**Cell Genomics, Volume *4***

## Supplemental information

# Effects of gene dosage on cognitive ability:

# A function-based association study

# across brain and non-brain processes

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# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

**List of supplementary tables and figures:**

**Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes**

## Supplementary tables

| Cohort | | Array type | N= | Ancestry | | Gender | | Age (year) | | Z-scored intelligence measure (adj) | | | Cognitive ability assessments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EUR | Others | F | M | Mean | SD | Mean | SD | Variables | |
| Unselected (n=258,292) | CaG | GSA | 2074 | 1982 | 92 | 1094 | 980 | 54.317 | 7.601 | 0.107 | 0.973 | Age, Age^2, sex, PC | g-factor, Reasoning, Memory, Reaction time |
| | | Omni2.5 | 515 | 490 | 25 | 281 | 234 | 52.437 | 8.602 | -0.009 | 0.956 | | |
| | | GSA + Omni2.5 | 2589 | 2472 | 117 | 1375 | 1214 | 53.943 | 7.845 | 0.084 | 0.970 | | |
| | G-Scot | 610Kq | 13715 | 13672 | 43 | 8081 | 5634 | 46.730 | 14.996 | 0.050 | 0.974 | Age, Age^2, sex, PC | g-factor, Logical Memory, Digit Symbol, Verbal fluency, Mill Hill Vocabulary |
| | Imagen | 610Kq; 660Wq | 1744 | 1624 | 120 | 891 | 853 | 14.450 | 0.366 | 0.441 | 0.977 | PC | WISC-IV |
| | LBC1936 | 610Kq | 503 | 500 | 3 | 246 | 257 | 69.825 | 0.829 | 0.047 | 0.946 | PC | Moray House Test |
| | SYS children | 610Kq | 559 | 557 | 2 | 298 | 261 | 15.058 | 1.894 | 0.361 | 0.882 | PC | WISC-III |
| | | HOE-12V | 408 | 408 | 0 | 207 | 201 | 14.906 | 1.760 | 0.212 | 0.848 | | |
| | | 610Kq + HOE-12V | 967 | 965 | 2 | 505 | 462 | 14.994 | 1.839 | 0.298 | 0.871 | | |
| | SYS parents | HOE-12V | 598 | 596 | 2 | 319 | 279 | 49.495 | 4.868 | -0.021 | 0.934 | Age, Age^2, sex, PC | g-factor, 12 cognitive measures‡ |
| | UKBB | Affymetrix | 73882 | 71364 | 2518 | 39317 | 34565 | 60.022 | 8.959 | 0.131 | 0.964 | Age, Age^2, sex, PC | g-factor [47] |
| | | | 62080 | 60484 | 1596 | 34335 | 27745 | 62.083 | 7.663 | 0.131 | 0.926 | | g-factor (online) |
| | | | 88441 | 80427 | 8014 | 47789 | 40652 | 58.139 | 8.304 | -0.035 | 0.961 | | FI |
| | | | 13773 | 13458 | 315 | 8284 | 5489 | 64.185 | 7.685 | -0.090 | 0.970 | | FI (online) |
| Autism (n=6,111) | SPARK | GSA | 2543 | 1984 | 559 | 540 | 2003 | 12.359 | 6.190 | -0.626 | 1.963 | PC | IQ |
| | MSSNG | WGS | 1007 | 768 | 239 | 202 | 805 | 9.503* | 4.600* | -0.529 | 1.590 | PC | IQ |
| | SSC | 1Mv1 | 332 | 279 | 53 | 44 | 288 | 9.538 | 3.240 | -0.602 | 1.558 | PC | WISC-IV n=19; DAS-II E-Y n=96; DAS-II S-A n=179; Mullen n=12; WASI-I n=26 |
| | | 1Mv3 | 1181 | 915 | 266 | 156 | 1025 | 8.769 | 3.523 | -0.982 | 1.638 | | WISC-IV n=16; DAS-II E-Y n=530; DAS-II S-A n=539; Mullen n=77; WASI-I n=19 |
| | | Omni2.5 | 1048 | 786 | 262 | 140 | 908 | 9.160 | 3.712 | -1.227 | 1.834 | | WISC-IV n=10; DAS-II E-Y n=403; DAS-II S-A n=494; Mullen n=124; WASI-I n=17 |
| | | 1Mv1 + 1Mv3 + Omni2.5 | 2561 | 1980 | 581 | 340 | 2221 | 9.028 | 3.576 | -1.033 | 1.722 | | WISC-IV n=45; DAS-II E-Y n=1,029; DAS-II S-A n=1,212; Mullen n=213; WASI-I n=62 |

Table S6. Cohort descriptions, Related to Table 1.

Cohorts include 264,403 individuals, including 258,292 general populations. †63 and ‡ 12 cognitive measures were respectively used to compute the g-factor in SYS children and parents (Huguet et al 2021). SYS: Saguenay Youth Study, CaG: CARTaGEN, LBC1936: Lothian Birth Cohort 1936, SSC: Simons Simplex Collection; n=number of individuals remaining for analysis after quality control. The mean and Standard Deviation (SD) for FI and g-factor slightly deviate from 0 and 1 in some cohorts since they were computed on all available data (before the exclusion of some individuals for poor quality array) and summarized here only for individuals included in the analyses. * The MSSNG cohort gave participants years but for not all, for 280 age was missing.

# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

| Field name | Clinic value | | Online value | |
|---|---|---|---|---|
| | code | Lyall et al 2016[47] | code | Gfact 5 Online |
| **Fluid intelligence score** | 20016 | use | 20191 | use |
| **Trail making #2** | 6350 | - | 20157 | use |
| **Symbol digit substitution** | 23324 | - | 20159 | use |
| **Pairs matching** | 399 | use | 20132 | use |
| **Numeric memory** | 4282 | use | 20240 | use |
| **Prospective memory** | 20018 | use | - | - |
| **Mean time to correctly identify matches (Reaction time)** | 20023 | use | - | - |

Table S7. Descriptions of cognitive ability used in UKBB, Related to STAR Methods.

| Name | HPA | | | | GTEx | | | | Cell types | SynGO | LOEUF catg. | GO-term |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SD≥0.5 | SD≥1 | SD≥1.5 | SD≥2 | SD≥0.5 | SD≥1 | SD≥1.5 | SD≥2 | | | | |
| **N lists** | 215 | 215 | 215 | 215 | 37 | 37 | 37 | 37 | 29 | 85 | 38 | 6,130 |
| **Mean list size** | 3,817 | 1,975 | 1,017 | 571 | 3,056 | 2,015 | 1,173 | 787 | 890 | 120 | 1,423 | 89 |
| **N unique coding gene** | 12,710 | 12,706 | 12,449 | 12,427 | 12,755 | 12,758 | 12,751 | 12,538 | 8,422 | 921 | 13,288 | 11,460 |

Table S8. Descriptions of Gene-sets, Related to STAR Methods.

# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

## Supplementary figures

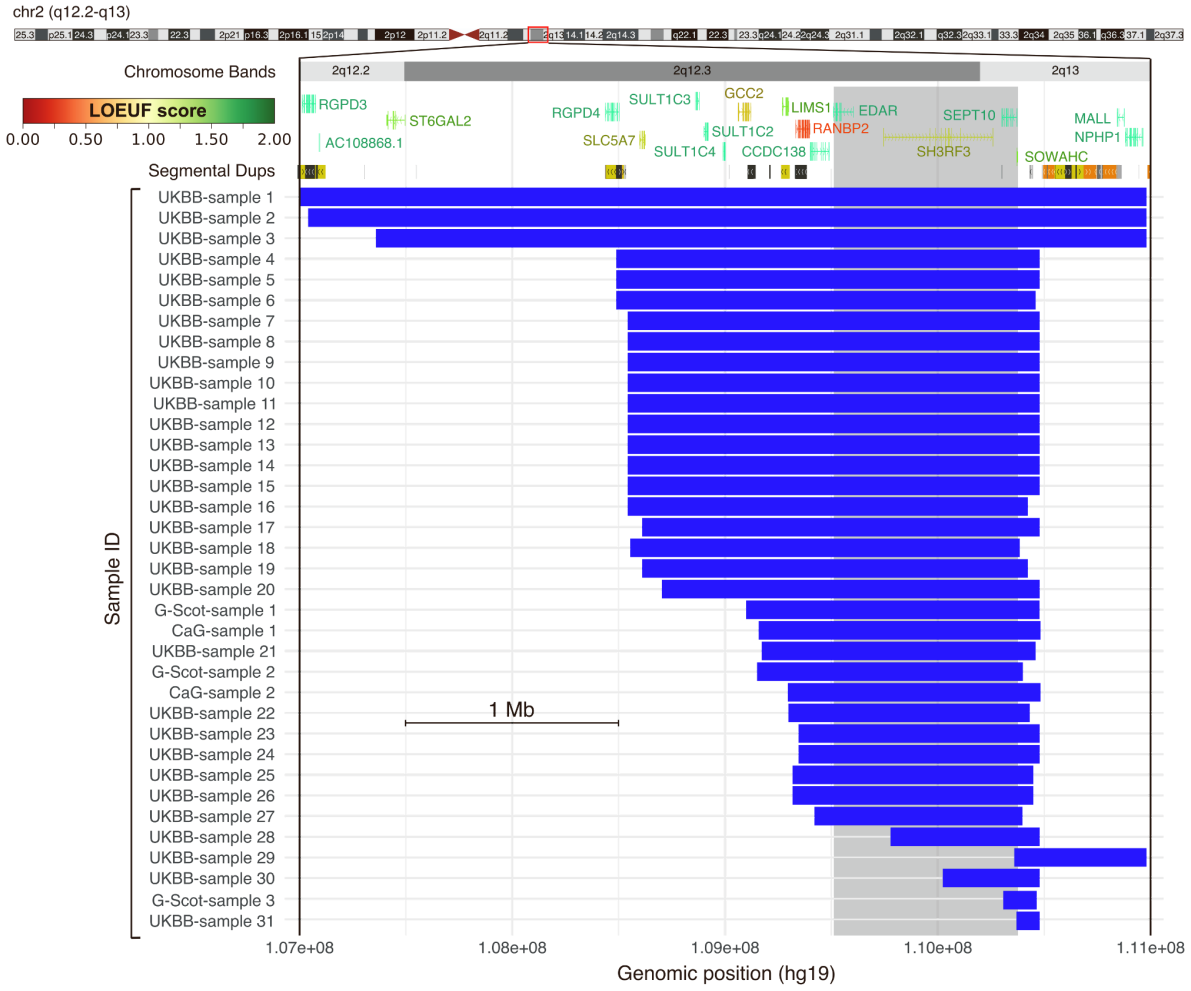


Figure S1: 36 duplications of the 2q12.3 observed in General Population, Related to Figure 1F.

This figure depicted genomic duplications (blue) occurring on chromosome 2 and overlapping with at least one of these genes: *EDAR, SH3RF3, SEPT10, SOWAHC*, in the general population. The x-axis repesented the genomic coordinates (hg19), and the y-axis listed the carriers' sample IDs. Three genomic annotations were included: chromosome bands; genes with their associated LOEUF scores; segmental duplications. LOEUF scores indicated the level of tolerance to loss-of-function for each gene, ranging from red (intolerant) to green (tolerant).

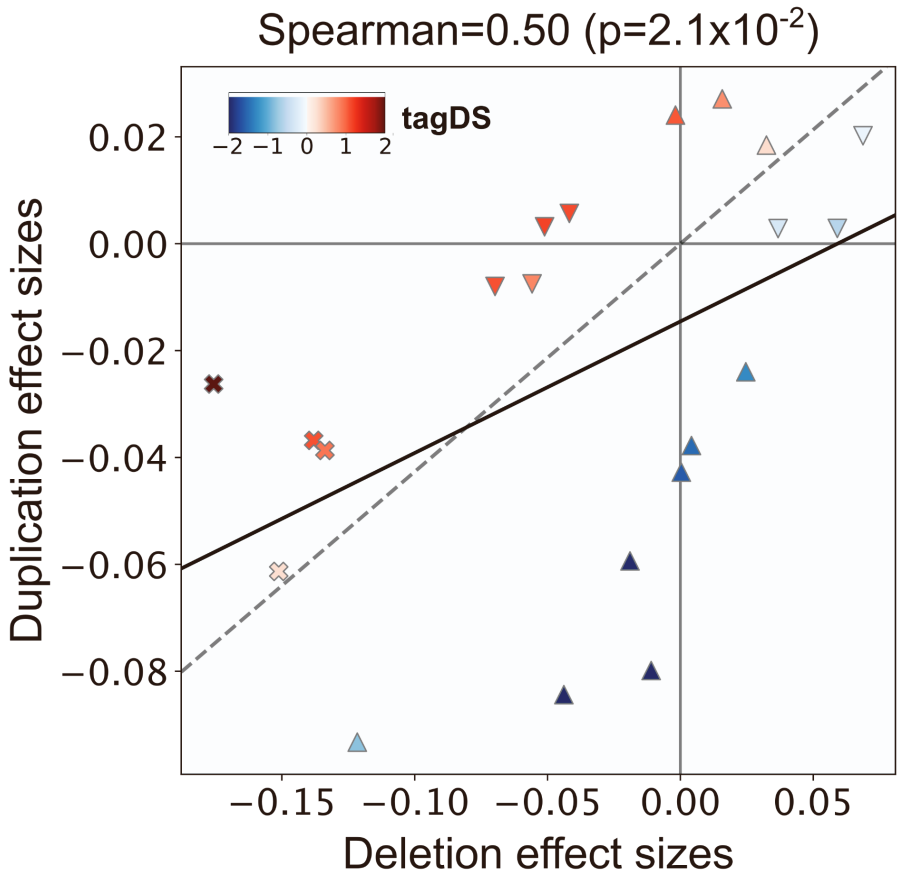


Figure S2: Correlation on cognitive ability of LOEUF categories, Related to Figure 2.

Spearman correlations (black line) between the effect sizes of deletions and duplications of gene-sets with FDR significant effects on cognitive ability for deletions (downward triangle), duplications (upward triangle), or both (cross). pvalue obtained from permutation test to account for the partial overlap between gene sets. Gene sets are color coded based on their tagDS. The dash line represents the average exome-wide duplication/deletion effect-sizes ratio

