

1 Supplementary Information

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10 1. List of excluded medical conditions from present study

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ICD-10 code	Medical condition name
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F00	Dementia in Alzheimer's Disease
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F01	Vascular Dementia
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F02	Dementia in other diseases classified elsewhere
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F03	Dementia (unspecified)
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F04	Organic amnesic syndrome (non-alcohol/substance related)
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F05	Delirium (non-alcohol/substance related)
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F06	Other mental disorders due to brain damage and dysfunction and to physical disease
-----	--

F07	Personality and behavioural disorders due to brain disease, damage, and dysfunction
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F09	Organic or symptomatic mental disorder (unspecified)
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R41	Other symptoms and signs involving cognitive functions and awareness
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S06	Intracranial injury
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S09.7	Multiple injuries of the head
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13 2. Description of variables used for linear regression analyses

14 - Fluid Intelligence score (UKB Field 20016)

15 Fluid intelligence (FI) was assessed via a fully-automated, 2-minute touch-screen test
16 which consisted of 13 verbal and numeric questions (UKB Field 20016)
17 [<https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/Fluidintelligence.pdf>].

18 Participants who attempted the test were given an ordinal score of 0-13
19 corresponding with the total number of correct answers achieved. Participants who
20 failed to finish the test within the allotted time were given zero for each unanswered
21 question. Participants ($n= 205,328$) attempted the touch-screen test at one of four
22 assessment centre visits. Some individuals had multiple attempts at the FI test, thus,
23 for these participants we included their first attempt as their FI score, similar to
24 previous studies^{1,2}. An additional 123,594 participants were administered the test in
25 online format (UKB Field 200191). We did not include these scores given that the two
26 modalities, online and in-person touch screen FI test, may not be directly comparable³.
27 FI scores were converted to z-scores by normalising to the cohort mean.

28

29 - Townsend Deprivation index score (UKB Field 189)

30 The Townsend Deprivation Index (TDI) is a socio-demographic measure of material
31 deprivation within a population⁴. TDI scores were calculated before the participant
32 joined the UKB based on national census output areas ($n= 501,901$). Scores were
33 assigned to participants based on the output area in which their postcode was located
34 in. It is a broad measure based on four categories: unemployment (economically
35 active residents >16yrs), non-car ownership, non-home ownership and household-

36 overcrowding (persons per room, occupancy rating). A combined, standardised
37 measure (z-score) of all four categories outputs a TDI score for that area. A positive
38 TDI score indicates greater deprivation whereas a negative TDI score indicates lesser
39 deprivation.

40

41 - **Educational attainment (UKB Field 6138)**

42 Educational attainment ($n = 498,765$) was collected as a touch-screen questionnaire
43 during assessment centres visits where participants were asked “which of the
44 following qualifications do you have?”. Participants had a choice of 8 categories. We
45 re-coded these categories to reflect the level of educational attainment of each
46 participant:

- 47 ▪ 0 = None of the above; Prefer not to answer.
- 48 ▪ 1 = A levels/AS levels; CSEs or equivalent; O levels/GCSEs or equivalent
- 49 ▪ 2 = NVQ or HND or HNC or equivalent; Other professional qualifications e.g.:
50 nursing, teaching.
- 51 ▪ 3 = College or University degree.

52

53 - **Employment status (UKB Field 6142)**

54 Employment status ($n = 501,559$) was collected as a touch-screen questionnaire
55 during assessment centres visits where participants were asked “Which of the
56 following describes your current situation? (You can select more than one answer)”.
57 Participants had a choice of 9 categories (described in Supplementary Table 2). We
58 decided not to recode this variable.

59

60 - Other variables used as predictors which are standard in genetic association analyses
61 and are self-explanatory, were sex, age at time of assessment, batch and array type
62 (for PGS models only), assessment centre location, and ancestry principal
63 components.

64 All analyses were tested for multi-collinearity using variance inflation factors (VIFs), condition
65 indices, and pairwise correlations to ensure only reliable and interpretable predictors would
66 be retained. However, to investigate the effect of correcting linear regression models for
67 educational attainment, we re-ran the analyses omitting the educational attainment
68 covariate (*Supplementary Tables 10. and 15.*).

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70

71 **3. Supplementary Tables 1-20.**

Supplementary Table 1 Demographics of excluded UKB participants who attempted the fluid intelligence (FI) test											
Variable	All ND-CNVs	15q11.2 del.	16p13.11 dup.	22q11.2 dup.	1q21.1 dup.	16p12.1 del.	NRXN1 del.	16p11.2 dup.	16p11.2 distal dup.	1q21.1 del.	Non-carriers
n max.	296	119	58	19	13	17	9	8	10	7	51,389
Sex (%male)	48	47	48	58	15	82	67	50	20	71	39
Age (years)	56.38 [8.72]	57.54 [8.38]	57.76 [9.00]	54.11 [9.42]	54.31 [8.46]	51.59 [8.05]	58.56 [8.28]	59.00 [8.31]	54.80 [8.35]	56.14 [9.21]	56.30 [8.79]
TDI score (z)	0.99 [0.12]	0.97 [0.16]	-0.74 [3.56]	1.50 [3.36]	1.30 [3.57]	0.99 [4.37]	-1.79 [2.05]	0.88 [3.52]	0.08 [3.68]	-0.31 [2.99]	-0.53 [0.08]
FI score (z)	-0.16 [0.96]	-0.25 [0.86]	-0.29 [1.04]	0.06 [1.00]	0.03 [1.26]	-0.58 [0.98]	-0.38 [0.98]	0.55 [0.92]	-0.02 [0.53]	-0.57 [0.85]	0.001 [1.00]
Ethnicity											
- British	157	68	30	10	2	8	3	7	4	4	24,289
- Any other white background	38	16	6	3	2	4	3	0	1	1	7,299
- Irish	38	16	7	2	0	4	3	0	2	0	5,737
- Indian	14	6	3	0	1	0	0	0	1	0	3,252
- Caribbean	12	3	2	1	2	0	0	0	1	1	2,522
- Other ethnic group	4	1	2	1	0	0	0	0	0	0	2,040
- African	4	2	1	0	1	0	0	0	0	0	1,523
- Any other Asian background	5	0	2	1	1	0	0	0	0	0	921
- Chinese	2	0	0	0	0	0	0	1	0	0	691
- Pakistani	0	0	0	0	0	0	0	0	0	0	648
- Any other mixed background	3	1	0	1	1	0	0	0	0	0	471
- White and Asian	2	1	0	0	0	0	0	0	0	1	417
- White and Black Caribbean	2	1	1	0	0	0	0	0	0	0	305
- White and Black African	0	0	0	0	0	0	0	0	0	0	174
- White	3	0	2	0	0	0	0	0	0	0	172
- Bangladeshi	1	1	0	0	0	0	0	0	0	0	66
- Any other Black background	0	0	0	0	0	0	0	0	0	0	63
- Asian or Asian British	0	0	0	0	0	0	0	0	0	0	21
- Mixed	0	0	0	0	0	0	0	0	0	0	16
- Black or Black British	0	0	0	0	0	0	0	0	0	0	12
- Prefer not to answer	11	3	2	0	3	1	0	0	1	0	669
- Do not know	0	0	0	0	0	0	0	0	0	0	65
- NA's	0	0	0	0	0	0	0	0	0	0	16

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73 **Supplementary Table 1. Excluded participants demographics.** The mean [s.d] are presented for quantitative phenotypes. FI scores are presented
74 as z-scores (Methods and *Supplementary Material*)

Supplementary Table 2 | Expanded description of ND-CNV carriers and non-carriers who attempted the fluid intelligence (FI) test with imputation data

Variable	All ND-CNVs	All dup. carriers	All del. carriers	15q11.2 del.	16p13.11 dup.	22q11.2 dup.	1q21.1 dup.	16p12.1 del.	NRXN1 del.	16p11.2 dup.	16p11.2 distal dup.	1q21.1 del.	Non-carriers
n max.	1,318	561	764	543	275	83	73	64	56	46	38	35	152,325
Sex - %male	51	52	50	50	49	53	53	47	46	52	55	40	47
Age (years)	57.16 [8.35] {40,80}	56.53 [8.33] {40, 78}	57.65 [8.36] {40, 80}	58.33 [8.35] {40,80}	57.32 [8.14] {40,77}	55.39 [8.31] {41,70}	57.77 [7.60] {40,73}	57.09 [8.08] {40,80}	56.82 [8.18] {40,74}	54.72 [8.51] {41,71}	55.37 [9.05] {40,72}	54.72 [8.70] {40,70}	58.53 [8.28] {40,82}
- male	57.60 [8.53] {40,80}	56.87 [8.40] {40, 78}	58.19 [8.64] {40, 80}	58.89 [8.52] {40,80}	57.05 [8.18] {40,77}	56.39 [8.56] {41,70}	57.08 [8.13] {40,73}	57.60 [8.53] {40,80}	58.77 [8.55] {44,74}	56.08 [9.13] {41,71}	57.67 [8.33] {40,67}	51.00 [8.69] {40,68}	58.97 [8.42] {40,81}
- female	56.71 [8.14] {40,79}	56.17 [8.26] {40, 73}	57.11 [8.05] {40, 79}	57.76 [8.15] {40,79}	57.58 [8.13] {40,73}	54.26 [7.98] {41,68}	58.56 [6.99] {43,69}	56.71 [8.14] {40,79}	55.13 [7.59] {40,66}	53.23 [7.71] {41,65}	52.53 [9.34] {41,72}	56.52 [8.17] {42,70}	58.15 [8.14] {40,82}
TDI score	-1.01 [2.99] {-6.18, 8.99}	-0.69 [3.12] {-6.16, 8.99}	-1.23 [2.89] {-6.18, 7.69}	-1.34 [2.77] {-6.17, 7.63}	-0.98 [3.08] {-5.55, 8.99}	-0.44 [2.87] {-4.93, 5.83}	-0.02 [3.39] {-6.16, 7.46}	-1.30 [2.86] {-5.03, 7.69}	-1.53 [3.36] {-5.88, 7.66}	-0.1 [3.19] {-4.88, 7.66}	-0.46 [3.27] {-5.09, 8.62}	-1.26 [2.76] {-5.80, 4.99}	-1.58 [2.77] {-6.26, 9.89}
- male	-1.12 [2.97] {-6.16 ,8.99}	-0.78 [3.14] {-5.23, 8.99}	-1.38 [2.82] {-6.18, 7.69}	-1.53 [2.76] {-6.17, 7.60}	-0.61 [3.08] {-5.55, 7.54}	0.04 [2.93] {-4.29, 5.83}	0.38 [3.23] {-4.42, 7.46}	-0.85 [3.07] {-4.91, 7.69}	-1.70 [3.37] {-5.88, 5.78}	-0.13 [3.57] {-4.29, 7.66}	-1.20 [3.11] {-4.60, 8.62}	-1.15 [2.53] {-4.49, 3.91}	-1.58 [2.81] {-6.26, 9.89}
- female	-0.89 [3.00] {-6.18, 7.66}	-0.60 [3.11] {-6.16, 7.54}	-1.86 [2.96] {-6.18, 7.66}	-1.15 [2.78] {-6.18, 7.63}	-1.37 [3.05] {-5.23, 8.99}	-0.98 [2.75] {-4.93, 4.78}	-0.50 [3.56] {-6.16, 5.98}	-7.67 [2.64] {-5.03, 6.46}	-1.38 [3.41] {-5.05, 7.66}	-0.34 [2.78] {-4.88, 4.69}	0.47 [3.32] {-5.09, 4.50}	-1.32 [2.96] {-5.80, 4.99}	-1.58 [2.74] {-6.26, 9.52}
FI score (z)	-0.41 [0.96] {-2.98, 2.75}	-0.45 [0.99] {-2.98, 2.75}	-0.38 [0.94] {-2.98, 2.28}	-0.33 [0.92] {-2.50, 2.28}	-0.3 [0.98] {-2.98, 2.75}	-0.58 [0.79] {-2.03, 0.84}	-0.37 [1.16] {-2.50, 2.75}	-0.58 [0.98] {-2.50, 2.28}	-0.23 [0.89] {-2.5, 1.32}	-1.04 [0.93] {-2.50, 1.32}	-0.35 [0.87] {-2.03, 1.80}	-0.55 [0.91] {-2.50, 0.84}	0.004 [0.1] {-2.98, 3.23}
- male	-0.39 [0.98] {-2.98, 2.75}	-0.44 [1.05] {-2.98, 2.75}	-0.35 [0.93] {-2.50, 2.28}	-0.27 [0.92] {-2.50, 2.28}	-0.26 [1.04] {-2.50, 2.75}	-0.54 [0.82] {-2.03, 0.84}	-0.42 [1.17] {-2.50, 2.75}	-0.47 [1.14] {-2.50, 2.28}	-0.35 [0.8] {-2.03, 1.32}	-1.09 [0.92] {-2.50, 1.32}	-0.21 [0.98] {-2.03, 1.80}	-0.87 [0.83] {-2.03, 0.36}	-0.06 [1.03] {-2.98, 3.23}
- female	-0.43 [0.94] {-2.98, 2.75}	-0.46 [0.93] {-2.98, 2.75}	-0.41 [0.94] {-2.98, 2.28}	-0.4 [0.91] {-2.50, 2.28}	-0.35 [0.91] {-2.98, 2.28}	-0.62 [0.76] {-2.03, 0.84}	-0.31 [1.17] {-2.50, 2.75}	-0.68 [0.82] {-2.03, 0.84}	-0.13 [0.97] {-2.5, 1.32}	-0.98 [0.96] {-2.50, 1.32}	-0.54 [0.69] {-2.03, 0.84}	-0.34 [0.91] {-2.50, 0.84}	-0.04 [0.97] {-2.98, 3.23}
Employment status													
- Employed/Self-employed	717	313	406	286	170	42	35	33	31	17	25	23	78,020
- Retired	462	185	281	215	91	28	29	21	20	16	7	7	62,824
- Student	0	0	0	0	0	0	0	0	0	0	0	0	271
- Carer / Looking after home	31	10	21	14	1	4	0	4	2	1	2	1	3,652
- Voluntary work	7	4	3	1	1	2	0	1	0	0	0	0	741
- Unable to work	60	29	31	16	6	5	4	3	2	9	2	3	3,350
- Unemployed	32	17	16	7	5	2	4	1	0	3	1	1	2,374
- Prefer not to answer	1	1	0	0	1	0	0	0	0	0	0	0	353
- None of the above	7	2	5	4	0	0	1	0	1	0	1	0	705
- NA	1	0	1	0	0	0	0	1	0	0	0	0	35
Ed. Attainment													
- primary	539	232	310	225	101	36	38	20	25	23	13	12	59,373
- secondary	183	66	119	88	32	8	10	13	7	3	5	3	17,920
- tertiary	319	136	184	122	83	18	10	16	19	6	10	15	53,567
- Prefer not to answer	276	127	150	108	59	21	15	14	5	14	10	5	21,430
- NA	1	0	1	0	0	0	0	1	0	0	0	0	35

76 **Supplementary Table 2. Expanded description of ND-CNV carriers and non-carriers who attempted the fluid intelligence (FI) test with**
77 **imputation data.** The mean [s.d] are presented for quantitative phenotypes. FI scores are presented as z-scores (Methods and *Supplementary*
78 *Material*).

