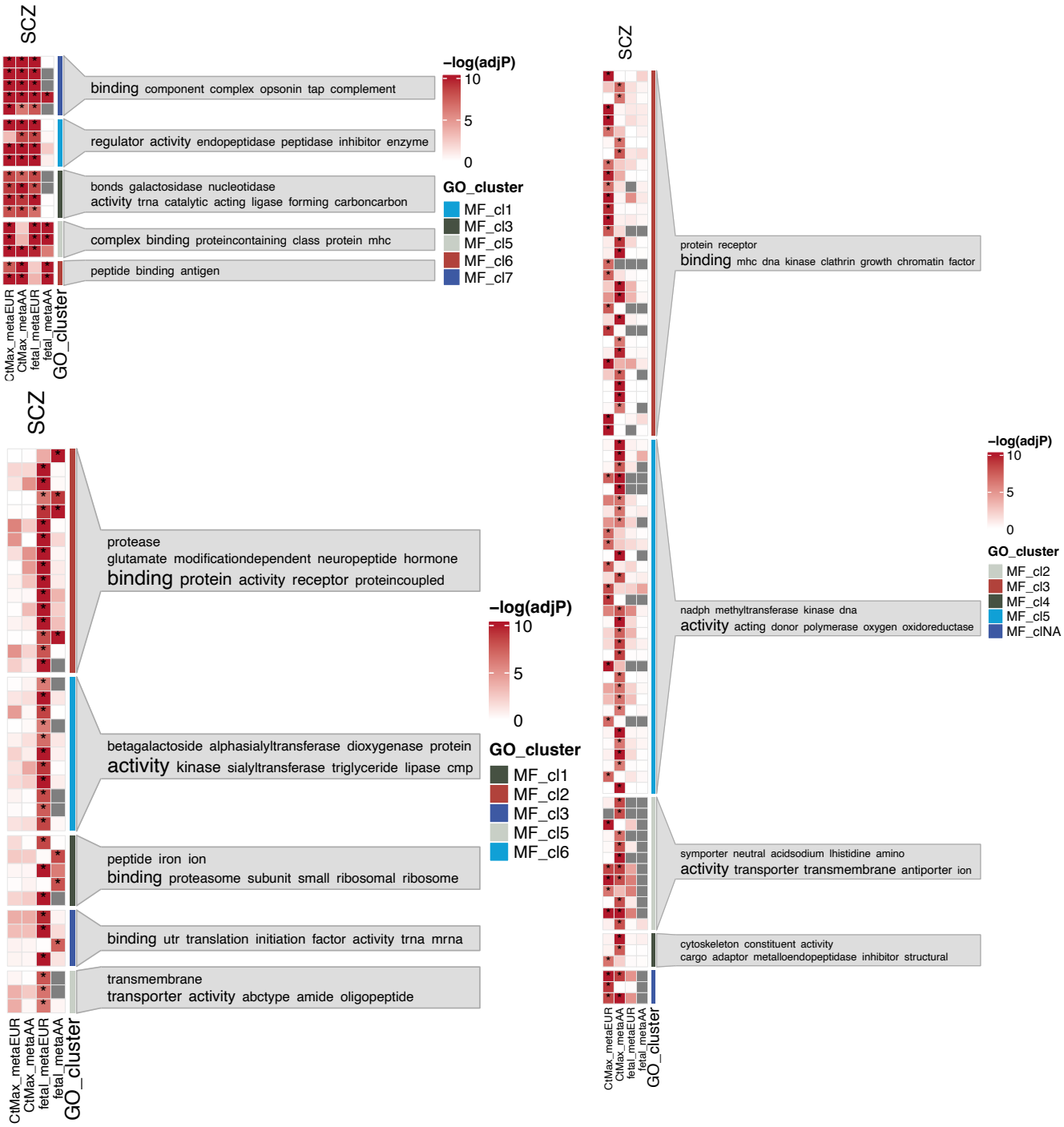


Figure S28: **fetal-specific and DLPFC-specific SCZ FDR-significant pathways**. Pathways are visualized similarly to **Figure 6**.