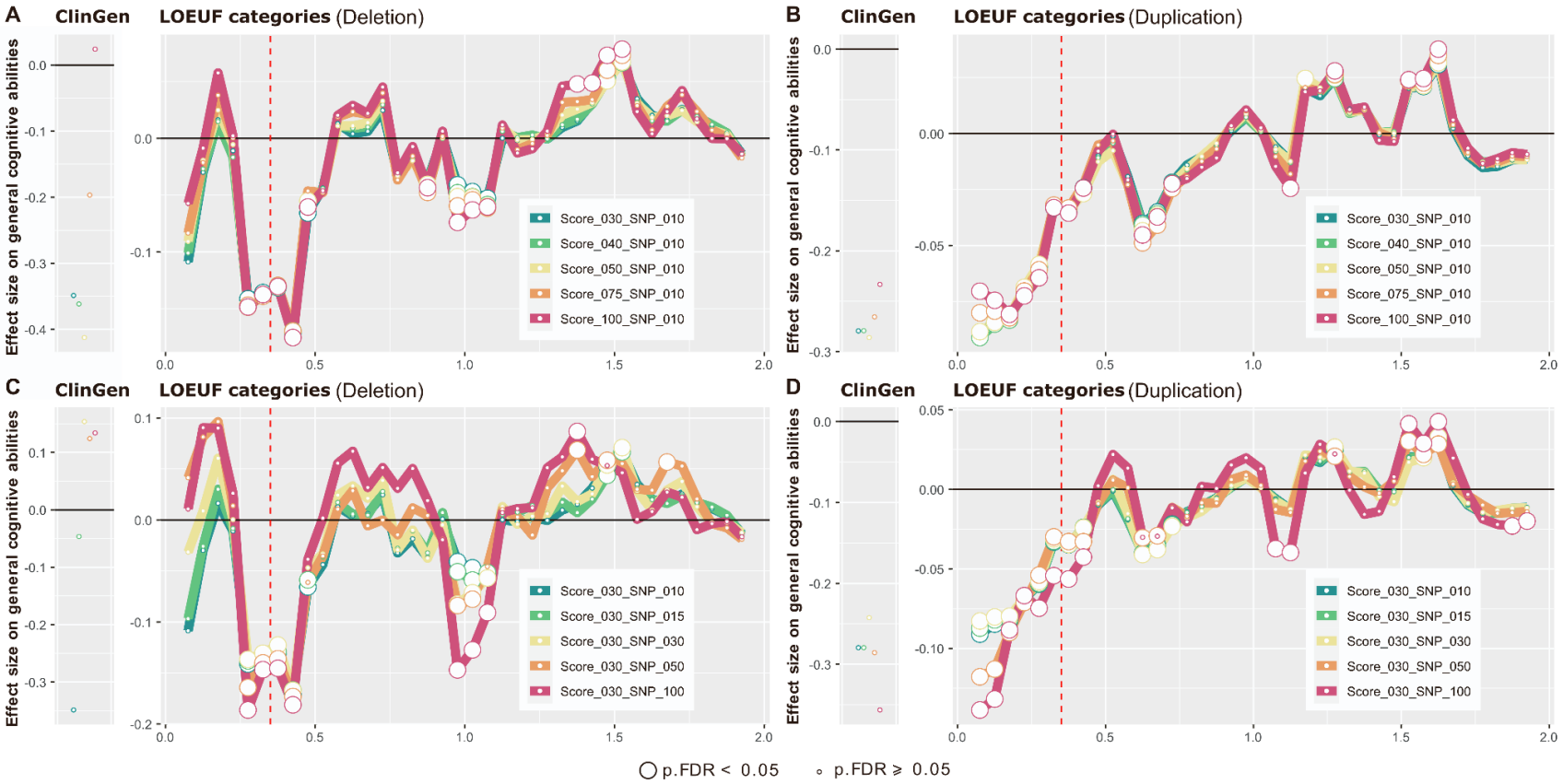


Figure S3: Effect sizes of autosomal coding genes on general cognitive abilities based on their LOEUF values, Related to Figure 2.

Sliding window estimating the effect size on cognitive ability of deletions (left) and duplications (right) for 38 LOEUF categories and definitive ID-genes curated by ClinGen (based on model 2). The line represents the estimated effect size of 38 categories of genes based on their LOEUF values in the model. Estimates were computed using a pooled dataset, large circles indicated significant pvalues adjusted by FDR and small one for non-significant. We ran sensitivity analyses based on different CNV cut-offs of quality controls with the likelihood score (Score ≥ 30, 40, 50, 75 and 100 and a fixed number of SNPs ≥10; for A and B) and numbers of SNPs inside CNV (SNPs ≥ 10, 15, 30, 50 and 100 and a fixed likelihood score ≥30; C and D).

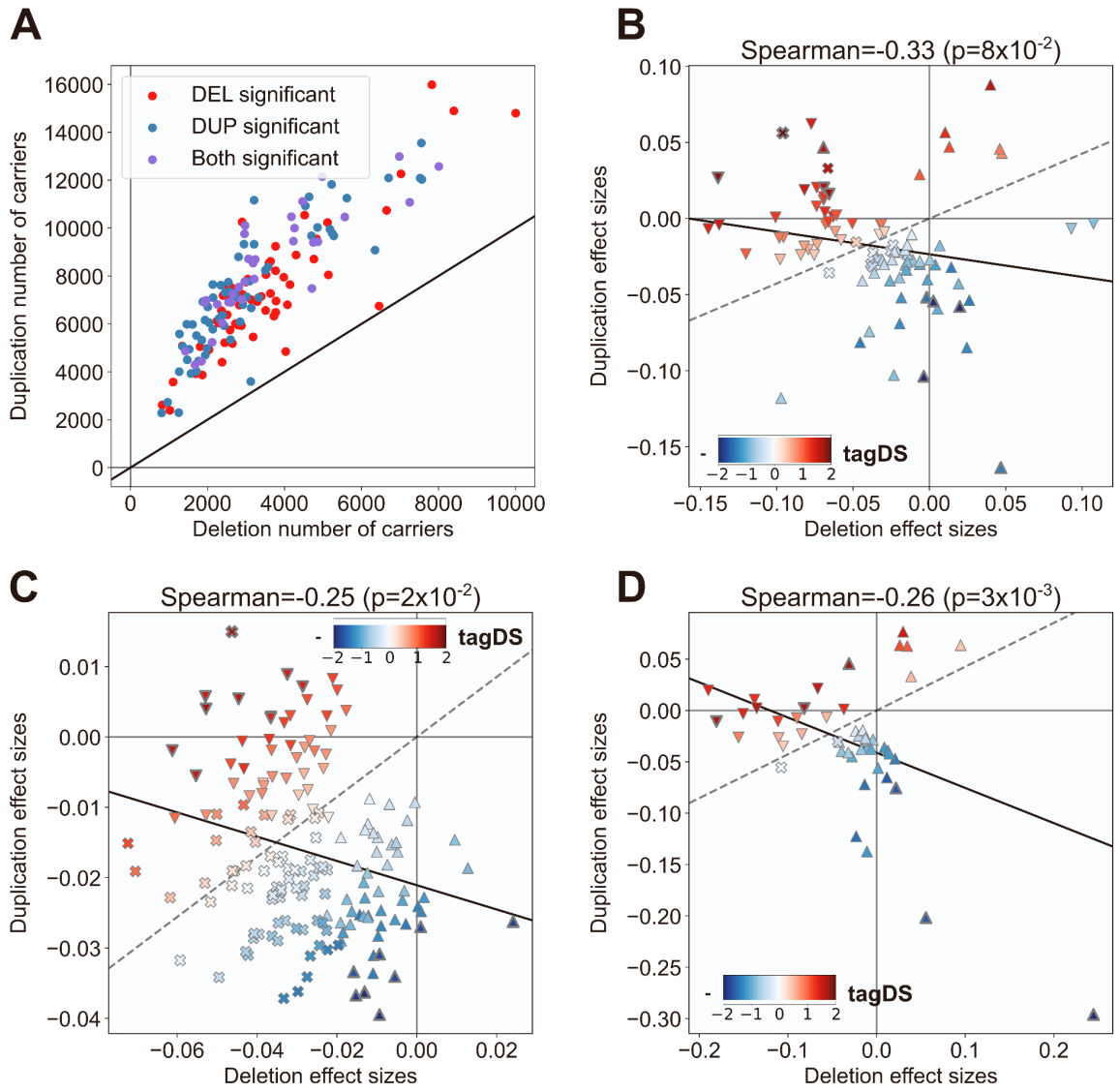


Figure S4: Sensitivity analysis on cognitive ability for multiple HPA gene expression thresholds, Related to Figure 3.

(A) Number of deletion and duplication carriers of genes for the 215 gene-sets analyzed in Figure 3. The black line represents the theoretical perfect concordance between Deletion and duplication carriers. Spearman correlations (black lines) between the effect sizes of deletions and duplications of tissue gene-sets with a normalized expression threshold >0.5SD (B), >1.5SD (C), and >2SD(D). FDR significant effects on cognitive ability for deletions (downward triangle), duplications (upward triangle), or both (cross). pvalues obtained from permutation tests to account for the partial overlap between gene sets. Gene sets are color coded based on their tagDS. The dash line represents the average exome-wide duplication/deletion effect-sizes ratio.