Supplementary Table 3 | Expanded description of ND-CNV carriers and non-carriers who attempted the fluid intelligence (FI) test with exome data

Variable	All ND-CNVs	All dup. carriers	All del. carriers	15q11.2 del.	16p13.11 dup.	22q11.2 dup.	1q21.1 dup.	16p12.1 del.	NRXN1 del.	16p11.2 dup.	16p11.2 distal dup.	1q21.1 del.	Non-carriers
n max.	1,275	542	740	523	267	81	68	62	55	44	37	33	146,894
Sex - %male	50	51	49	50	49	53	51	47	45	52	55	40	47
Age (years)	57.23 [8.33] {40,80}	56.67 [8.32] {40, 78}	56.67 [8.32] {40, 80}	58.36 [8.33] {40,80}	57.39 [8.13] {40,77}	55.68 [8.19] {41,70}	57.94 [7.77] {40,73}	57.19 [7.95] {42,77}	56.98 [8.17] {40,74}	55.18 [8.38] {41,71}	55.57 [9.09] {40,72}	55.18 [8.70] {40,70}	58.53 [8.28] {40,82}
- male	57.69 [8.54] {40,80}	57.03 [8.40] {40, 78}	58.22 [8.65] {40, 80}	58.87 [8.56] {40,80}	57.14 [8.13] {40,77}	56.74 [8.32] {41,70}	57.46 [8.46] {40,73}	57.41 [8.51] {42,77}	59.20 [8.44] {44,74}	55.00 [9.16] {41,71}	57.67 [8.33] {40,67}	55.18 [8.69] {40,68}	58.96 [8.42] {40,81}
- female	56.78 [8.10] {40,79}	56.29 [8.24] {40, 73}	57.15 [8.00] {40, 79}	57.86 [8.08] {40,79}	57.64 [8.15] {40,73}	54.47 [7.97] {41,68}	58.45 [7.07] {43,69}	57.00 [7.55] {43,75}	55.13 [7.59] {40,66}	53.81 [7.39] {43,65}	52.81 [9.58] {41,72}	56.52 [8.17] {42,70}	58.14 [8.14] {40,82}
TDI score	-1.03 [2.99] {-6.18, 8.99}	-0.71 [3.13] {-6.16, 8.99}	-1.25 [2.89] {-6.18, 7.69}	-1.37 [2.76] {-6.18, 7.63}	-0.98 [3.09] {-5.55, 8.99}	-0.40 [2.89] {-4.93, 5.83}	-0.06 [3.45] {-6.16, 7.46}	-1.29 [2.90] {-5.03, 7.69}	-1.62 [3.33] {-5.88, 7.66}	-0.23 [3.11] {-4.88, 7.66}	-0.57 [3.24] {-5.09, 8.62}	-1.26 [2.76] {-5.80, 4.99}	-1.58 [2.77] {-6.26, 9.89}
- male	-1.15 [2.97] {-6.16, 8.99}	-0.08 [3.14] {-5.23, 8.99}	-1.41 [2.82] {-6.16, 7.69}	-1.55 [2.76] {-6.16, 7.60}	-1.36 [3.06] {-5.23, 8.99}	-0.06 [2.96] {-4.29, 5.83}	0.42 [3.45] {-4.41, 7.46}	-0.85 [3.12] {-4.91, 7.69}	-1.91 [3.33] {-5.88, 5.78}	-0.14 [3.39] {-4.29, 7.66}	-1.21 [3.11] {-4.60, 8.62}	-1.15 [2.53] {-4.49, 3.91}	-1.58 [2.81] {-6.26, 9.89}
- female	-0.91 [3.01] {-6.18, 7.66}	-0.61 [3.12] {-6.16, 7.54}	-1.10 [2.95] {-6.18, 7.66}	-1.18 [2.76] {-6.18, 7.63}	-0.61 [3.09] {-5.55, 7.54}	-0.91 [2.76] {-4.93, 4.78}	-0.56 [3.59] {-6.16, 5.98}	-1.68 [2.68] {-5.03, 6.46}	-1.38 [3.41] {-5.05, 7.66}	-0.32 [2.86] {-4.88, 4.69}	0.27 [3.31] {5.09, 4.50}	-1.32 [2.96] {-5.80, 4.99}	-1.58 [2.74] {-6.26, 9.52}
FI score (z)	-0.38 [0.98] {-2.98, 2.76}	-0.43 [1.00] {-2.98, 2.76}	-0.38 [0.93] {-2.98, 2.28}	-0.34 [0.91] {-2.51, 2.28}	-0.29 [0.98] {-2.98, 2.76}	-0.56 [0.78] {-2.03, 0.84}	-0.32 [1.19] {-2.51, 2.76}	-0.58 [0.98] {-2.51, 2.28}	-0.20 [0.87] {-2.51, 1.32}	-1.03 [0.94] {-2.51, 1.32}	-0.35 [0.88] {-2.03, 1.80}	-0.55 [0.91] {-2.50, 0.84}	0.003 [1.00] {-2.98, 3.23}
- male	-0.38 [0.98] {-2.98, 2.76}	-0.41 [1.05] {-2.98, 2.76}	-0.36 [0.93] {-2.51, 2.28}	-0.28 [0.91] {-2.51, 2.28}	-0.22 [1.04] {-2.51, 2.76}	-0.54 [0.83] {-2.03, 0.84}	-0.36 [1.21] {-2.51, 2.76}	-0.43 [1.15] {-2.51, 2.28}	-0.29 [0.74] {-1.55, 1.32}	-1.05 [0.92] {-2.51, 1.32}	-0.21 [0.98] {-2.03, 1.80}	-0.87 [0.83] {-2.03, 0.36}	0.06 [1.04] {-2.98, 3.23}
- female	-0.43 [0.93] {-2.98, 2.76}	-0.45 [0.94] {-2.98, 2.76}	-0.41 [0.93] {-2.98, 2.28}	-0.40 [0.90] {-2.51, 1.80}	-0.35 [0.91] {-2.98, 2.28}	-0.58 [0.73] {-2.03, 0.84}	-0.29 [1.18] {-2.51, 2.76}	-0.71 [0.81] {-2.03, 0.84}	-0.13 [0.97] {-2.51, 1.32}	-1.00 [0.98] {-2.51, 1.32}	-0.53 [0.72] {-2.03, 0.84}	-0.34 [0.92] {-2.50, 0.84}	0.84 [0.97] {-2.98, 3.23}
Employment status													
- Employed/Self-employed	694	301	395	276	164	41	32	33	31	16	24	23	75,262
- Retired	450	181	273	208	90	28	27	20	20	16	7	7	60,569
- Student	0	0	0	0	0	0	0	0	0	0	0	0	264
- Carer / Looking after home	31	10	21	14	1	4	0	4	2	1	2	1	3,541
- Voluntary work	7	4	3	1	1	2	0	1	0	0	0	0	713
- Unable to work	54	27	27	14	5	5	4	2	1	8	2	3	3,218
- Unemployed	30	16	15	6	5	1	4	1	0	3	1	0	2,276
- Prefer not to answer	1	1	0	0	1	0	0	0	0	0	0	0	334
- None of the above	7	2	5	4	0	0	1	0	1	0	1	0	682
- NA	1	0	1	0	0	0	0	1	0	0	0	0	35
Ed. Attainment													
- primary	522	225	300	219	98	36	35	18	24	22	13	12	57,251
- secondary	175	61	116	85	31	8	9	13	7	2	4	3	17,296
- tertiary	311	134	178	116	82	17	10	16	19	6	10	15	51,607
- Prefer not to answer	266	122	145	103	56	20	14	14	5	14	10	5	20,705
- NA	1	0	1	0	0	0	0	1	0	0	0	0	35

80 ***Supplementary Table 3. Expanded description of ND-CNV carriers and non-carriers who attempted the fluid intelligence (FI) test with exome***
81 ***data.*** The mean [s.d] are presented for quantitative phenotypes. FI scores are presented as z-scores (Methods and Supplementary Materials

Supplementary Table 4 | List of 49 ND-CNVs from Kendall et al., 2019

<i>ND-CNV</i>	<i>Location (hg19)</i>	<i>Max. genes in region</i>	<i>Penetrance (%)</i>	<i>Associated NDDs & references</i>
1p36 del.	chr1:0-2,50	76	100	ID, DD ⁵
1p36 dup.	chr1:0-2,50	76	-	ID, DD ⁶
1q21.1 del.	chr1:146,53-147,39	91	35	ID, DD, ASD, ADHD, SCZ ⁷
1q21.1 dup.	chr1:146,53-147,39	91	18	ID, DD, ASD, ADHD ⁷
2p16.3 del. (NRXN1)	chr2:50,14-51,26	1	26	ID, DD, ASD, SCZ ^{8,9}
2q21.2 del.	chr2:131,48-131,93	5	-	ID, DD ¹⁰
2q37 del.	chr2:239,72-243,2	51	100	ID, DD ¹¹
3q29 del.	chr3:195,72-197,35	28	53	ID, DD, ASD, ADHD, SCZ ¹²
4p16.3 del. (Wolf-Hirschhorn)	chr4:1,55-2,09	13	100	ID, DD ¹³
4p16.3 dup. (Wolf-Hirschhorn)	chr4:1,55-2,09	13	100	ID, DD ¹⁴
5q35 del. (Sotos syndrome)	chr5:175,72-177,05	39	100	ID, DD ¹⁵
7q11.23 del. (William-Beuren syndrome)	chr7:72,74-74,14	26	100	ID, DD, ADHD ¹⁶
7q11.23 dup. (William-Beuren syndrome)	chr7:72,74-74,14	26	44	ID, DD, ADHD, SCZ ¹⁶
8p23.1 del.	chr8:8,10-11,87	35	97	ID, DD, ASD, ADHD ¹⁷
8p23.1 dup.	chr8:8,10-11,87	35	100	ID, DD ¹⁸
9q34.3 del. (EHMT1)	chr9:140,51-140,73	2	100	ID, DD ¹⁹
10q23 del.	chr10:82,05-88,93	29	100	ID, DD ²⁰
11p11.2 del. (Potocki-Shaffer)	chr11:43,94-46,02	22	-	ID, DD ²¹
15q11.2 del.	chr15:22,81-23,09	5	11	ID, DD, ASD, ADHD, SCZ ²²
15q11-q13 del. (Prader-Willi/Angelman Syndrome)	chr15:23,68-28,39	116	100	ID, DD, ASD ²³
15q11-q13 dup. (Prader-Willi/Angelman syndrome)	chr15:23,68-28,39	116	54	ID, DD, ASD ²³
15q13.3 del. BP4-BP5	chr15:29,16-32,46	17	89	ID, DD, ASD, ADHD ²⁴
15q24 del.	chr15:72,90-78,15	77	100	ID, DD, ASD, ADHD ²⁵
15q24 dup.	chr15:72,90-78,15	77	100	ID, DD, ASD, ADHD ²⁵
15q25 del.	chr15:83,22-85,72	34	100	ID, DD, ASD ²⁶
16q13.11 del.	chr16:15,51-16,29	7	14	ID, DD, ASD, SCZ ²⁷
16q13.11 dup.	chr16:15,51-16,29	7	8.4	ID, DD, ASD, ADHD, SCZ ²⁸
16p12.1 del.	chr16:21,95-22,43	8	13	ID, DD ²⁹
16p11.2 distal del.	chr16:28,82-29,05	11	23	ID, DD, ASD, ADHD, SCZ ³⁰
16p11.2 distal dup.	chr16:28,82-29,05	11	5.3	ID, DD, ASD, ADHD, SCZ ³¹
16p11.2 del.	chr16:29,65-30,20	30	8	ID, DD, ASD, ADHD, SCZ ³⁰
16p11.2 dup.	chr16:29,65-30,20	30	26	ID, DD ³¹
17p13.3 del. (YWHAE)	chr17:1,25-1,30	1	14	ID, DD ³²
17p13.3 dup. (YWHAE)	chr17:1,25-1,30	1	9	ID, DD, ASD ³³
17p13.3 del. (PAFAH1B1)	chr17:2,49-2,59	1	17	ID, DD ³²
17p13.3 dup. (PAFAH1B1)	chr17:2,49-2,59	1	17	ID, DD ³³
17q11.2 del. (Smith-Magenis Syndrome)	chr17:16,81-20,21	59	100	ID, DD, ADHD, ASD ³⁴
17p11.2 dup. (Potocki-Lupski)	chr17:16,81-20,21	59	98	ID, DD, ASD, ADHD ³⁵
17q11.2 del. (NF1)	chr17:29,12-30,27	19	38	ID, DD, ASD ³⁶
17q11.2 dup. (NF1)	chr17:29,12-30,27	19	98	ID, DD ³⁷
17q12 dup.	chr17:34,81-36,22	19	17	ID, DD, ASD, SCZ ³⁸
17q12 del.	chr17:34,81-36,22	19	39	ID, DD, ASD, SCZ ³⁸
17q21.31 del.	chr17:43,70-44,29	10	100	ID, DD ³⁹
22q11.2 del.	chr22:19,04-21,47	61	100	ID, DD, ASD, SCZ, ADHD ^{40,41}
22q11.2 dup.	chr22:19,04-21,47	61	14	ID, DD ⁴²
22q11.2 distal del.	chr22:21,92-23,65	26	100	ID, DD, SCZ ⁴³
22q11.2 distal dup.	chr22:21,92-23,65	26	16	ID, DD ⁴⁴
22q13 del. (SHANK3)	chr22:51,11-51,17	1	100	ID, DD, ASSD, SCZ ⁴⁵
22q13 dup. (SHANK3)	chr22:51,11-51,17	1	100	ID, DD, ADHD ⁴⁵

83 **Supplementary Table 4. List of 49 ND-CNV defined by Kendall et al. 2019⁴⁶.** The list of CNV
84 loci defined as ND-CNVs in this analysis. Consensus penetrance estimates were derived from
85 Kirov et al.⁴⁷ and Rosenfeld et al.⁴⁸.