Figure 29

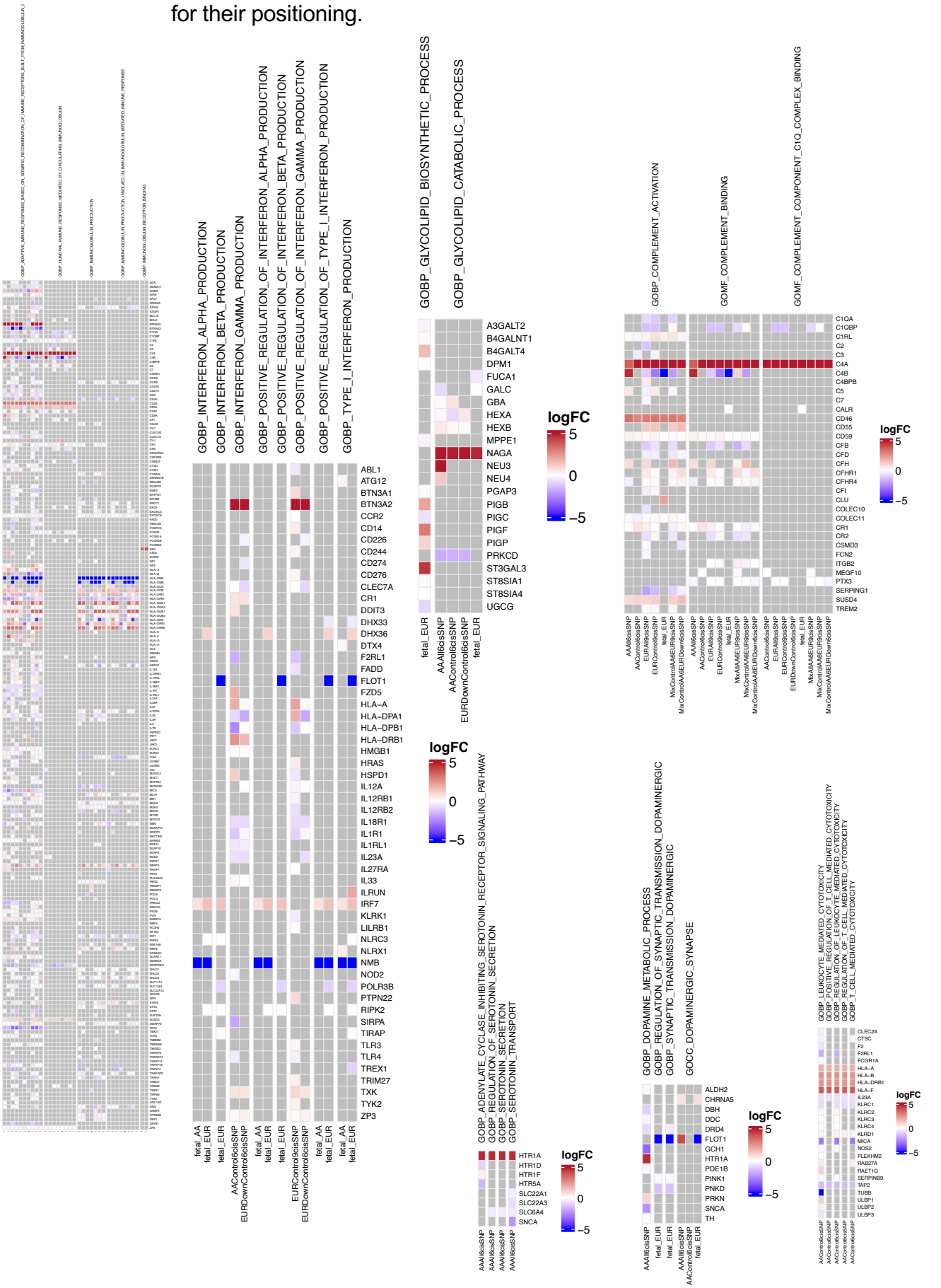


Figure 29: Heatmaps were created to visualize the association levels of genes within selected SCZ FDR TWAS-pathways across GReX models. Genes were annotated with cytoband information to provide additional context for their positioning.