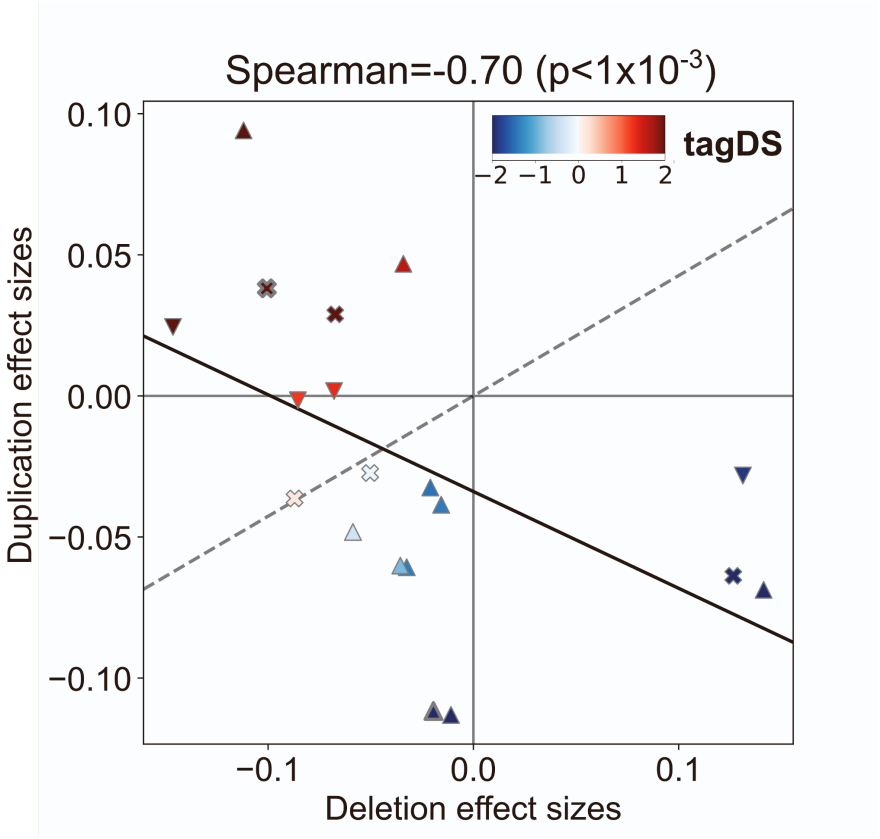


Figure S5: Correlation on cognitive ability of cell type, Related to Figure 3.

Spearman correlation (black line) between the effect sizes of deletions and duplications of gene-sets with FDR significant effects on cognitive ability for deletions (downward triangle), duplications (upward triangle), or both (cross). pvalues obtained from permutation tests to account for the partial overlap between gene sets. Gene sets are color coded based on their tagDS. The dash line represents the average exome-wide duplication/deletion effect-sizes ratio.

# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

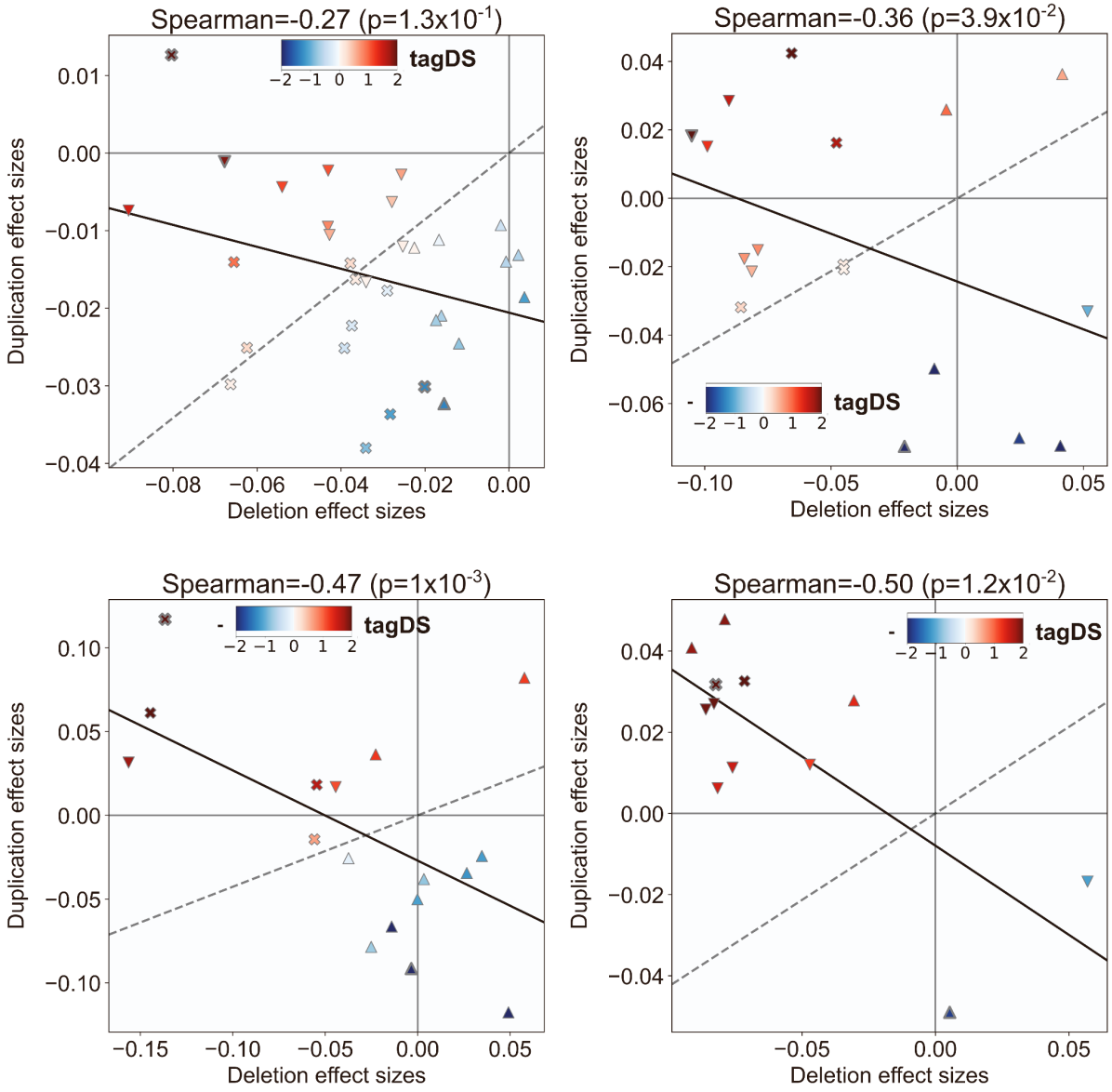


Figure S6: Correlations on cognitive ability of multiple GTEx gene specificity thresholds, Related to Figure 4.

Spearman correlations (black lines) between the effect sizes of deletions and duplications of tissue gene-sets with a normalized relative expression threshold >0.5SD (A), >1.5SD (B), >2SD(C) and >1SD without low-tissue-specificity genes(D). FDR significant effects on cognitive ability for deletions (downward triangle), duplications (upward triangle), or both (cross). pvalues obtained from permutation tests to account for the partial overlap between gene sets. Gene sets are color coded based on their tagDS. The dash line represents the average exome-wide duplication/deletion effect-sizes ratio.

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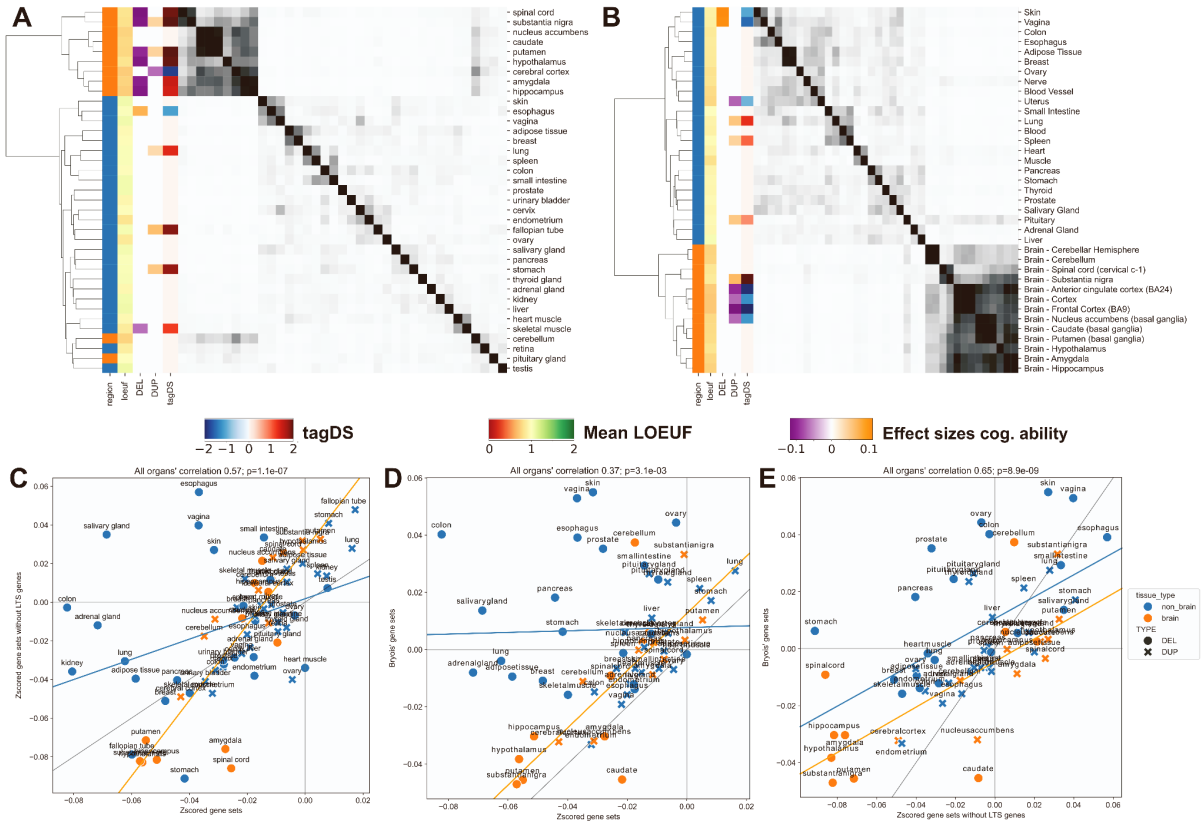