Supplementary Table 5 | ND-CNVs loci carried by included participants

ND-CNV locus	<i>n</i> (PGS)	<i>n</i> (Exome)	<i>n</i> (UKB)	Location (hg19)	<i>Max no. genes in region</i>	<i>Penetrance % (DD, ASD, CM)</i>	<i>Penetrance % (SCZ)</i>	<i>Associated NDDs & References</i>
15q11.2 del.	543	514	1,748	chr15:22,81-23,09	5	11.0	2.0	ID, DD, ASD, ADHD, SCZ ²²
16p13.11 dup.	275	258	888	chr16:15,51-16,29	7	8.4	2.2	ID, DD, ASD, ADHD, SCZ ²⁸
22q11.2 dup.	83	80	294	chr22:19,04-21,47	61	14.0	0.0	ID, DD ⁴²
1q21.1 dup.	73	64	193	chr1:146,53-147,39	9	18.0	2.9	ID, DD, ASD, ADHD, SCZ ⁷
16p12.1 del.	64	58	260	chr16:21,95-22,43	8	13.0	3.1	ID, DD ²⁹
NRXN1 del.	56	52	175	chr2:50,14-51,26	1	26.0	6.4	ID, DD, ASD, SCZ ^{8,9}
16p11.2 dup.	46	43	142	chr16:29,65-30,20	30	26.0	8.0	ID, DD ³¹
16p11.2 distal dup.	38	37	144	chr16:28,82-29,05	11	5.3	0.7	ID, DD, ASD, ADHD, SCZ ³¹
1q21.1 del.	35	33	119	chr1:146,53-147,39	9	35.0	5.2	ID, DD, ASD, SCZ ⁷
16p11.2 del.	28	27	123	chr16:29,65-30,20	30	8.0	0.3	ID, DD, ASD, ADHD, SCZ ³⁰
17q12 dup.	27	26	104	chr17:34,81-36,22	17	17.0	1.7	ID, DD, ASD, SCZ ³⁸
16p11.2 distal del.	14	11	62	chr16:28,82-29,05	11	23.0	2.6	ID, DD, ASD, ADHD, SCZ ³⁰
17q11.2 (<i>NF1</i>) del.	7	7	11	chr17:29,12-30,27	19	38.0	0.0	ID, DD, ASD ³⁶
17p13.3 (<i>YWHAE</i>) del.	6	6	27	chr17:1,25-1,30	1	14.0	0.0	ID, DD ³²
17q12 del.	4	4	9	chr17:34,81-36,22	19	39.0	4.0	ID, DD, ASD, SCZ ³⁸
17p13.3 (<i>YWHAE</i>) dup.	4	4	8	chr17:1,25-1,30	1	9.0	1.3	ID, DD ³³
15q24 dup.	3	2	10	chr15:72,90-78,15	77	100.0	0.0	ID, DD, ASD, ADHD ²⁵
WBS dup.	3	3	16	chr7:72,74-74,14	26	44.0	6.0	ID, DD, ASD, SCZ ¹⁶
22q11.2 del.	3	3	10	chr22:19,04-21,47	61	88.0	12.0	ID, DD, ASD, SCZ ^{40,41}
PWS dup.	2	2	19	chr15:23,68-28,39	116	4.2	0.5	ID, DD, ASD ²³
8p23.1 del.	2	2	4	chr8:8,10-11,87	6	97.0	3.3	ID, DD, ASD, ADHD ¹⁷
8p23.1 dup.	2	2	8	chr8:8,10-11,87	6	100.0	0.0	ID, DD ¹⁸
3q29 del.	2	2	9	chr3:195,72-197,35	28	53.0	18.0	ID, DD, ASD, ADHD, SCZ ¹²
22q11.2 distal dup.	2	1	14	chr22:21,92-23,65	26	16.0	0.0	ID, DD ⁴⁴
10q23 del.	1	1	3	chr10:82,05-88,93	29	100.0	0.0	ID, DD ²⁰
Wolf-Hirschhorn del.	1	1	3	chr4:1,55-2,09	13	100.0	0.0	ID, DD ¹³
2p37 del.	1	1	1	chr2:239,72-243,2	51	100.0	0.0	ID, DD, ASD ¹¹
22q11.2 distal del.	1	1	5	chr22:21,92-23,65	26	100.0	0.0	ID, DD ⁴³
17p13.3 (<i>PAFAH1B1</i>) dup.	1	1	3	chr17:2,49-2,59	1	17.0	0.0	ID, DD ³³
17q11.2 (<i>NF1</i>) dup.	1	1	3	chr17:29,12-30,27	19	98.0	1.7	ID, DD ³⁷

87 **Supplementary Table 5. ND-CNVs carried by included participants.** Consensus penetrance estimates were derived from Kirov et al.⁴⁷ and
88 Rosenfeld et al.⁴⁸. All identified ND-CNV loci were heterozygous. *n (PGS)* = no. of participants included in polygenic score analysis with ND-CNV;
89 *n (Exome)* = no. of participants included in rare variant analysis with ND-CNV; *n (UKB)* = no. of participants identified in the UK Biobank with ND-
90 CNV.

Supplementary Table 6 Multicollinearity testing for PS_Cog models			
Cohort	Variable	Tolerance	VIF
All ND-CNV carriers	PS_Cog	0.99	1.01
	Ed. Attainment	0.98	1.02
	TDI score	0.98	1.02
	Batch	1.00	1.00
ND-CNV (without 15q/16p)	PS_Cog	0.99	1.01
	Ed. Attainment	0.94	1.06
	TDI score	0.95	1.06
	PC3	1.00	1.00
All deletions	PS_Cog	0.98	1.02
	Age	0.69	1.45
	Employment Status	0.69	1.45
	Ed. Attainment	0.95	1.06
	TDI score	0.94	1.07
	Batch	0.99	1.01
	PC13	1.00	1.00
Deletions (without 15q)	PS_Cog	0.94	1.06
	Ed. Attainment	0.96	1.04
	TDI score	0.94	1.06
	Assessment Centre	0.95	1.05
	PC18	0.92	1.09
All duplications	PS_Cog	0.99	1.01
	Employment Status	0.96	1.04
	Ed. Attainment	0.94	1.07
	TDI score	0.97	1.04
	PC3	0.99	1.01
Duplications (without 16p)	PS_Cog	0.99	1.01
	Ed. Attainment	0.99	1.01
	PC3	0.99	1.01
15q11.2 deletion	PS_Cog	0.98	1.02
	Ed. Attainment	0.99	1.01
	TDI score	0.98	1.02
	Batch	1.00	1.00
	PC13	0.99	1.01
	PC14	0.96	1.05
	PC18	0.96	1.04
16p13.11 duplication	PS_Cog	0.99	1.01
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
Non-carriers	PS_Cog	0.97	1.04
	Age	0.62	1.62
	Sex (Male)	0.99	1.01
	Employment Status	0.67	1.50
	Ed. Attainment	0.94	1.06
	TDI score	0.97	1.03
	Assessment Centre	0.89	1.13
	PC3	0.95	1.05
	PC4	0.54	1.87
	PC5	0.57	1.74
	PC7	0.94	1.07
	PC9	0.94	1.06
	PC11	0.91	1.10
	PC14	0.95	1.05
	PC16	0.99	1.01
	PC19	1.00	1.00
PC20	1.00	1.00	

92 **Supplementary Table 6. Multicollinearity testing for cognition polygenic score linear**
93 **regression models.** Variance inflation factors were calculated for each model to ensure no
94 multicollinearity before and after backwards elimination of variables from each model. The
95 VIFs displayed are for the final models for each cohort. A threshold of >3 was used to remove
96 variables. VIFs were calculated using the *olsrr* package in R. Condition indices were also
97 calculated and a threshold of >10 was used to remove variables. *VIF = variance inflation*
98 *factor; PS_Cog = cognition polygenic score.*

99

Supplementary Table 7 Multicollinearity testing for PS_EA models			
Cohort	Variable	Tolerance	VIF
All ND-CNV carriers	PS_EA	1.00	1.00
	TDI score	0.99	1.01
	Employment Status	0.99	1.01
	Batch	1.00	1.00
	PC1	1.00	1.00
ND-CNV (without 15q/16p)	PS_EA	0.99	1.01
	TDI score	0.99	1.01
	Employment Status	0.99	1.01
	PC3	1.00	1.00
All deletions	PS_EA	0.99	1.01
	TDI score	0.98	1.02
	Employment Status	0.99	1.01
	Batch	1.00	1.00
	PC13	1.00	1.00
Deletions (without 15q)	PS_EA	1.00	1.00
	TDI score	0.99	1.01
	PC13	0.99	1.01
All duplications	PS_EA	1.00	1.00
	TDI score	1.00	1.00
	Employment Status	0.99	1.01
Duplications (without 16p)	PS_EA	0.99	1.01
	TDI score	0.98	1.02
	Employment Status	0.98	1.03
	PC3	1.00	1.00
15q11.2 deletion	PS_EA	0.97	1.03
	TDI score	0.96	1.04
	Employment Status	0.98	1.02
	Batch	1.00	1.00
	PC14	0.95	1.05
	PC18	0.96	1.04
16p13.11 duplication	PS_EA	0.99	1.01
	TDI score	1.00	1.00
	Employment Status	0.99	1.01
Non-carriers	PS_EA	0.98	1.10
	Age	0.62	1.61
	Sex (Male)	1.00	1.00
	TDI score	0.98	1.02
	Employment Status	0.67	1.49
	Assessment Centre	0.90	1.11
	PC3	0.95	1.05
	PC4	0.54	1.87
	PC5	0.59	1.72
	PC7	0.97	1.04
	PC11	0.91	1.10
	PC14	0.95	1.06
	PC16	0.99	1.00
	PC18	0.99	1.01
	PC19	1.00	1.00
PC20	0.99	1.01	

101 ***Supplementary Table 7. Multicollinearity testing for educational attainment polygenic score***
102 ***linear regression models.*** Variance inflation factors were calculated for each model to ensure
103 no multicollinearity before and after backwards elimination of variables from each model.
104 The VIFs displayed are for the final models for each cohort. A threshold of >3 was used to
105 remove variables. VIFs were calculated using the *olsrr* package in R. Condition indices were
106 also calculated and a threshold of >10 was used to remove variables. *VIF = variance inflation*
107 *factor; PS_EA = educational attainment polygenic score.*

108

Supplementary Table 8 Multicollinearity testing for PS_ASD models			
Cohort	Variable	Tolerance	VIF
All ND-CNV carriers	PS_ASD	1.00	1.00
	Employment Status	0.96	1.04
	Ed. Attainment	0.95	1.05
	TDI score	0.98	1.03
	Batch	1.00	1.00
ND-CNV (without 15q/16p)	PS_ASD	0.99	1.01
	Ed. Attainment	0.95	1.06
	TDI score	0.95	1.06
	PC3	0.99	1.01
All deletions	PS_ASD	0.99	1.01
	Age	0.95	1.05
	Ed. Attainment	0.96	1.04
	TDI score	0.96	1.04
	Batch	1.00	1.00
	PC13	0.99	1.01
Deletions (without 15q)	PS_ASD	0.99	1.01
	Ed. Attainment	0.97	1.03
	TDI score	0.96	1.04
	Assessment Centre	0.95	1.05
	PC18	0.95	1.05
All duplications	PS_ASD	1.00	1.00
	Employment Status	0.96	1.04
	Ed. Attainment	0.94	1.07
	TDI score	0.97	1.04
	PC3	0.99	1.01
Duplications (without 16p)	PS_ASD	1.00	1.00
	Ed. Attainment	0.99	1.01
	PC3	0.99	1.01
15q11.2 deletion	PS_ASD	0.98	1.02
	Ed. Attainment	0.99	1.01
	TDI score	0.98	1.02
	Batch	0.99	1.01
	PC13	0.99	1.01
	PC14	0.96	1.04
	PC18	0.96	1.04
16p13.11 duplication	PS_ASD	1.00	1.00
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
Non-carriers	PS_ASD	1.00	1.00
	Age	0.62	1.62
	Sex (Male)	0.99	1.01
	Employment Status	0.67	1.50
	Ed. Attainment	0.95	1.06
	TDI score	0.97	1.03
	Assessment Centre	0.89	1.13
	PC3	0.95	1.05
	PC4	0.53	1.87
	PC5	0.55	1.81
	PC7	0.92	1.08
	PC8	0.84	1.19
	PC9	0.94	1.07
	PC11	0.84	1.19
	PC14	0.94	1.06
	PC16	0.98	1.01
	PC17	1.00	1.00
	PC18	0.99	1.01
	PC19	1.00	1.00
	PC20	0.99	1.01

110 **Supplementary Table 8. Multicollinearity testing for autism polygenic score linear**
111 **regression models.** Variance inflation factors were calculated for each model to ensure no
112 multicollinearity before and after backwards elimination of variables from each model. The
113 VIFs displayed are for the final models for each cohort. A threshold of >3 was used to remove
114 variables. VIFs were calculated using the *olsrr* package in R. Condition indices were also
115 calculated and a threshold of >10 was used to remove variables. *VIF = variance inflation*
116 *factor; PS_ASD = autism polygenic score.*

117

Supplementary Table 9 Relationship between FI scores and PGS in ND-CNV carriers (excluding 16p11.13 dup. & 15q11.2 del.)							
<u>ND-CNV Cohort</u>	<u>n</u>	<u>IV</u>	<u>β</u>	<u>Adj. R²</u>	<u>P</u>	<u>Cohen's f²</u> <u>(Global)</u>	<u>Cohen's f²</u> <u>(Local)</u>
All ND-CNV carriers (excluding 16p11.3 dup. & 15q11.2 del.)	503	PS_Cog	0.1	0.20	0.02	-	-
		PS_EA	0.14	0.09	1.04x10^{-3*}	0.10	0.03
		PS_ASD	-0.01	0.19	0.84	-	-
All Del. Carriers (excluding 15q11.2 del.)	220	PS_Cog	0.04	0.29	0.51	-	-
		PS_EA	0.17	0.10	8.54x10^{-3*}	0.11	0.03
		PS_ASD	-0.03	0.13	0.57	-	-
All Dup. Carriers (excluding 16p11.13 dup.)	286	PS_Cog	0.11	0.14	0.05	-	-
		PS_EA	0.13	0.13	0.02	-	-
		PS_ASD	0.01	0.29	0.83	-	-

118

119 **Supplementary Table 9. Relationship between FI scores and rare variants in ND-CNV carriers and non-carriers (excluding 16p13.11 dup. &**
120 **15q11.2 del.).** All analyses were adjusted for covariates (Methods) and only covariates with significant associations were retained. The standard
121 β estimates are reported along with the adjusted (adj.) R² from multiple linear regression. IV = independent variable.

Supplementary Table 10. I Relationship between FI scores and PGS in ND-CNV carriers and non-carriers (excluding educational attainment covariate)

<u>ND-CNV Cohort</u>	<i>n</i>	<i>IV</i>	<i>β</i>	<i>Adj. R²</i>	<i>P</i>	<i>Cohen's f²</i> (Global)	<i>Cohen's f²</i> (Local)
All ND-CNV carriers	1,317	PS_Cog	0.17	0.08	5.29x10^{-8*}	0.08	0.02
		PS_ASD	0.01	0.06	0.74	-	-
All Del. Carriers	764	PS_Cog	0.15	0.09	8.29x10^{-6*}	0.10	0.03
		PS_ASD	0.01	0.06	0.68	-	-
All Dup. Carriers	561	PS_Cog	0.13	0.08	1.15x10^{-3*}	0.09	0.02
		PS_ASD	2.49x10 ⁻³	0.06	0.95	-	-
15q11.2 del.	543	PS_Cog	0.20	0.10	2.48x10^{-6*}	0.12	0.04
		PS_ASD	-0.01	0.07	0.84	-	-
16p13.11 dup.	275	PS_Cog	0.12	0.05	0.04	0.05	0.01
		PS_ASD	0.04	0.04	0.49	-	-
All ND-CNV carriers (excluding 15q11.2 del. & 16p13.11 dup.)	503	PS_Cog	0.12	0.07	4.79x10 ^{-3*}	0.08	0.01
		PS_ASD	2.98x10 ⁻³	0.07	0.94	-	-
Deletion carriers (excluding 15q11.2 del.)	220	PS_Cog	0.10	0.07	0.11	-	-
		PS_ASD	0.03	0.06	0.65	-	-
Duplication carriers (excluding 16p11.13 dup.)	286	PS_Cog	0.13	0.03	0.03	-	-
		PS_ASD	-0.03	0.15	0.61	-	-
Non-carriers	152,290	PS_Cog	0.13	0.05	< 2.00x10^{-16*}	0.05	0.02
		PS_ASD	0.02	0.03	1.50x10^{-12*}	0.02	3.19x10 ⁻⁴

123 **Supplementary Table 10. Relationship between *FI* scores and PGS in ND-CNV carriers and non-carriers (excluding Ed. attainment covariate).**

124 All analyses were adjusted for covariates (Methods; excluding ed. attainment) and only covariates with significant associations were retained.