Figure 30

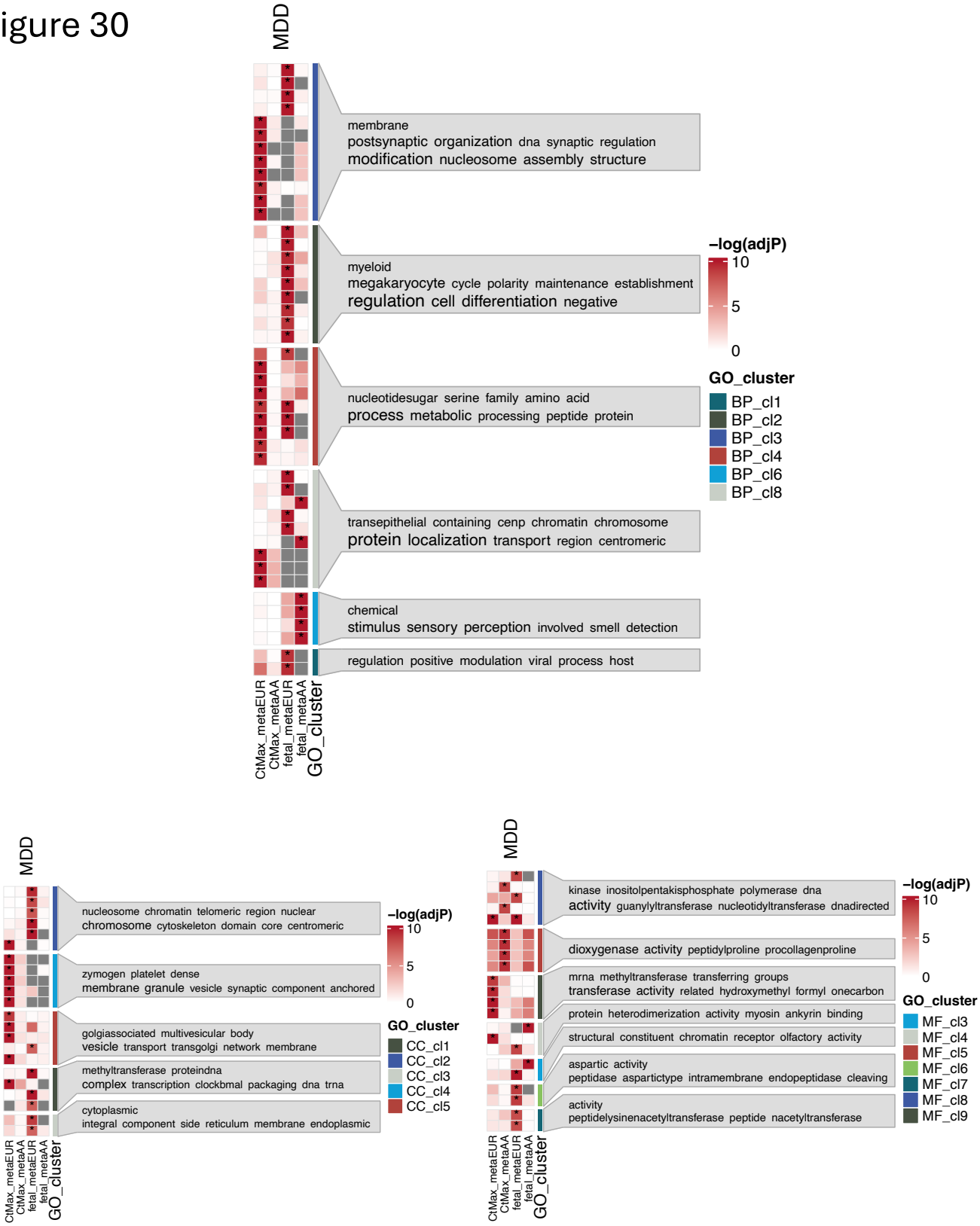


Figure S29: fetal-specific and DLPFC-specific MDD FDR-significant pathways. Pathways are visualized similarly to **Figure 6**.

Figure S31: **Shared FDR-significant pathways across pairs of disorders**. Pathways are visualized similarly to **Figure 6**.

Figure S32: Shared FDR-significant pathways across disorders. Pathways are visualized similarly to **Figure 6.**