**Figure S7: Comparisons of effect sizes for different gene-set associations**, Related to Figure 4.

Clustering of gene-sets computed with z-score minus 8,194 low-tissue-specificity genes (A) and computed with TDEP (Bryois et al) (B). Orange represents brain tissues and blue non-brain tissues. Gene-set overlap matrix show high overlap between brain gene-sets and much lower overlap across non-brain tissues for both association methods. 2nd columns represent the average LOEUF score of the gene-set. 3rd and 4th columns represent the effect of gene-sets on cognitive ability when deleted and duplicated, respectively. The 5th column is the resulting tagDS. Correlation of effect-sizes for multiple gene-set definitions, z-scored gene-sets with all coding genes versus z-scored gene-sets without low-tissue-specificity genes (C), z-scored gene-sets with all coding genes versus TDEP gene-sets (D) and z-scored gene-sets without low-tissue-specificity genes versus TDEP gene-sets (E). Orange lines show the Spearman correlation between brain gene-sets (r=0.84 p=1e-6; r=0.82 p=9e-6; r=0.76 p=1e-4 for B, C and D respectively) and blue lines show correlation for non-brain gene-sets (r=0.47 p=4e-4; r=0.16 p=3e-1; r=0.58 p=4e-5 for B, C and D respectively). The grey line represents a theoretical perfect concordance between estimates. Pvalues are nominal pvalues without permutation tests.

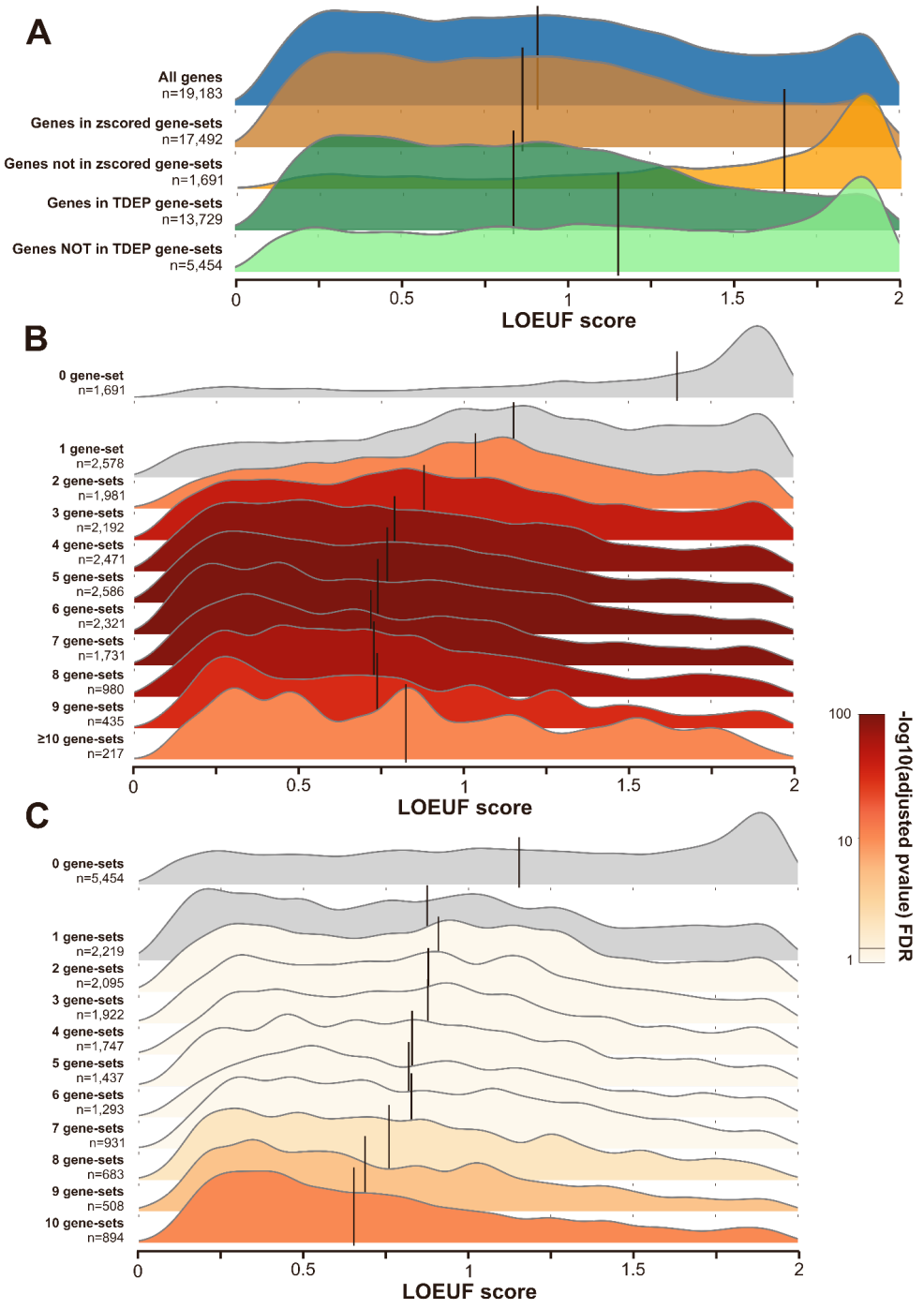


Figure S8: Ridgeplots representing the LOEUF distribution across multiple levels of specificity, Related to Figure 4.

(A) Distribution of LOEUF values for the whole coding exome, for genes assigned to at least one GTEx gene-set defined by z-score, for genes not assigned to any GTEx tissue (Z-score), for genes assigned to at least one GTEx tissue defined by TDEP and for genes not assigned to any GTEx gene-set (TDEP). Distribution of LOEUF for genes present in one or multiple gene-sets defined by Z-score (B) and TDEP (C) methods. The color represents the FDR-adjusted pvalue of the Mann-Whitney test between the distribution of LOEUF for specific genes (present in only one gene-set) and the distribution of interest. Black line represents the median LOEUF score for each category.