125 Seven individuals carried both a deletion and duplication of which four carried both 15q11.2 del. and 16p13.11 dup. All ND-CNV carriers includes

126 carriers of 15q11.2 del. and 16p13.11 dup as well as other loci (See Supplementary Table 5.). The standard β estimates are reported along with

127 the adjusted (adj.) R^2 from multiple linear regression. Both the global and local *Cohen's f^2* are reported for significant p-values. The local *Cohen's*

128 *f^2* is only calculated for IVs. * = P-values that survived Bonferroni correction for 18 analyses (two PGS and nine sub-groups; $p < 2.78 \times 10^{-3}$). IV =

129 *independent variable.*

Supplementary Table 11. Relationship between fluid intelligence (FI) scores and rare variants in ND-CNV carriers and non-carriers						
ND-CNV Cohort	<i>n</i>	<i>IV</i>	<i>n RV carriers</i>	<i>β</i>	<i>Adj. R²</i>	<i>P</i>
All ND-CNV carriers	1,274	DDD	310	-3.58x10 ⁻³	0.16	0.89
		SFARI	198	0.02	0.16	0.37
		LOF	925	-0.03	0.16	0.15
All Deletion carriers	739	DDD	167	-6.88x10 ⁻³	0.16	0.84
		SFARI	114	0.03	0.15	0.41
		LOF	534	-0.04	0.16	0.20
All Duplication carriers	542	DDD	146	-4.43x10 ⁻³	0.17	0.91
		SFARI	87	0.02	0.17	0.58
		LOF	396	-0.03	0.17	0.51
15q11.2 del.	523	DDD	114	-0.04	0.14	0.33
		SFARI	80	-2.60x10 ⁻³	0.14	0.94
		LOF	378	-0.01	0.14	0.70
16p13.11 dup.	267	DDD	63	-0.17	0.19	0.11
		SFARI	44	0.01	0.18	0.82
		LOF	182	0.01	0.18	0.87
All ND-CNV carriers (excluding 15q11.2 del. & 16p13.11 dup.)	488	DDD	134	0.09	0.21	0.03
		SFARI	76	0.05	0.20	0.22
		LOF	358	-0.07	0.20	0.09
Deletion carriers (excluding 15q11.2 del.)	216	DDD	53	0.09	0.31	0.12
		SFARI	34	0.08	0.30	0.17
		LOF	156	-0.08	0.31	0.13
Duplication carriers (excluding 16p11.13 dup.)	275	DDD	83	0.08	0.14	0.13
		SFARI	43	0.02	0.13	0.67
		LOF	204	-0.05	0.13	0.41
Non-carriers	146,859	DDD	37,321	-9.69x10 ⁻⁴	0.15	0.95
		SFARI	24,885	3.32x10 ⁻⁴	0.15	0.89
		LOF	106,082	-6.26x10 ⁻³	0.15	9.51x10^{-3*}

130

131 **Supplementary Table 11. Relationship between FI scores and rare variants in ND-CNV**

132 **carriers and non-carriers.** All analyses were adjusted for covariates (Methods) and only

133 covariates with significant associations were retained. Seven individuals carried both a

134 deletion and duplication of which four individuals carried both 15q11.2 del. and 16p13.11

135 dup. and were included in both analyses. All ND-CNV carriers includes carriers of 15q11.2 del.

136 and 16p13.11 dup as well as other loci (See Supplementary Table 4.). The standard β

137 estimates are reported along with the adjusted (adj.) R^2 from multiple linear regression. P-

138 values which passed Bonferroni correction are highlighted in bold with a star. Global and local

139 *Cohen's f^2* estimates for LOF were 0.17 and 1.17×10^{-4} , respectively. *IV = independent variable.*

140 *N RV carriers = no. of participants that carried >1 rare variant.*

141

142

143

Supplementary Table 12 Multicollinearity testing for SFARI models			
Cohort	Variable	Tolerance	VIF
All ND-CNV carriers	SFARI	1.00	1.00
	Ed. Attainment	0.98	1.02
	TDI score	0.98	1.02
ND-CNV (without 15q/16p)	SFARI	1.00	1.00
	Ed. Attainment	0.92	1.06
	TDI score	0.92	1.06
	PC3	1.00	1.00
All deletions	SFARI	1.00	1.00
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
Deletions (without 15q)	SFARI	0.99	1.01
	Ed. Attainment	0.97	1.03
	TDI score	0.96	1.04
	Assessment Centre	0.95	1.05
	PC18	0.95	1.06
All duplications	SFARI	1.00	1.00
	Employment Status	0.96	1.04
	Ed. Attainment	0.96	1.04
	TDI score	1.00	1.00
Duplications (without 16p)	SFARI	1.00	1.00
	Ed. Attainment	0.99	1.01
	PC3	1.00	1.00
15q11.2 deletion	SFARI	0.99	1.01
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
	PC4	0.96	1.04
	PC13	0.99	1.01
	PC14	0.93	1.07
	PC18	0.95	1.05
16p13.11 duplication	SFARI	1.00	1.00
	Ed. Attainment	0.99	1.01
	PC3	0.99	1.01
Non-carriers	SFARI	1.00	1.00
	Age	0.62	1.62
	Sex (Male)	0.99	1.01
	Employment Status	0.67	1.50
	Ed. Attainment	0.95	1.06
	TDI score	0.97	1.03
	Assessment Centre	0.89	1.13
	PC3	0.95	1.05
	PC4	0.53	1.87
	PC5	0.55	1.81
	PC7	0.92	1.08
	PC8	0.84	1.19
	PC9	0.94	1.07
	PC11	0.84	1.19
	PC14	0.94	1.06
	PC16	0.99	1.01
PC18	0.99	1.01	
PC19	1.00	1.00	
PC20	1.00	1.00	

145 **Supplementary Table 12. Multicollinearity testing for SFARI rare variants linear regression**
146 **models.** Variance inflation factors were calculated for each model to ensure no
147 multicollinearity before and after backwards elimination of variables from each model. The
148 VIFs displayed are for the final models for each cohort. A threshold of >3 was used to remove
149 variables. VIFs were calculated using the *olsrr* package in R. Condition indices were also
150 calculated and a threshold of >10 was used to remove variables. *VIF = variance inflation*
151 *factor; SFARI = autism associated rare variants with SFARI scores of 1.*

152

Supplementary Table 13 Multicollinearity testing for DDD models			
Cohort	Variable	Tolerance	VIF
All ND-CNV carriers	DDD	1.00	1.00
	Ed. Attainment	0.98	1.02
	TDI score	0.98	1.02
ND-CNV (without 15q/16p)	DDD	1.00	1.00
	Ed. Attainment	0.94	1.06
	TDI score	0.94	1.06
	PC3	1.00	1.00
	PC18	1.00	1.00
All deletions	DDD	1.00	1.00
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
	PC13	1.00	1.00
	PC19	1.00	1.00
Deletions (without 15q)	DDD	0.98	1.02
	Ed. Attainment	0.97	1.03
	TDI score	0.96	1.05
	Assessment Centre	0.95	1.06
	PC18	0.95	1.05
All duplications	DDD	1.00	1.00
	Ed. Attainment	0.96	1.04
	TDI score	0.96	1.04
	PC3	1.00	1.00
Duplications (without 16p)	DDD	1.00	1.00
	Ed. Attainment	1.00	1.00
	PC3	1.00	1.00
15q11.2 deletion	DDD	0.99	1.01
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
	PC4	0.96	1.04
	PC13	0.99	1.01
	PC14	0.93	1.08
16p13.11 duplication	DDD	1.00	1.00
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
Non-carriers	DDD	0.99	1.00
	Age	0.62	1.62
	Sex (Male)	0.99	1.01
	Employment Status	0.67	1.50
	Ed. Attainment	0.95	1.06
	TDI score	0.97	1.03
	Assessment Centre	0.88	1.13
	PC3	0.95	1.05
	PC4	0.54	1.87
	PC5	0.56	1.77
	PC7	0.95	1.06
	PC8	0.85	1.18
	PC11	0.84	1.19
	PC14	0.94	1.06
	PC16	1.00	1.00
	PC17	1.00	1.00
	PC18	0.99	1.01
PC19	1.00	1.00	
PC20	0.99	1.01	

154 **Supplementary Table 13. Multicollinearity testing for DDD rare variant linear regression**
155 **models.** Variance inflation factors were calculated for each model to ensure no
156 multicollinearity before and after backwards elimination of variables from each model. The
157 VIFs displayed are for the final models for each cohort. A threshold of >3 was used to remove
158 variables. VIFs were calculated using the *olsrr* package in R. Condition indices were also
159 calculated and a threshold of >10 was used to remove variables. *VIF = variance inflation*
160 *factor; DDD = ID/DD associated rare variants with DDD confirmed scores.*

161

Supplementary Table 14 Multicollinearity testing for LOF models			
Cohort	Variable	Tolerance	VIF
All ND-CNV carriers	LOF	0.99	1.00
	Ed. Attainment	0.98	1.02
	TDI score	0.98	1.02
ND-CNV (without 15q/16p)	LOF	0.98	1.02
	Ed. Attainment	0.94	1.06
	TDI score	0.94	1.06
	PC3	0.98	1.02
All deletions	LOF	1.00	1.00
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
	PC13	1.00	1.00
Deletions (without 15q)	LOF	0.98	1.00
	Ed. Attainment	0.97	1.03
	TDI score	0.96	1.04
	Assessment Centre	0.95	1.05
	PC18	0.93	1.07
All duplications	LOF	1.00	1.00
	Ed. Attainment	0.97	1.04
	TDI score	0.96	1.04
	PC18	1.00	1.00
Duplications (without 16p)	LOF	0.98	1.02
	Ed. Attainment	0.99	1.01
	PC3	0.98	1.02
15q11.2 deletion	LOF	0.99	1.01
	Ed. Attainment	0.99	1.01
	TDI score	0.98	1.02
	PC4	0.96	1.04
	PC13	0.99	1.01
	PC14	0.93	1.08
	PC18	0.95	1.05
16p13.11 duplication	LOF	1.00	1.00
	Ed. Attainment	0.99	1.01
	TDI score	0.99	1.01
Non-carriers	LOF	1.00	1.00
	Age	0.62	1.62
	Sex (Male)	0.99	1.01
	Employment Status	0.67	1.50
	Ed. Attainment	0.95	1.06
	TDI score	0.97	1.03
	Assessment Centre	0.89	1.13
	PC3	0.95	1.05
	PC4	0.54	1.87
	PC5	0.56	1.77
	PC7	0.95	1.06
	PC8	0.85	1.18
	PC11	0.84	1.19
	PC14	0.94	1.06
	PC16	1.00	1.00
	PC17	1.00	1.00
PC18	0.99	1.01	
PC19	1.00	1.00	
PC20	0.99	1.01	

163 **Supplementary Table 14. Multicollinearity testing for autism polygenic score linear**
164 **regression models.** Variance inflation factors were calculated for each model to ensure no
165 multicollinearity before and after backwards elimination of variables from each model. The
166 VIFs displayed are for the final models for each cohort. A threshold of >3 was used to remove
167 variables. VIFs were calculated using the *olsrr* package in R. Condition indices were also
168 calculated and a threshold of >10 was used to remove variables. *VIF = variance inflation*
169 *factor; LOF = rare variants in brain-expressed, intolerant to loss-of-function loci.*

170

Supplementary Table 15. I Relationship between fluid intelligence (FI) scores and rare variants in ND-CNV carriers and non-carriers (excluding ed. attainment covariate)						
ND-CNV Cohort	<i>n</i>	<i>IV</i>	<i>n RV carriers</i>	β	<i>Adj. R²</i>	<i>P</i>
All ND-CNV carriers	1,274	DDD	310	-0.20	0.05	0.92
		SFARI	198	0.04	0.05	0.14
		LOF	925	-0.03	0.05	0.29
All Deletion carriers	739	DDD	167	4.07×10^{-3}	0.05	0.91
		SFARI	114	0.04	0.05	0.29
		L.O.F	534	-0.03	0.04	0.35
All Duplication carriers	542	DDD	146	-9.54×10^{-3}	0.06	0.82
		SFARI	87	0.04	0.06	0.40
		LOF	396	-0.03	0.06	0.52
15q11.2 del.	523	DDD	114	-0.02	0.05	0.64
		SFARI	80	0.02	0.06	0.69
		LOF	378	4.57×10^{-3}	0.06	0.91
16p13.11 dup.	267	DDD	63	-0.09	0.06	0.13
		SFARI	44	0.02	0.04	0.70
		LOF	182	0.03	0.04	0.62
All ND-CNV carriers (excluding 15q11.2 del. & 16p13.11 dup.)	488	DDD	134	0.07	0.07	0.10
		SFARI	76	0.07	0.06	0.10
		LOF	358	-0.08	0.07	0.07
Deletion carriers (excluding 15q11.2 del.)	216	DDD	53	0.06	0.05	0.35
		SFARI	34	0.11	0.06	0.09
		LOF	156	-0.11	0.07	0.09
Duplication carriers (excluding 16p11.13 dup.)	275	DDD	83	0.08	0.08	0.18
		SFARI	43	0.04	0.07	0.45
		LOF	204	-0.11	0.07	0.09
Non-carriers	146,859	DDD	37,321	-1.85×10^{-4}	0.03	0.94
		SFARI	24,885	2.22×10^{-4}	0.03	0.93
		LOF	106,082	-0.01	0.03	2.22×10^{-4} *

171

172 **Supplementary Table 15. Relationship between FI scores and rare variants in ND-CNV**173 **carriers and non-carriers (excluding Ed. Attainment covariate).** All analyses were adjusted

174 for covariates (Methods; excluding ed. attainment) and only covariates with significant

175 associations were retained. Seven individuals carried both a deletion and duplication of which

176 four individuals carried both 15q11.2 del. and 16p13.11 dup. and were included in both

177 analyses. All ND-CNV carriers includes carriers of 15q11.2 del. and 16p13.11 dup as well as

178 other loci (See Supplementary Table 4.). The standard β estimates are reported along with179 the adjusted (adj.) R^2 from multiple linear regression. P-values which passed Bonferroni

180 correction are highlighted in bold with a star. Global and local *Cohen's* f^2 estimates for LOF
181 were 0.03 and 8.25×10^{-5} , respectively. *IV = independent variable. N RV carriers = no. of*
182 *participants that carried >1 rare variant.*