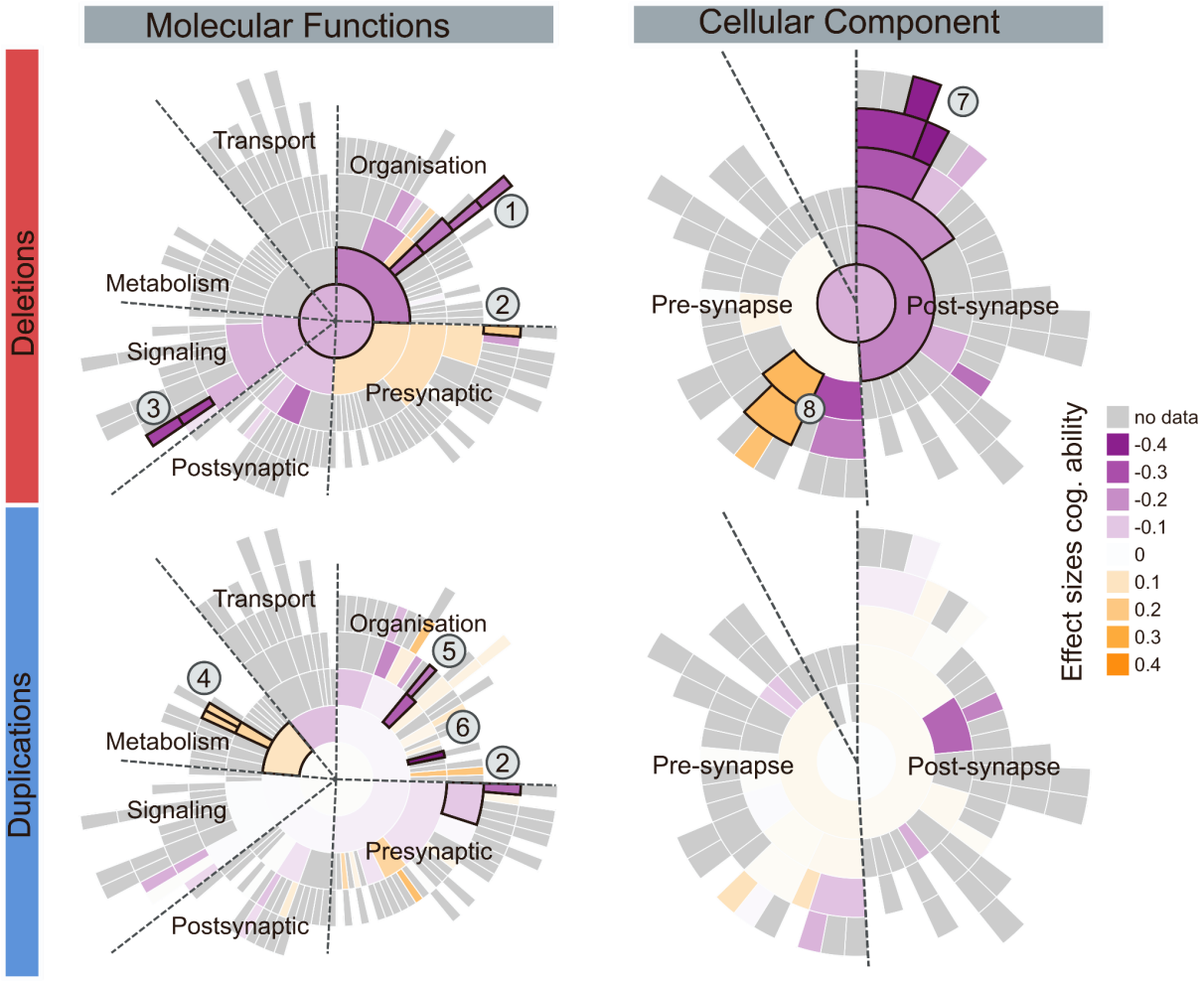


Figure S9: Effect sizes of Deletion and duplication on cognitive ability for SynGO gene-sets, Related to Figure 5.

Effect sizes of synaptic molecular functions and cellular component gene-sets as defined by SynGO[48] on cognitive ability. Purple and orange represent negative and positive effect size on cognitive ability, respectively. Ontologies with black edges indicate significant effects (FDR). The results are shown only for SynGO terms with more than 10 genes, observed at least 30 times in our dataset, and with a coverage greater than 20%. Note: 1) Regulation of modification of postsynaptic actin cytoskeleton, 2) Regulation of calcium-dependent activation of synaptic vesicle fusion, 3) Presynaptic modulation of chemical synaptic transmission, 4) translation at synapse, 5) regulation of postsynapse organization, 6) synapse adhesion between pre- and post-synapse, 7) Integral component of postsynaptic density membrane, 8) Synaptic vesicle membrane.

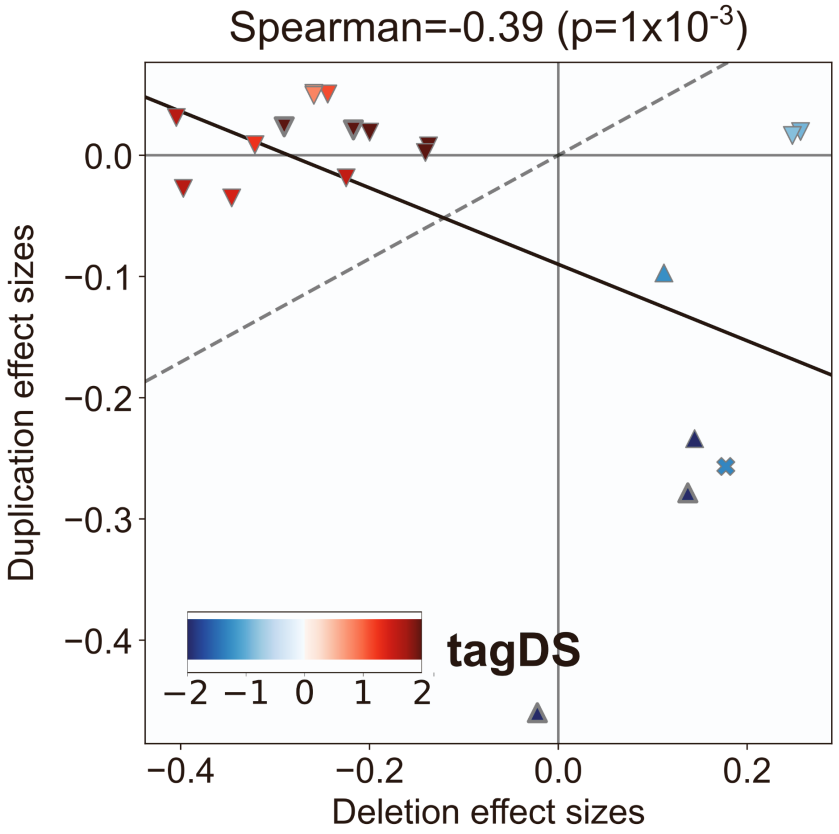


Figure S10: Correlation on cognitive ability of SynGO, Related to Figure 5.
Spearman correlations between the effect sizes of deletions and duplications of gene-sets with FDR significant effects on cognitive ability for deletions (downward triangle), duplications (upward triangle), or both (cross). pvalues obtained from permutations to account for the partial overlap between gene sets. Gene sets are color coded based on their tagDS.

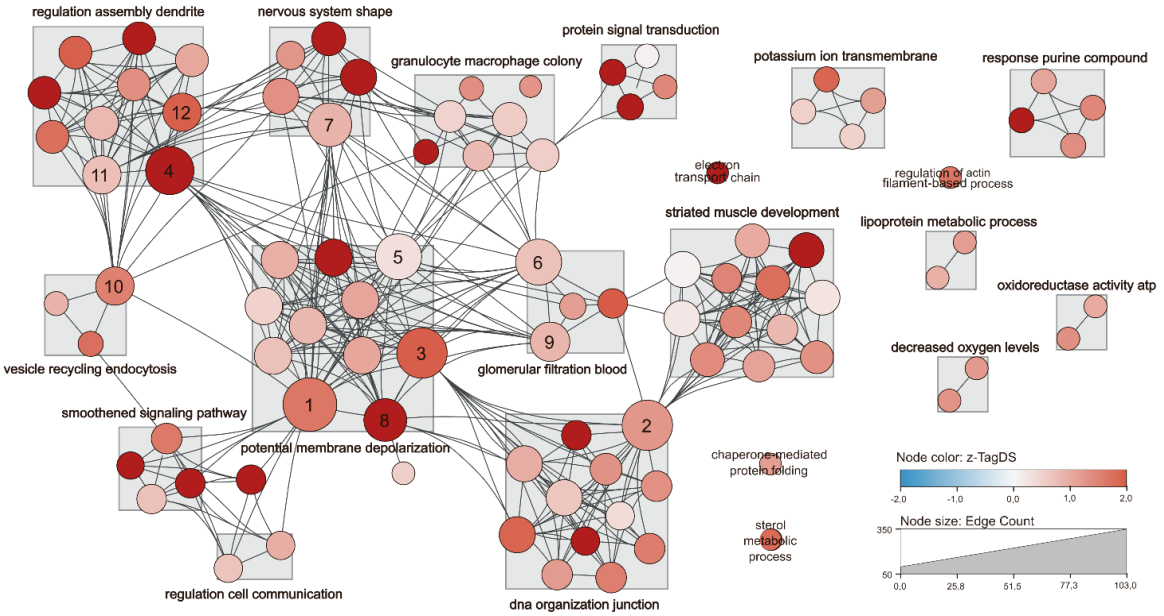


Figure S11: Network of GO-Terms associated with positive tagDS and negative impact on cognitive ability, Related to Figure 5.