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185

Supplementary Table 16. Relationship between FI scores and ND-CNVs adjusted for additional variants								
Independent variable	<i>n</i> (+ non-carriers)	<i>PGS + RVs</i> <i>covariates</i>	β	<i>Adj. R</i> ²	<i>p</i>	F-test (<i>p</i>)	<i>Cohen's f</i> ² (Global)	<i>Cohen's f</i> ² (Local)
All ND-CNVs	148,133	+	-0.37	0.07	<2.00x10 ^{-16*}	<2.2 x10 ⁻¹⁶	0.06	1.15x10 ⁻³
		-	-0.39	0.04	<2.00x10 ^{-16*}			
All Deletions	147,598	+	-0.35	0.08	<2.00x10 ^{-16*}	<2.2 x10 ⁻¹⁶	0.08	6.50x10 ⁻⁴
		-	-0.38	0.03	<2.00x10 ^{-16*}			
All Duplications	147,401	+	-0.40	0.08	<2.00x10 ^{-16*}	<2.2 x10 ⁻¹⁶	0.08	6.28x10 ⁻⁴
		-	-0.41	0.03	<2.00x10 ^{-16*}			
15q11.2 del.	147,382	+	-0.30	0.08	1.63x10 ^{-12*}	<2.2 x10 ⁻¹⁶	0.08	3.35x10 ⁻⁴
		-	-0.33	0.03	2.15x10 ^{-14*}			
16p13.11 dup.	147,126	+	-0.25	0.08	1.49x10 ^{-5*}	<2.2 x10 ⁻¹⁶	0.08	1.19x10 ⁻⁴
		-	-0.28	0.03	2.86x10 ^{-6*}			
All ND-CNVs (excluding 15q11.2 del. & 16p13.11 dup.)	147,347	+	-0.51	0.08	<2.00x10 ^{-16*}	<2.2 x10 ⁻¹⁶	0.08	9.31x10 ⁻⁴
		-	-0.51	0.04	<2.00x10 ^{-16*}			
All Deletions (excluding 15q11.2 del.)	147,075	+	-0.48	0.08	2.97x10 ^{-13*}	<2.2 x10 ⁻¹⁶	0.08	3.46x10 ⁻⁴
		-	-0.49	0.03	2.48x10 ^{-13*}			
All Duplications (excluding 16p13.11 dup.)	147,134	+	-0.54	0.08	<2.00x10 ^{-16*}	<2.2 x10 ⁻¹⁶	0.08	5.84x10 ⁻⁴
		-	-0.54	0.03	<2.00x10 ^{-16*}			

186

187 **Supplementary Table 16. Relationship between FI scores and ND-CNVs adjusted for additional variants.** All analyses were adjusted for
188 covariates (Methods). *n* represents the ND-CNV of interest plus non-carriers. Three participants carried both 15q11.2 del. and 16p13.11 dup.
189 and were included in both analyses. All ND-CNV carriers includes carriers of 15q11.2 del. and 16p13.11 dup as well as other loci. A “+/- “symbol
190 in *PGS+ RV covariates* indicates whether the model was adjusted for additional common and rare genetic variants. The standard β estimates are
191 reported along with the adjusted (adj.) from multiple linear regression. Bonferroni correction *p*-value < 0.008. *n ND-CNV carriers = 1,274; n*
192 *deletion carriers = 789; n duplication carriers = 542; n 15q11.2 del. carriers = 523; n 16p13.11 carriers = 267; n ND-CNV carriers (excluding 15q11.2*

193 *del. carriers*) = 488; *n deletion carriers (excluding 15q11.2 carriers)* = 216; *n deletion carriers (excluding 16p13.11 dup. carriers)* = 275; *n non-*
194 *carriers* = 146,859. See table S6 for numbers of ND-CNV carriers without non-carriers.

Supplementary Table 17 PPVs for lower fluid intelligence (FI) scores based on PS_Cog				
Percentile of PS_Cog	Group	PPV	95% C.I	p
<10	All ND-CNVs	0.127	[0.077, 0.193]	0.01
	All Duplications	0.194	[0.104, 0.314]	3.38x10⁻³
	All Deletions	0.075	[0.028, 0.156]	0.48
	15q11.2_del.	0.083	[0.028, 0.184]	0.09
	16p13.11_dup.	0.143	[0.040, 0.327]	0.02
	Non-carrier	0.044	[0.041, 0.047]	<2.2x10⁻¹⁶
<25	All ND-CNVs	0.090	[0.063, 0.123]	0.13
	All Duplications	0.108	[0.064, 0.167]	0.19
	All Deletions	0.078	[0.046, 0.121]	0.32
	15q11.2_del.	0.067	[0.034, 0.116]	0.11
	16p13.11_dup.	0.062	[0.020, 0.138]	0.26
	Non-carrier	0.039	[0.037, 0.041]	<2.2x10⁻¹⁶
<50	All ND-CNVs	0.094	[0.073, 0.118]	0.02
	All Duplications	0.101	[0.068, 0.141]	0.19
	All Deletions	0.071	[0.048, 0.100]	0.35
	15q11.2_del.	0.058	[0.048, 0.101]	0.11
	16p13.11_dup.	0.048	[0.019, 0.096]	0.53
	Non-carrier	0.034	[0.033, 0.036]	2.15x10⁻¹²
>50	All ND-CNVs	0.061	[0.046, 0.078]	0.28
	All Duplications	0.072	[0.049, 0.102]	0.65
	All Deletions	0.052	[0.035, 0.074]	0.47
	15q11.2_del.	0.034	[0.018, 0.058]	0.69
	16p13.11_dup.	0.031	[0.011, 0.066]	0.71
	Non-carrier	0.025	[0.024, 0.026]	<2.2x10⁻¹⁶
>75	All ND-CNVs	0.053	[0.037, 0.074]	0.10
	All Duplications	0.062	[0.037, 0.098]	0.32
	All Deletions	0.045	[0.026, 0.073]	0.31
	15q11.2_del.	0.026	[0.009, 0.055]	0.32
	16p13.11_dup.	0.031	[0.009, 0.077]	0.82
	Non-carrier	0.023	[0.022, 0.024]	<2.2x10⁻¹⁶
>90	All ND-CNVs	0.018	[0.002, 0.063]	0.02
	All Duplications	0.025	[0.001, 0.132]	0.37
	All Deletions	0.014	[0, 0.074]	0.13
	15q11.2_del.	0.018	[0, 0.097]	0.73
	16p13.11_dup.	0.000	[0, 0.206]	1.00
	Non-carrier	0.016	[0.014, 0.018]	<2.2x10⁻¹⁶

195

196 **Supplementary Table 17. Positive predictive values for lower FI scores based on PS_Cog.**

197 Here is shown the positive predictive values (PPVs) for participants grouped by cognition
198 polygenic score (PS_Cog) percentile stratified by ND-CNV carrier group. PPVs for are given for
199 lower FI scores (< 2 s.d. from cohort mean) against non-carriers. 7% of ND-CNV carriers, 4%
200 of deletion carriers, 6% of duplication carriers, 4% of 15q11.2 del. carriers, 4% of 16p13.11
201 dup. carriers, and 3% of non-carriers had FI scores two standard deviations below the cohort

202 mean and was taken as the pre-test probability. The confidence intervals are also presented.

203 *PS_Cog* = cognition polygenic score.

204

Supplementary Table 18 PPVs for lower fluid intelligence (FI) scores based on PS_Cog				
Percentile of PS_EA	Group	PPV	95% C.I	p
<10	ND-CNV	0.107	[0.064, 0.166]	0.08
	All Duplications	0.090	[0.034, 0.185]	0.66
	All Deletions	0.120	[0.061, 0.204]	0.03
	15q11.2_del.	0.118	[0.052, 0.219]	5.71x10⁻³
	16p13.11_dup.	0.030	[0, 0.158]	1.00
	Non-carrier	0.057	[0.053, 0.061]	<2.2x10⁻¹⁶
<25	ND-CNV	0.093	[0.066, 0.127]	0.09
	All Duplications	0.097	[0.056, 0.156]	0.46
	All Deletions	0.090	[0.056, 0.135]	0.07
	15q11.2_del.	0.086	[0.048, 0.140]	7.43x10⁻³
	16p13.11_dup.	0.013	[0, 0.068]	0.38
	Non-carrier	0.048	[0.046, 0.05]	<2.2x10⁻¹⁶
25-50	ND-CNV	0.089	[0.069, 0.113]	0.05
	All Duplications	0.106	[0.073, 0.148]	0.10
	All Deletions	0.076	[0.053, 0.106]	0.18
	15q11.2_del.	0.056	[0.048, 0.101]	0.11
	16p13.11_dup.	0.048	[0.019, 0.096]	0.53
	Non-carrier	0.038	[0.037, 0.04]	<2.2x10⁻¹⁶
>50	ND-CNV	0.059	[0.045, 0.077]	0.22
	All Duplications	0.076	[0.052, 0.106]	0.86
	All Deletions	0.046	[0.030, 0.067]	0.20
	15q11.2_del.	0.029	[0.012, 0.058]	0.51
	16p13.11_dup.	0.051	[0.024, 0.092]	0.36
	Non-carrier	0.022	[0.021, 0.023]	<2.2x10⁻¹⁶
>75	ND-CNV	0.046	[0.031, 0.065]	0.02
	All Duplications	0.057	[0.033, 0.094]	0.21
	All Deletions	0.038	[0.020, 0.064]	0.09
	15q11.2_del.	0.026	[0.013, 0.047]	0.19
	16p13.11_dup.	0.031	[0.009, 0.077]	0.82
	Non-carrier	0.019	[0.018, 0.02]	<2.2x10⁻¹⁶
>90	ND-CNV	0.019	[0.002, 0.066]	0.03
	All Duplications	0.020	[0, 0.109]	0.37
	All Deletions	0.020	[0, 0.092]	0.26
	15q11.2_del.	0.022	[0, 0.118]	1.00
	16p13.11_dup.	0.000	[0, 0.142]	1.00
	Non-carrier	0.012	[0.010, 0.013]	<2.2x10⁻¹⁶

205

206 **Supplementary Table 18. Positive predictive values for lower FI scores based on PS_EA.** Here

207 is shown the positive predictive values (PPVs) for participants grouped by cognition education

208 attainment polygenic score (PS_EA) percentile stratified by ND-CNV carrier group. PPVs for

209 are given for lower *FI* scores (< 2 s.d. from cohort mean) against non-carriers. 7% of ND-CNV
210 carriers, 4% of deletion carriers, 6% of duplication carriers, 4% of 15q11.2 del. carriers, 4% of
211 16p13.11 dup. carriers, and 3% of non-carriers had *FI* scores two standard deviations below
212 the cohort mean and was taken as the pre-test probability. The confidence intervals are also
213 presented.

Supplementary Table 19 Polygenic score differences between and within ND-CNV carriers and non-carriers													
PGS	ND-CNV group	ND-CNV Carrier vs Non-Carriers					Sex differences within Groups						
		n	mean [s.d]	p	Cor. p	d	Male (n)	Female (n)	Male mean [s.d]	Female mean [s.d]	p	Cor. p	d
PS_Cog	All ND-CNV	1,318	-0.08 [0.99]	2.54x10⁻³	0.11	-	666	652	-0.08 [0.96]	-0.08 [1.03]	0.94	-	-
	All duplications	561	-0.08 [0.96]	0.05	-	-	290	271	-0.07 [0.89]	-0.09 [1.02]	0.81	-	-
	All deletions	764	-0.08 [1.03]	0.02	0.99	-	380	384	-0.09 [1.01]	-0.07 [1.04]	0.74	-	-
	All ND-CNVs (excluding 15q11.2 del. & 16p11.13 dup.)	504	-0.027 [0.99]	0.53	-	-	261	243	-0.06 [0.91]	3.01x10 ⁻⁴ [1.07]	0.68	-	-
	Duplications (excluding 16p11.13 dup.)	286	-0.04 [1.00]	0.48	-	-	154	132	-0.09 [0.90]	0.01 [1.10]	0.39	-	-
	Deletions (excluding 15q11.2 del.)	221	-0.01 [0.98]	0.79	-	-	108	113	-0.01 [0.93]	-0.01 [1.03]	0.96	-	-
	15q11.2 del.	543	-0.11 [1.05]	0.02	0.49	-	272	271	-0.13 [1.05]	-0.09 [1.05]	0.69	-	-
	16p13.11 dup.	275	-0.13 [0.91]	0.02	0.86	-	136	139	-0.06 [0.88]	-0.20 [0.93]	0.21	-	-
	22q11.2 dup.	83	-0.10 [1.04]	0.35	-	-	44	39	-0.06 [0.93]	-0.15 [1.17]	0.70	-	-
	1q21.1 dup.	73	-0.03 [1.07]	0.78	-	-	39	34	-0.04 [0.86]	-0.02 [1.28]	0.95	-	-
	16p12.1 del.	64	-1.39x10 ⁻³ [0.96]	0.99	-	-	-	-	-	-	-	-	-
	NRXN1 del.	56	-0.05 [1.04]	0.69	-	-	-	-	-	-	-	-	-
	16p11.2 dup.	46	-0.34 [1.01]	0.81	-	-	-	-	-	-	-	-	-
	16p11.2 distal dup.	38	-0.03 [0.94]	0.87	-	-	-	-	-	-	-	-	-
	1q21.1 del.	35	-0.07 [1.16]	0.66	-	-	-	-	-	-	-	-	-
Non-carrier	152,325	7.16x10 ⁻⁴ [1.00]	-	-	-	71,534	80,791	-9.71x10 ⁻⁴ [1.00]	2.21x10 ⁻³ [1.00]	0.54	-	-	
PS_EA	All ND-CNV	1,318	-0.09 [1.02]	4.41x10⁻⁴	0.02	0.097	666	652	-0.11 [0.98]	-0.08 [1.05]	0.60	-	-
	All duplications	561	-0.07 [1.02]	0.10	-	-	290	271	-0.01 [1.00]	0.01 [1.00]	0.35	-	-
	All deletions	764	-0.11 [1.01]	1.15x10 ⁻³	0.05	-	380	384	-0.11 [0.98]	-0.12 [1.04]	0.93	-	-
	All ND-CNVs (excluding 15q11.2 del. & 16p11.13 dup.)	504	-0.06 [1.00]	0.17	-	-	261	243	-0.13 [0.96]	0.01 [1.04]	0.12	-	-
	Duplications (excluding 16p11.13 dup.)	286	-0.03 [1.00]	0.57	-	-	154	132	-0.15 [0.96]	-0.10 [1.03]	0.04	1.00	-
	Deletions (excluding 15q11.2 del.)	221	-1.00 [0.99]	0.15	-	-	108	113	-0.09 [0.96]	-0.10 [1.03]	0.99	-	-
	15q11.2 del.	543	-0.13 [1.02]	3.23x10 ⁻³	0.15	-	272	271	-0.12 [0.99]	-0.13 [1.05]	0.93	-	-
	16p13.11 dup.	275	-0.11 [1.03]	0.08	-	-	136	139	-0.06 [0.98]	-0.15 [1.08]	0.49	-	-
	22q11.2 dup.	83	-0.10 [1.01]	0.34	-	-	44	39	-0.22 [1.00]	0.03 [1.01]	0.26	-	-
	1q21.1 dup.	73	-0.04 [0.91]	0.75	-	-	39	34	-0.11 [0.76]	0.05 [1.06]	0.47	-	-
	16p12.1 del.	64	-0.35 [0.89]	4.85x10 ⁻³	0.22	-	-	-	-	-	-	-	-
	NRXN1 del.	56	0.01 [1.12]	0.93	-	-	-	-	-	-	-	-	-
	16p11.2 dup.	46	0.17 [1.04]	0.24	-	-	-	-	-	-	-	-	-
	16p11.2 distal dup.	38	-0.22 [1.14]	0.17	-	-	-	-	-	-	-	-	-
	1q21.1 del.	35	0.19 [0.88]	0.25	-	-	-	-	-	-	-	-	-
Non-carrier	152,325	8.33x10 ⁻⁴ [1.00]	-	-	-	71,534	80,791	-0.01 [1.00]	0.01 [1.00]	4.21x10 ⁻⁶	1.39x10 ⁻⁴	0.024	
PS_ASD	All ND-CNV	1,318	0.04 [1.02]	0.11	-	-	666	652	0.04 [1.06]	0.04 [0.97]	0.98	-	-
	All dup. carriers	561	0.06 [1.01]	0.17	-	-	290	271	0.06 [1.10]	0.06 [0.89]	0.99	-	-
	All del. carriers	764	0.04 [1.03]	0.30	-	-	380	384	0.03 [1.04]	0.04 [1.02]	0.91	-	-
	All ND-CNVs (excluding 15q11.2 del. & 16p11.13 dup.)	504	0.02 [1.02]	0.71	-	-	261	243	-0.01 [1.09]	0.05 [0.94]	0.52	-	-
	Duplications (excluding 16p11.13 dup.)	286	0.04 [1.01]	0.45	-	-	154	132	0.04 [1.10]	0.03 [0.90]	0.96	-	-
	Deletions (excluding 15q11.2 del.)	221	-0.02 [1.03]	0.80	-	-	108	113	-0.10 [1.06]	0.06 [1.00]	0.23	-	-
	15q11.2 del.	543	0.06 [1.03]	0.16	-	-	272	271	0.09 [1.02]	0.03 [1.03]	0.54	-	-
	16p13.11 dup.	275	0.07 [1.00]	0.23	-	-	136	139	0.07 [1.10]	0.07 [0.89]	0.99	-	-
	22q11.2 dup.	83	0.06 [1.23]	0.61	-	-	44	39	0.14 [1.36]	-0.04 [1.08]	0.51	-	-
	1q21.1 dup.	73	0.05 [0.88]	0.68	-	-	39	34	0.03 [0.91]	0.07 [0.84]	0.88	-	-
	16p12.1 del.	64	0.08 [1.07]	0.50	-	-	-	-	-	-	-	-	-
	NRXN1 del.	56	0.12 [1.20]	0.38	-	-	-	-	-	-	-	-	-
	16p11.2 dup.	46	0.20 [0.80]	0.18	-	-	-	-	-	-	-	-	-
	16p11.2 distal dup.	38	-0.05 [1.02]	0.77	-	-	-	-	-	-	-	-	-
	1q21.1 del.	35	-0.02 [1.02]	0.92	-	-	-	-	-	-	-	-	-
Non-carrier	152,325	-3.76x10 ⁻⁴ [1.00]	-	-	-	71,534	80,791	-0.01 [1.00]	0.01 [1.00]	0.02	0.60	-	