This figure presents a Revigo-generated[49] network of GOterms based on GOterm associted with negative impact on cognitive ability and positive tagDS. Each node symbolizes a specific GOterm or GOterm cluster (clustering by standard Revigo criteria[49]). Node color denotes the tagDS value associated (red for positive tagDS). The node size of each node correlates with its edge count, reflecting the extent of its connectivity and relevance within the network. Larger nodes represent higher numbers of interactions with other GO-terms. Links between nodes depict the connection between GO-Terms. The bold text represents the supra-cluster defined by ReviGO[49], represented by a grey square. Nodes had at least 15 edge counts: 1) positive regulation of excitatory postsynaptic potential; 2) axonogenesis; 3) regulation of cellular component size; 4) regulation of synapse organization; 5) positive regulation of vasoconstriction; 6) regulation of glomerular filtration; 7) regulation of cell shape; 8) cell volume homeostasis; 9) negative regulation of blood pressure; 10) positive regulation of endocytosis; 11) positive regulation of dendrite development; 12) regulation of dendrite development.

# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

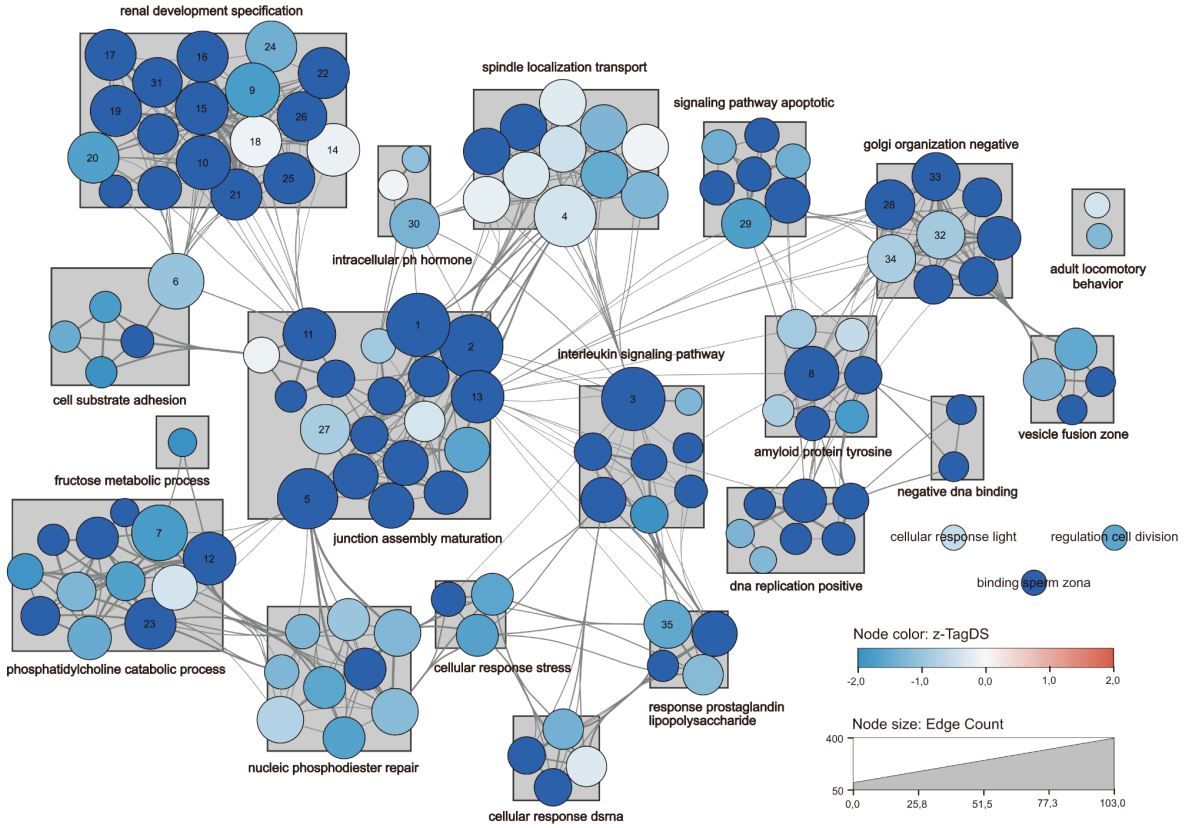


Figure S12: Network of GO-Terms associated with negative tagDS and negative impact on cognitive ability, Related to Figure 5.

This figure presents a Revigo-generated[49] network of GOterms based on GOterm associted with negative impact on cognitive ability and negative tagDS. Each node symbolizes a specific GOterm or GOterm cluster (clustering by standard Revigo criteria[49]). Node color denotes the tagDS value associated (blue for negative tagDS). The node size of each node correlates with its edge count, reflecting the extent of its connectivity and relevance within the network. Larger nodes represent higher numbers of interactions with other GO-terms. Links between nodes depict the connection between GO-Terms. The bold text represents the supra-cluster defined by ReviGO[49], represented by a grey square. Nodes had at least 15 edge counts: 1) vesicle fusion; 2) phagolysosome assembly; 3) signal release; 4) establishment of spindle localization; 5) telomere maintenance; 6) neuron migration; 7) NAD metabolic process; 8) negative regulation of translation; 9) cardiocyte differentiation; 10) cardiac neural crest cell development involved in heart development; 11) synapse maturation; 12) nucleoside phosphate biosynthetic process; 13) mitotic G2/M transition checkpoint; 14) muscle tissue development; 15) formation of primary germ layer; 16) trachea development; 17) somite development; 18) skeletal muscle organ development; 19) segmentation; 20) renal tubule development; 21) embryonic pattern specification; 22) cerebellar cortex development; 23) ceramide biosynthetic process; 24) blastocyst formation; 25) axis specification; 26) trachea morphogenesis; 27) nuclear division; 28) negative regulation of cell projection organization; 29) negative regulation of apoptotic signaling pathway; 30) hormone transport; 31) anterior/posterior axis specification; 32) negative regulation of supramolecular fiber organization; 33) negative regulation of neuron projection development; 34) negative regulation of cytoskeleton organization; 35) lipopolysaccharide-mediated signaling pathway.