214

215 **Supplementary Table 19. Additional common variant load differences between and within**216 **ND-CNV carriers and non-carriers.** The table shows results for both differences in PGS

217 between ND-CNV carriers and non-carriers, and sex differences in PGS with groups of ND-CNV

218 carriers. Highlighted in bold are significant *p*-values that passed Bonferroni correction (*p*

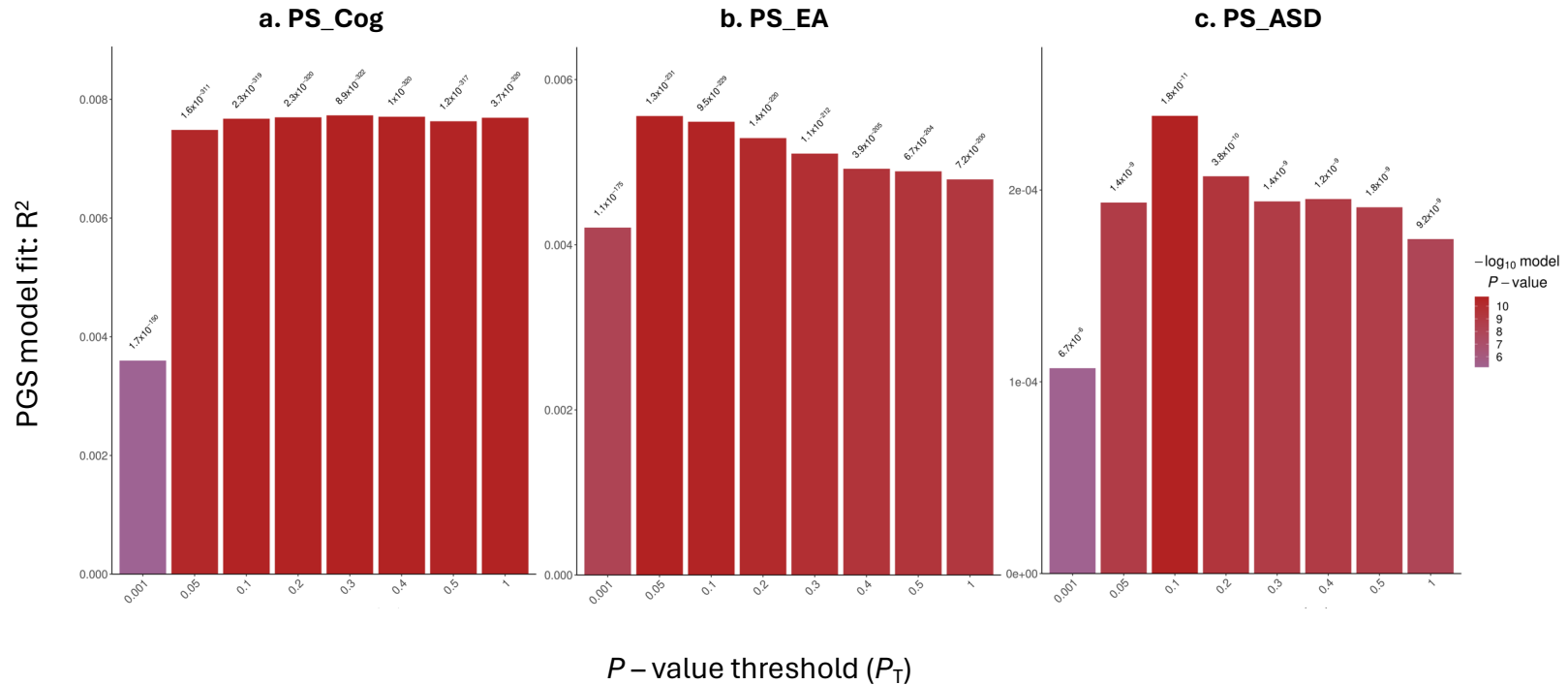
219 $<1.11 \times 10^{-3}$, 45 tests). Cohen's d was calculated for significant p -values after Bonferroni
220 correction. Cohen's d : $> 0.15 = \text{small effect}$; $>0.4 = \text{medium effect}$; $> 0.75 = \text{large effect}$.
221 $PS_Cog = \text{Cognition polygenic score}$; $PS_EA = \text{educational attainment polygenic score}$; PS_ASD
222 $= \text{autism polygenic score}$; $Cor. p = \text{corrected } p\text{-value}$; $d = \text{Cohen's } d$.

Supplementary Table 20 Additional rare variant load differences between and within ND-CNV carriers and non-carriers												
RV	ND-CNV Group	Carrier vs Control				Sex differences within Groups						
		n	median [range]	p	Corrected p	Male (n)	Female (n)	Male median	Female median	p	Corrected p	r
DDD	All ND-CNVs	1,275	0 [0, 3]	0.34	-	637	638	0 [0, 3]	0 [0, 3]	0.07	-	-
	All duplications	542	0 [0, 3]	0.47	-	277	265	0 [0, 3]	0 [0, 3]	0.19	-	-
	All deletions	740	0 [0, 3]	0.08	-	364	376	0 [0, 3]	0 [0, 3]	0.23	-	-
	All ND-CNVs (excluding 15q11.2 del. & 16p11.13 dup.)	489	0 [0, 3]	0.35	-	251	238	0 [0, 3]	0 [0, 2]	0.09	-	-
	Duplications (excluding 16p11.13 dup.)	275	0 [0, 3]	0.08	-	147	128	0 [0, 3]	0 [0, 3]	0.49	-	-
	Deletions (excluding 15q11.2 del.)	217	0 [0, 3]	0.74	-	105	112	0 [0, 3]	0 [0, 1]	0.10	-	-
	15q11.2 del.	523	0 [0, 3]	0.06	-	259	264	0 [0, 3]	0 [0, 3]	0.72	-	-
	16p13.11 dup.	267	0 [0, 3]	0.45	-	130	137	0 [0, 3]	0 [0, 2]	0.29	-	-
	22q11.2 dup.	81	0 [0, 3]	2.04x10 ⁻³	0.06	-	-	-	-	-	-	-
	Non-carrier	146,894	0 [0,5]	-	-	68,983	77,911	0 [0, 5]	0 [0, 5]	0.06	-	-
SFARI	All ND-CNVs	1,275	0 [0, 2]	0.19	-	637	638	0 [0, 2]	0 [0, 2]	0.08	-	-
	All duplications	542	0 [0, 2]	0.55	-	277	265	0 [0, 2]	0 [0, 2]	0.27	-	-
	All deletions	740	0 [0, 2]	0.30	-	364	376	0 [0, 2]	0 [0, 2]	0.15	-	-
	All ND-CNVs (excluding 15q11.2 del. & 16p11.13 dup.)	489	0 [0, 2]	0.42	-	251	238	0 [0, 1]	0 [0, 2]	0.94	-	-
	Duplications (excluding 16p11.13 dup.)	275	0 [0, 2]	0.51	-	147	128	0 [0, 1]	0 [0, 2]	0.98	-	-
	Deletions (excluding 15q11.2 del.)	217	0 [0, 2]	0.70	-	105	112	0 [0, 1]	0 [0, 2]	1.00	-	-
	15q11.2 del.	523	0 [0, 2]	0.33	-	259	264	0 [0, 2]	0 [0, 2]	0.08	-	-
	16p13.11 dup.	267	0 [0, 2]	0.84	-	130	137	0 [0, 2]	0 [0, 1]	0.11	-	-
	22q11.2 dup.	81	0 [0, 2]	0.82	-	-	-	-	-	-	-	-
	Non-carrier	146,894	0 [0,4]	-	-	68,983	77,911	0 [0, 4]	0 [0, 4]	0.70	-	-
LOF	All ND-CNVs	1,275	1 [0, 6]	0.96	-	637	638	1 [0, 6]	1 [0, 6]	0.02	0.50	-
	All duplications	542	1 [0, 6]	0.67	-	277	265	1 [0, 5]	1 [0, 6]	0.04	1.00	-
	All deletions	740	1 [0, 6]	0.65	-	364	376	1 [0, 6]	1 [0, 6]	0.14	-	-
	All ND-CNVs (excluding 15q11.2 del. & 16p11.13 dup.)	489	1 [0, 6]	0.95	-	251	238	1 [0, 6]	1 [0, 6]	0.05	-	-
	Duplications (excluding 16p11.13 dup.)	275	1 [0, 6]	0.51	-	147	128	1 [0, 5]	1 [0, 6]	0.02	0.74	-
	Deletions (excluding 15q11.2 del.)	217	1 [0, 6]	0.49	-	105	112	1 [0, 6]	1 [0, 6]	0.57	-	-
	15q11.2 del.	523	1 [0, 5]	0.92	-	259	264	1 [0, 5]	1 [0, 5]	0.17	-	-
	16p13.11 dup.	267	1 [0, 5]	0.95	-	130	137	1 [0, 5]	1 [0, 5]	0.46	-	-
	22q11.2 dup.	81	1 [0, 4]	0.93	-	-	-	-	-	-	-	-
	Non-carrier	146,894	0 [0,10]	-	-	68,983	77,911	0 [0, 10]	0 [0, 9]	1.05x10 ⁻¹¹	3.16x10 ⁻¹⁰	0.02

224 **Supplementary Table 20. Additional rare variant load differences between and within ND-CNV carriers and non-carriers.** Listed are the
225 uncorrected p -values from two-tailed Wilcoxon rank sum tests assessing the difference in rare variant counts between carriers of ND-CNVs and
226 non-carriers, and between males and females within each group. Highlighted in bold are significant p -values that passed Bonferroni correction
227 ($p < 1.66 \times 10^{-3}$, 30 tests). r effect sizes were calculated for significant p -values after Bonferroni correction. r : $>0.1 = \textit{small effect}$; $>0.3 = \textit{medium}$
228 \textit{effect} ; $>0.5 = \textit{large effect}$. *RV – rare variant gene-set*

229 **4. Supplementary Figures 1-15**

Supplementary Figure 1.

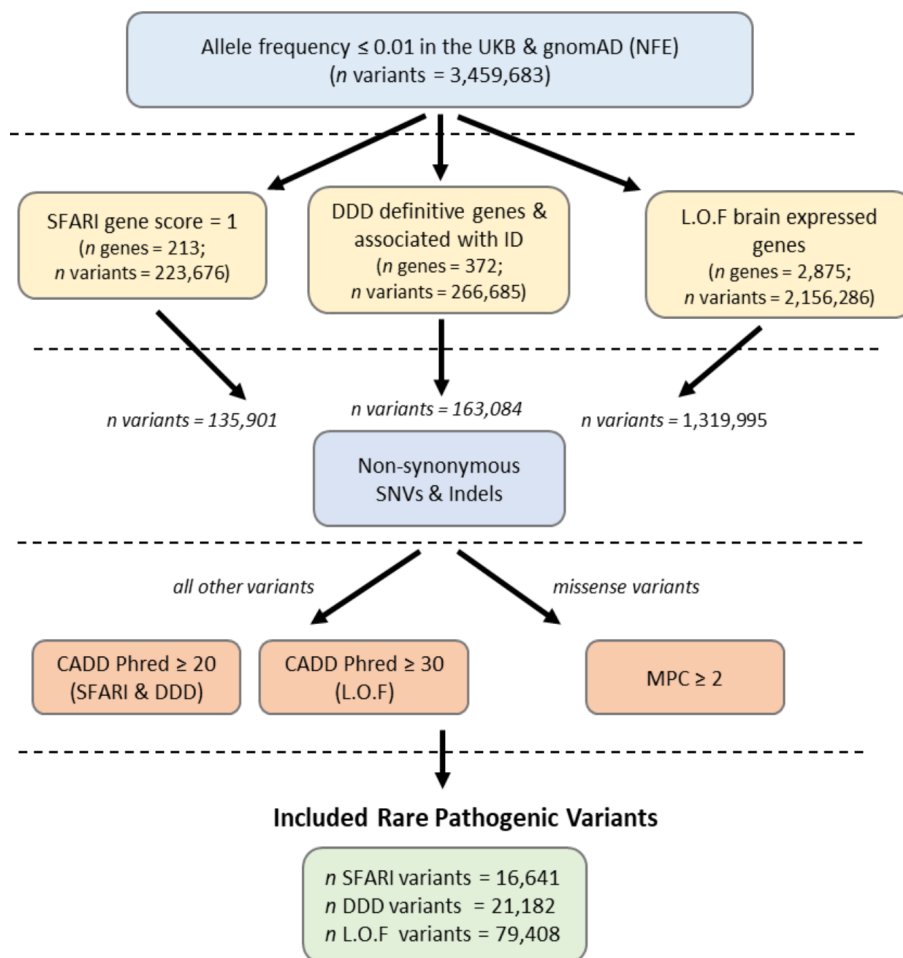


231 **Supplementary Figure 1. P-value threshold selection for polygenic scores.** Polygenic scores (PGS) were generated for cognition (PS_Cog),
 232 educational attainment (PS_EA) and autism (PS_ASD) (Methods). 153,607 samples were included in the analysis (1,317 ND-CNV carriers and
 233 152,290 non-carriers). R^2 values were calculated for P -value thresholds at 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 1. This figure was generated using

234 PRSice-2⁴⁹. **a.** 232,122 variants were included in PS_Cog after clumping. **b.** 281,280 variants were included in PS_EA after clumping. **c.** 129,955
235 variants were included in PS_ASD after clumping. A p-value threshold of 0.1 was selected for further analyses.

236 Supplementary Figure 2.

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238 **Supplementary Figure 2. Flow diagram of rare variant filtration.** Variants were first passed
 239 through an allele frequency filter of ≤ 0.01 in gnomAD (NFE). Variants were then filtered based
 240 on gene set – SFARI (autism associated genes), DDD (ID associated genes, and L.O.F (brain
 241 expressed genes). Total no. genes in SFARI gene set = 960. Total no. genes in DDD gene set =
 242 2,580. Transcripts annotated as intronic, synonymous, upstream gene variant, downstream
 243 gene variant or nonsense-mediated decay, were not included for analysis. *NFE = Non-Finnish*
 244 *European.*

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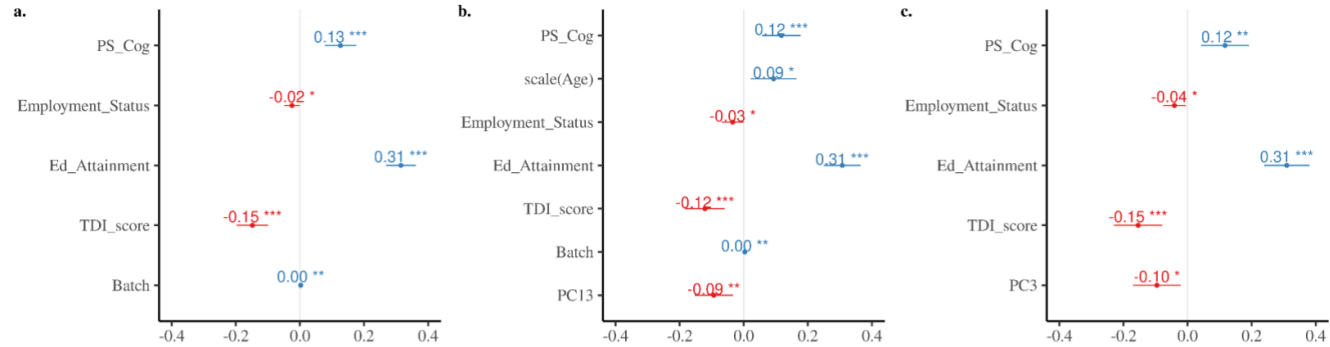
246 Supplementary Figure 3.

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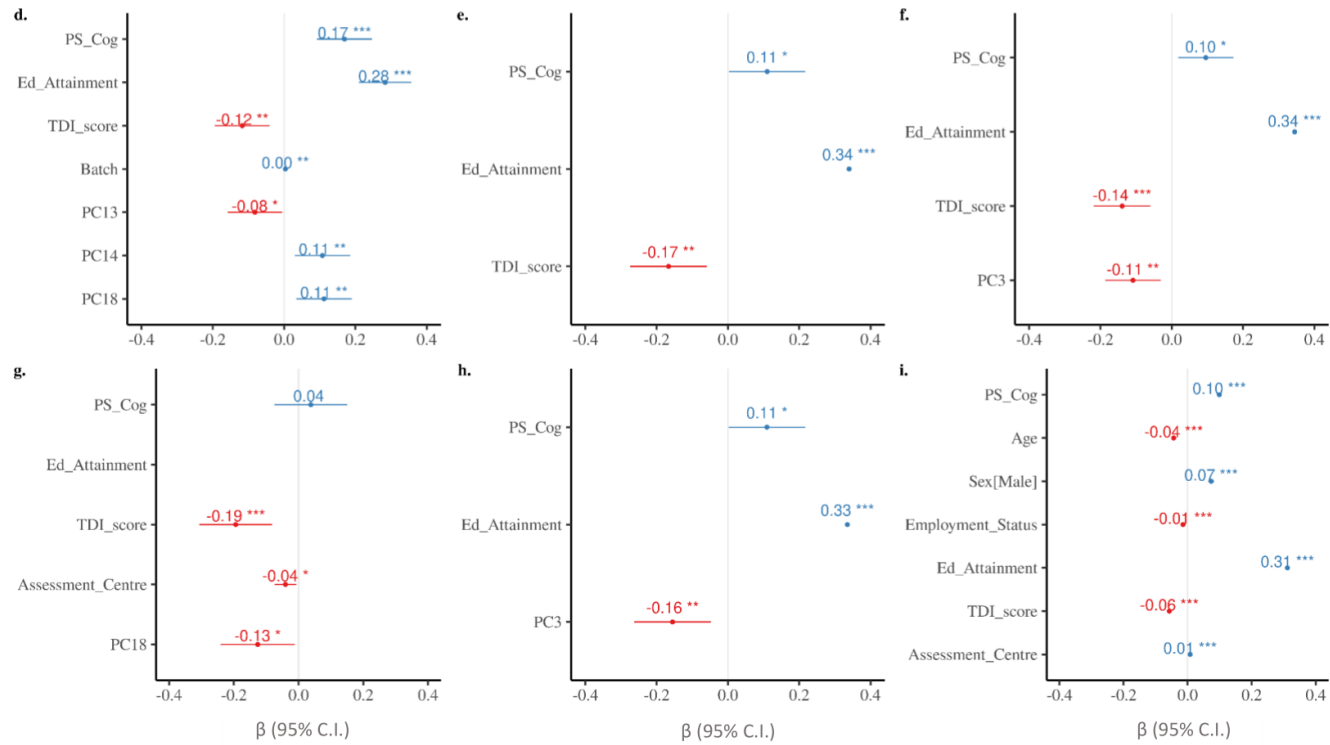
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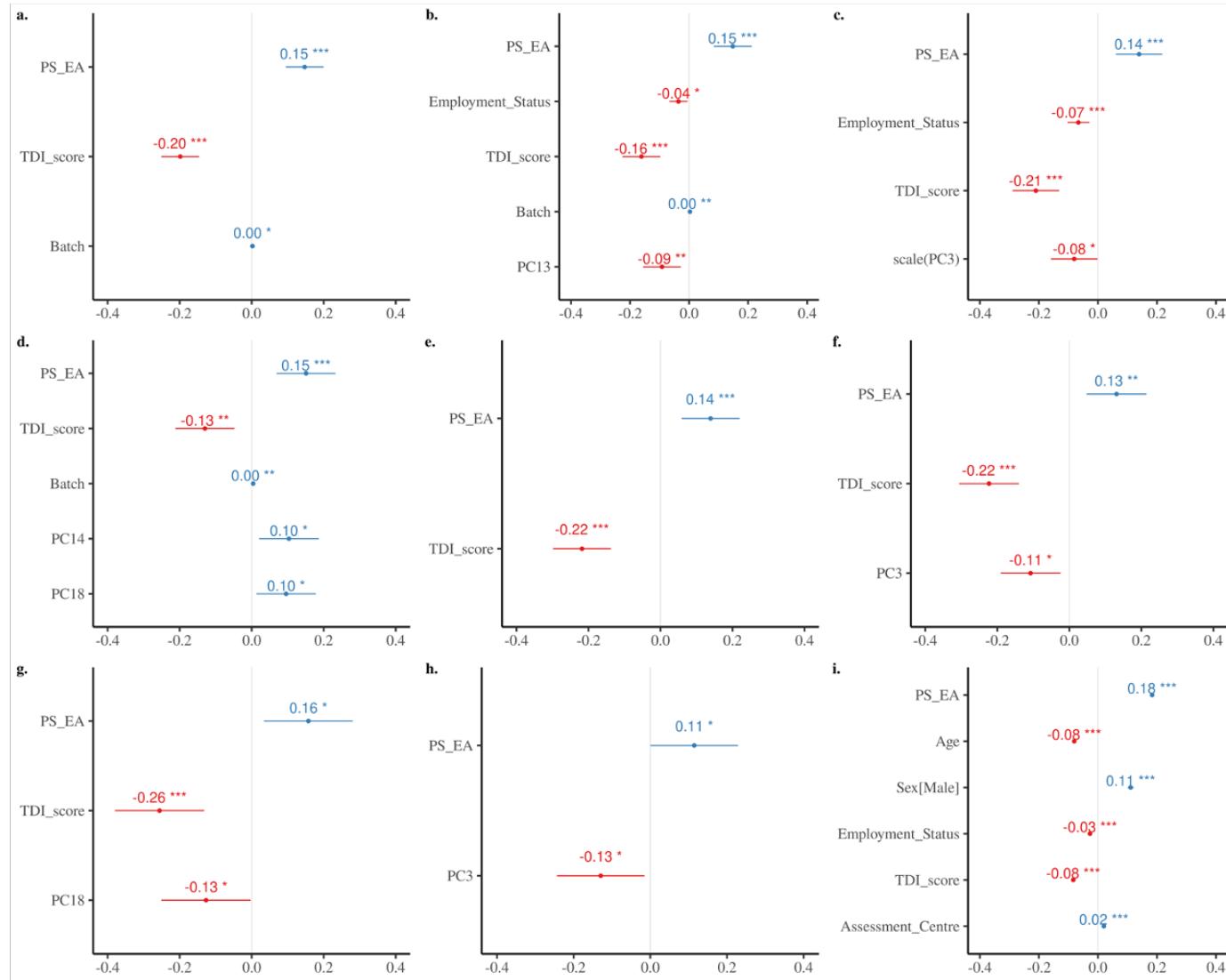
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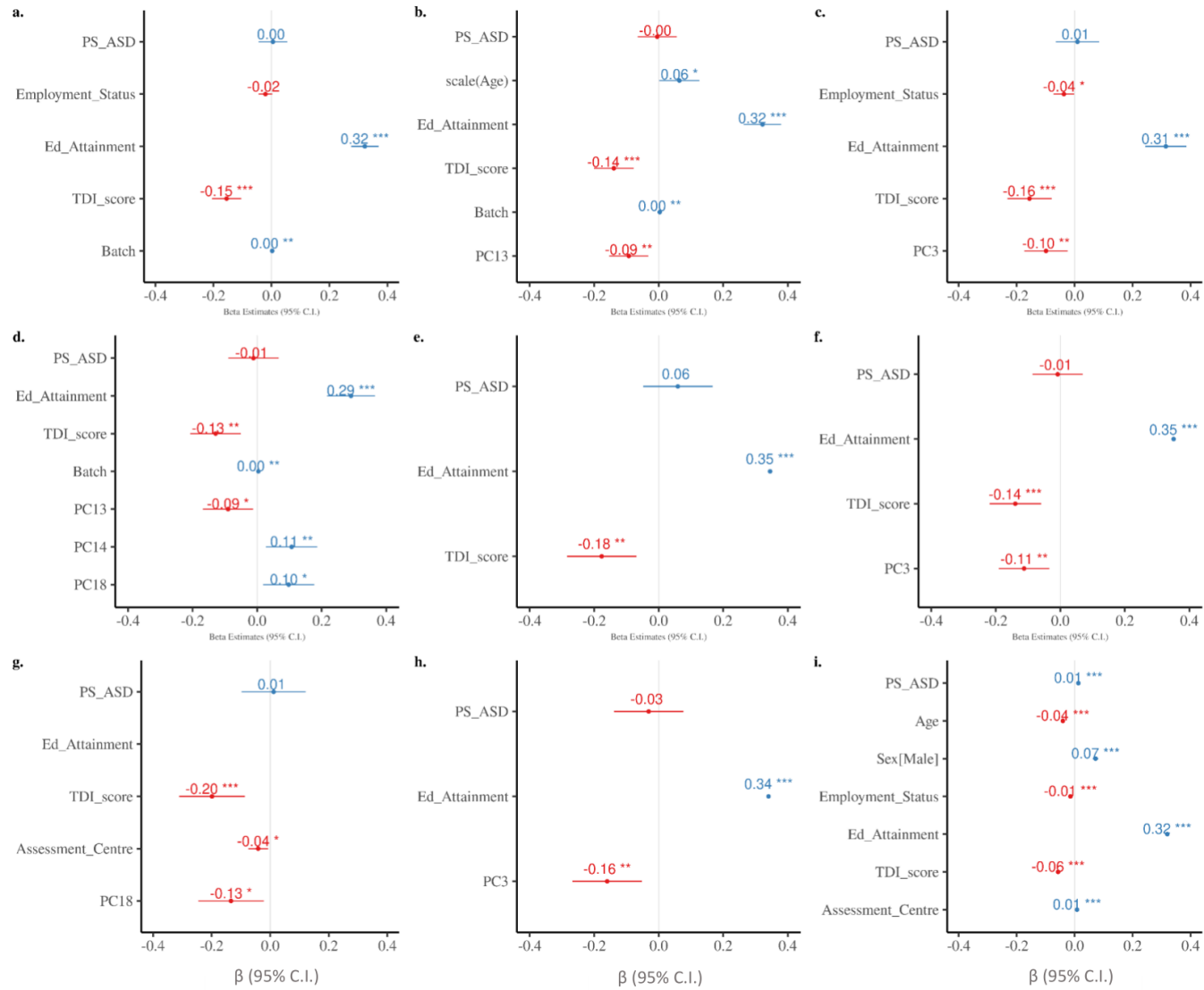
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257 **Supplementary Figure 3. Forest plots of linear regression analyses of participant *FI* scores vs Cognition PGS.** The plots show the β coefficients
258 from linear regression analyses (Table 2.) testing the association of participant *FI* with PGS for cognition (PS_Cog) within all **a.** ND-CNV carriers
259 (n = 1,317), **b.** deletion carriers (n = 763), **c.** duplication carriers (n = 561), **d.** 15q11.2 del. carriers (n = 543), **e.** 16p13.11 dup. carriers (n = 275),
260 **f.** ND-CNV carriers (excluding 15q11.2 del. and 16p13.11 dup.) (n = 503), **g.** deletion carriers (excluding 15q11.2 del.) (n = 220), **h.** duplications
261 carriers (excluding 16p13.11 dup.) (n = 286), and **i.** non-carriers (n = 152,290). Significant principal components (PCs) were not plotted for non-
262 carriers visualisation purposes. *Red* = $\beta < 0$, *Blue* = $\beta > 0$. *Del.* = *deletion*; *Dup.* = *duplication*; *TDI* = *Townsend Deprivation Index*; * = $p < 0.05$, **
263 = $p < 0.01$, *** = <0.001 .



265 **Supplementary Figure 4. Forest plots of linear regression analyses of participant *FI* scores vs Educational Attainment PGS.** The plots show the
266 β coefficients from linear regression analyses (Table 2.) testing the association of participant *FI* with PGS for educational attainment (PS_EA)
267 within all **a.** ND-CNV carriers (n = 1,317), **b.** deletion carriers (n = 763), **c.** duplication carriers (n = 561), **d.** 15q11.2 del. carriers (n = 543), **e.**
268 16p13.11 dup. carriers (n = 275), **f.** ND-CNV carriers (excluding 15q11.2 del. and 16p13.11 dup.) (n = 503), **g.** deletion carriers (excluding 15q11.2
269 del.) (n = 220), **h.** duplications carriers (excluding 16p13.11 dup.) (n = 286), and **i.** non-carriers (n = 152,290). Significant principal components
270 (PCs) were not plotted for non-carriers visualisation purposes. *Red* = $\beta < 0$, *Blue* = $\beta > 0$. *Del.* = *deletion*; *Dup.* = *duplication*; *TDI* = *Townsend*
271 *Deprivation Index*; * = $p < 0.05$, ** = $p < 0.01$, *** = <0.001 .