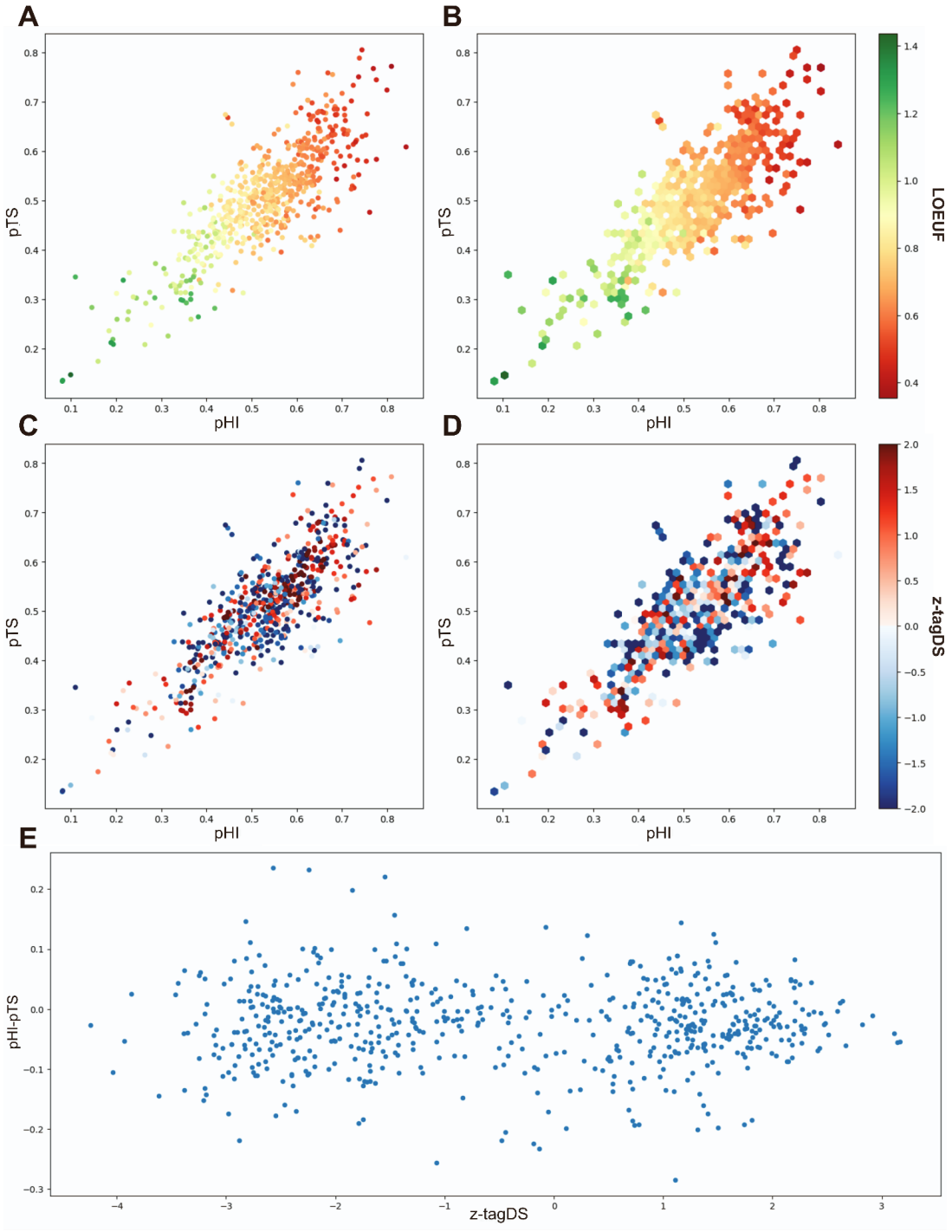


Figure S13: Comparison between Collins et al.'s hapoinsufficiency, triplosensitive scores and tagDS, Related to Figure 5.

Scatter (A) and hexbin (B) plots of the distribution of mean pHI and pTS of genes coming from the 645 significant GO-terms. The color-code represent the average LOEUF value of GO-terms. Hexbin plots visualize the average between overlapping points. Scatter (C) and hexbin (D) plots representing again the distribution of mean pHI and pTS of genes coming from the 645 significant GO-terms. The color-code represent the z-tagDS value extract from Figure 6. (E) Comparison between gene dosage specificity for cognitive ability as describe by z-tagDS and gene dosage specificity based on pHI, pTS difference.

# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

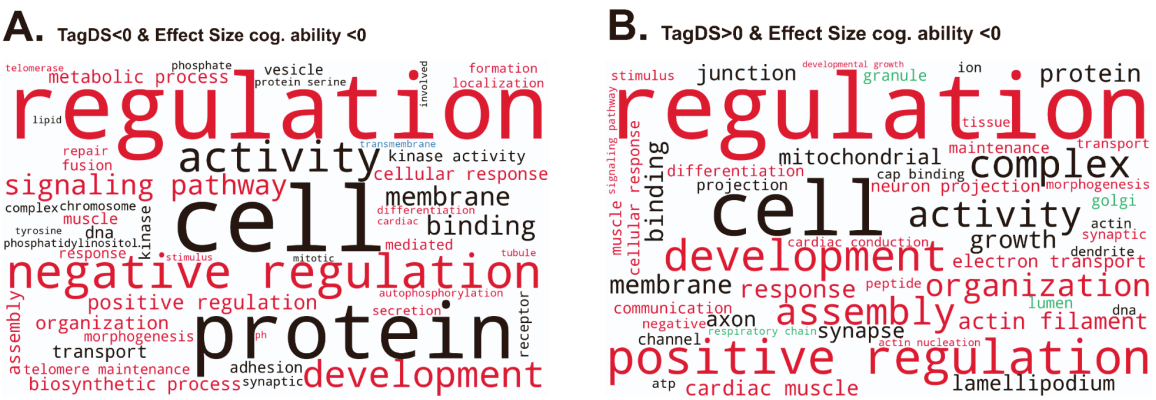


Figure S14: Word-cloud plots on effects on cognitive ability of gene clustered, based on Gene ontology annotation, Related to Figure 5.

Word-cloud plots (A) and (B) display the 50 most frequent words within GO-term names and having a negative effect on cognitive abilities, with negative (n GO-term = 279) and positive ($n_{GO\text{-}term}$ = 242) tagDS, respectively. Red, blue, and green words represent biological processes, molecular functions and cellular components terms, respectively. Black words are observed in multiple categories.

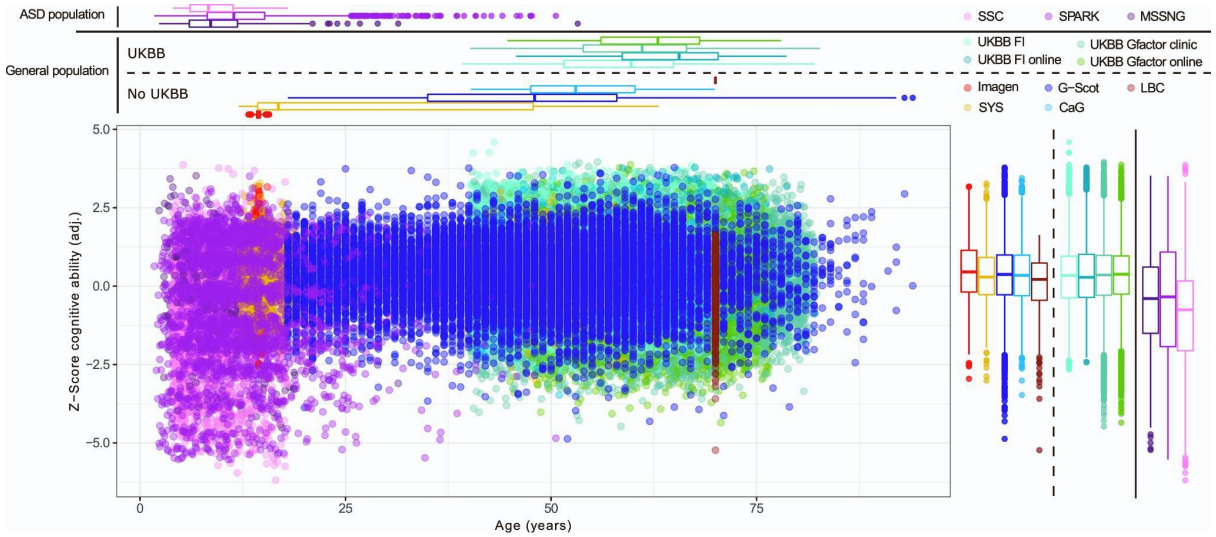


Figure S15: Description of cohorts in the dataset, Related to Table 1.

The figure showed the cognitive ability z-score adjusted (sex, age, PC1 to 10 and cognitive test) with age for each participant.

# Supplementary data : Effects of gene dosage on cognitive ability: A function-based association study across brain and non-brain processes

**Supplementary reference :**


1. Naj, A.C., Beecham, G.W., Martin, E.R., Gallins, P.J., Powell, E.H., Konidari, I., Whitehead, P.L., Cai, G., Haroutunian, V., Scott, W.K., et al. (2010). Dementia revealed: novel chromosome 6 locus for late-onset Alzheimer disease provides genetic evidence for folate-pathway abnormalities. PLoS Genet *6*, e1001130. https://doi.org/10.1371/journal.pgen.1001130.
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