284 **Supplementary Figure 5. Forest plots of linear regression analyses of participant *FI* scores vs Autism PGS.** The plots show the β coefficients
285 from linear regression analyses (Table 2.) testing the association of participant *FI* with PGS for autism (PS_ASD) within all **a.** ND-CNV carriers (n
286 = 1,317), **b.** deletion carriers (n = 763), **c.** duplication carriers (n = 561), **d.** 15q11.2 del. carriers (n = 543), **e.** 16p13.11 dup. carriers (n = 275), **f.**
287 ND-CNV carriers (excluding 15q11.2 del. and 16p13.11 dup.) (n = 503), **g.** deletion carriers (excluding 15q11.2 del.) (n = 220), **h.** duplications
288 carriers (excluding 16p13.11 dup.) (n = 286), and **i.** non-carriers (n = 152,290). Significant principal components (PCs) were not plotted for non-
289 carriers visualisation purposes. *Red* = $\beta < 0$, *Blue* = $\beta > 0$. *Del.* = *deletion*; *Dup.* = *duplication*; *TDI* = *Townsend Deprivation Index*; * = $p < 0.05$, **
290 = $p < 0.01$, *** = <0.001 .

291 Supplementary Figure 6.

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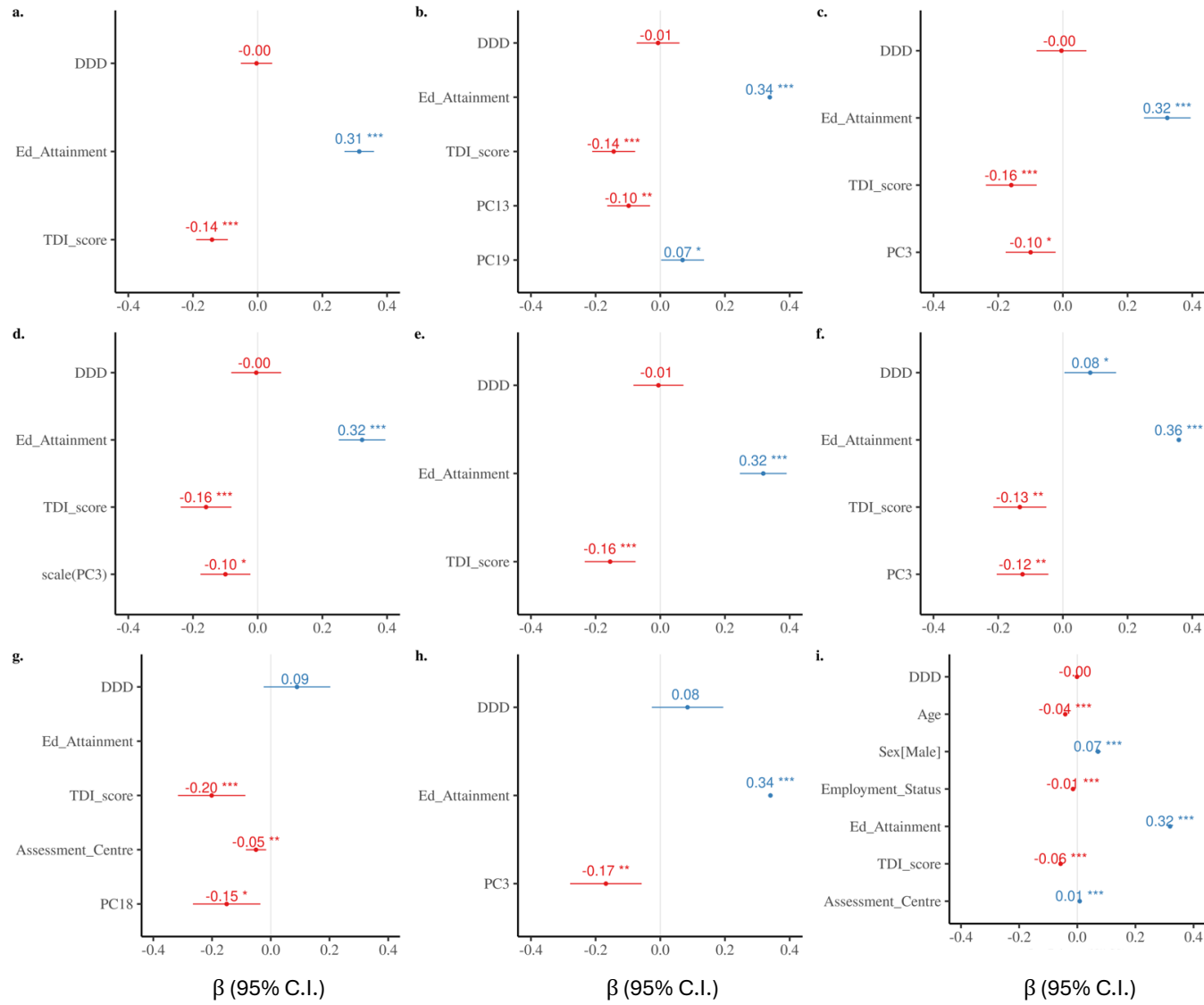
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303 **Supplementary Figure 6. Forest plots of linear regression analyses of participant *FI* scores vs DDD variants.** The plots show the β coefficients
304 from linear regression analyses (Table 2.) testing the association of participant *FI* with normalised counts of DDD variants within all **a.** ND-CNV
305 carriers (n = 1,274), **b.** deletion carriers (n = 739), **c.** duplication carriers (n = 542), **d.** 15q11.2 del. carriers (n = 523), **e.** 16p13.11 dup. carriers (n
306 = 267), **f.** ND-CNV carriers (excluding 15q11.2 del. and 16p13.11 dup.) (n = 488), **g.** deletion carriers (excluding 15q11.2 del.) (n = 216), **h.**
307 duplications carriers (excluding 16p13.11 dup.) (n = 275), and **i.** non-carriers (n = 146,859). Significant principal components (PCs) were not
308 plotted for non-carriers visualisation purposes. *Red* = $\beta < 0$, *Blue* = $\beta > 0$. *Del.* = *deletion*; *Dup.* = *duplication*; *TDI* = *Townsend Deprivation Index*;
309 *DDD* = *Deciphering Developmental Disorders*; * = $p < 0.05$, ** = $p < 0.01$, *** = <0.001 .

310 Supplementary Figure 7.

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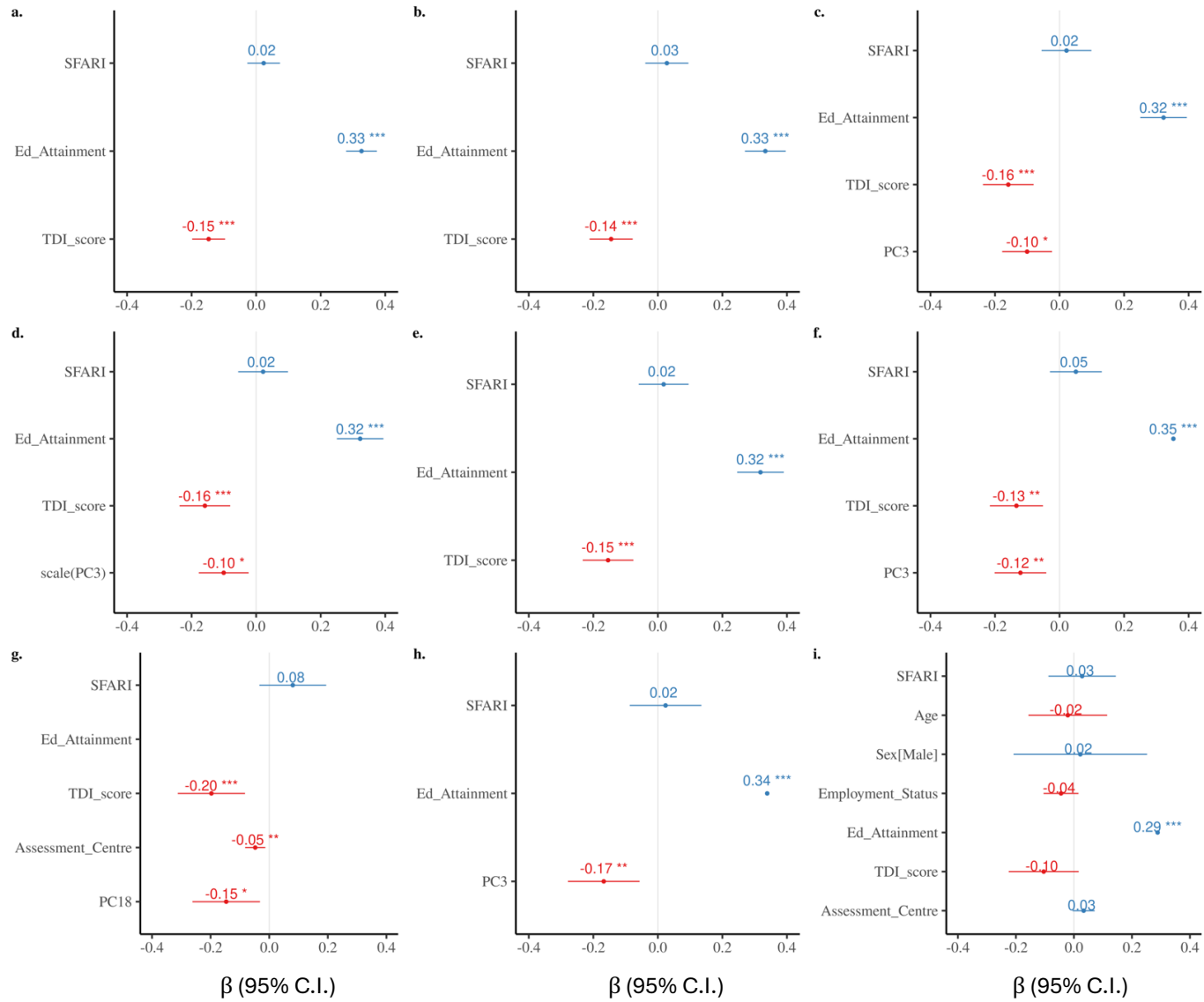
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321 **Supplementary Figure 7. Forest plots of linear regression analyses of participant *FI* scores vs SFARI variants.** The plots show the β coefficients
322 from linear regression analyses (Table 2.) testing the association of participant *FI* with normalised counts of SFARI variants within all **a.** ND-CNV
323 carriers (n = 1,274), **b.** deletion carriers (n = 739), **c.** duplication carriers (n = 542), **d.** 15q11.2 del. carriers (n = 523), **e.** 16p13.11 dup. carriers (n
324 = 267), **f.** ND-CNV carriers (excluding 15q11.2 del. and 16p13.11 dup.) (n = 488), **g.** deletion carriers (excluding 15q11.2 del.) (n = 216), **h.**
325 duplications carriers (excluding 16p13.11 dup.) (n = 275), and **i.** non-carriers (n = 146,859). Significant principal components (PCs) were not
326 plotted for non-carriers visualisation purposes. *Red* = $\beta < 0$, *Blue* = $\beta > 0$. *Del.* = *deletion*; *Dup.* = *duplication*; *TDI* = *Townsend Deprivation Index*;
327 *SFARI* = *Simons Foundation Autism Research Initiative*; * = $p < 0.05$, ** = $p < 0.01$, *** = <0.001 .

328 Supplementary Figure 8.

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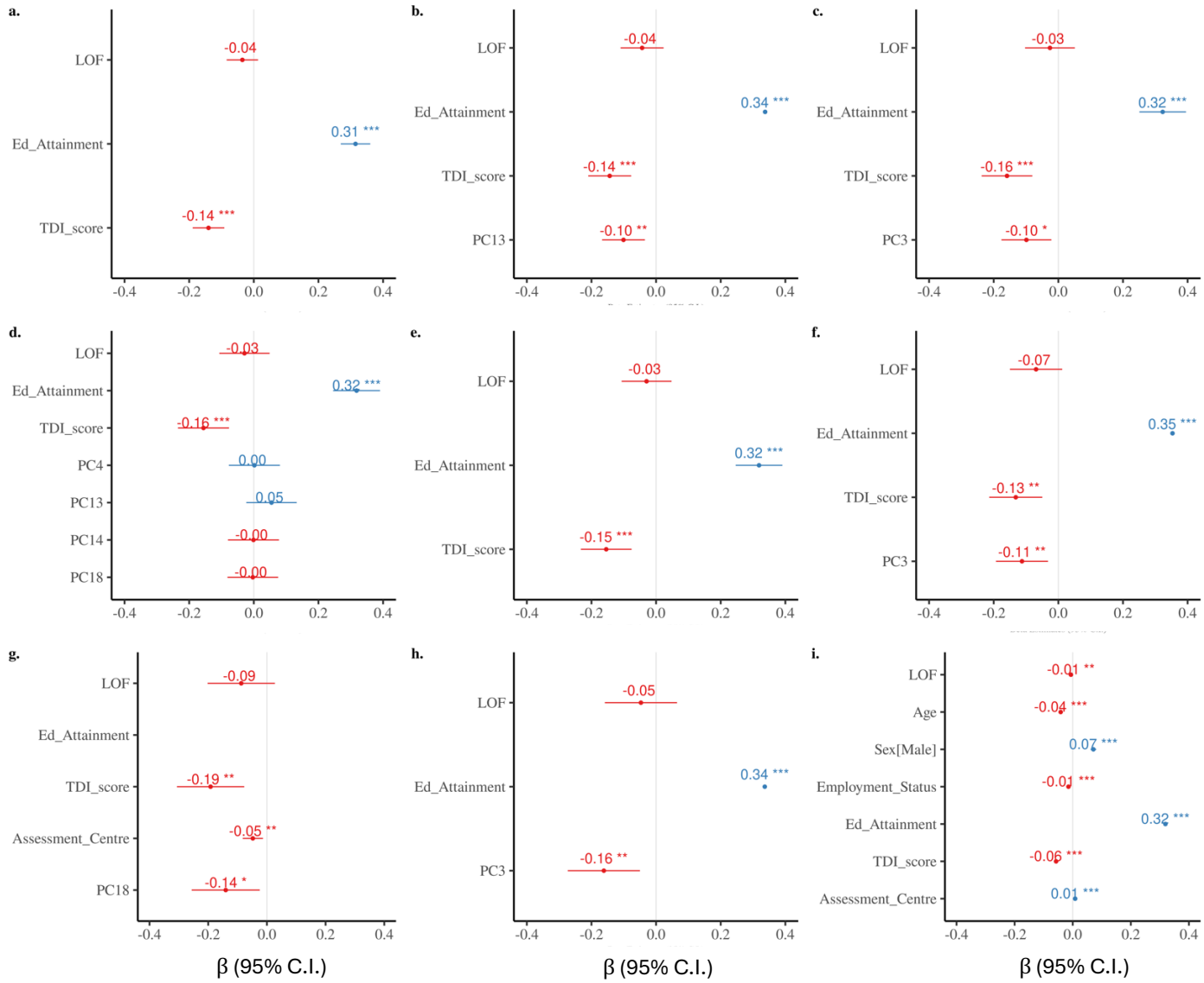
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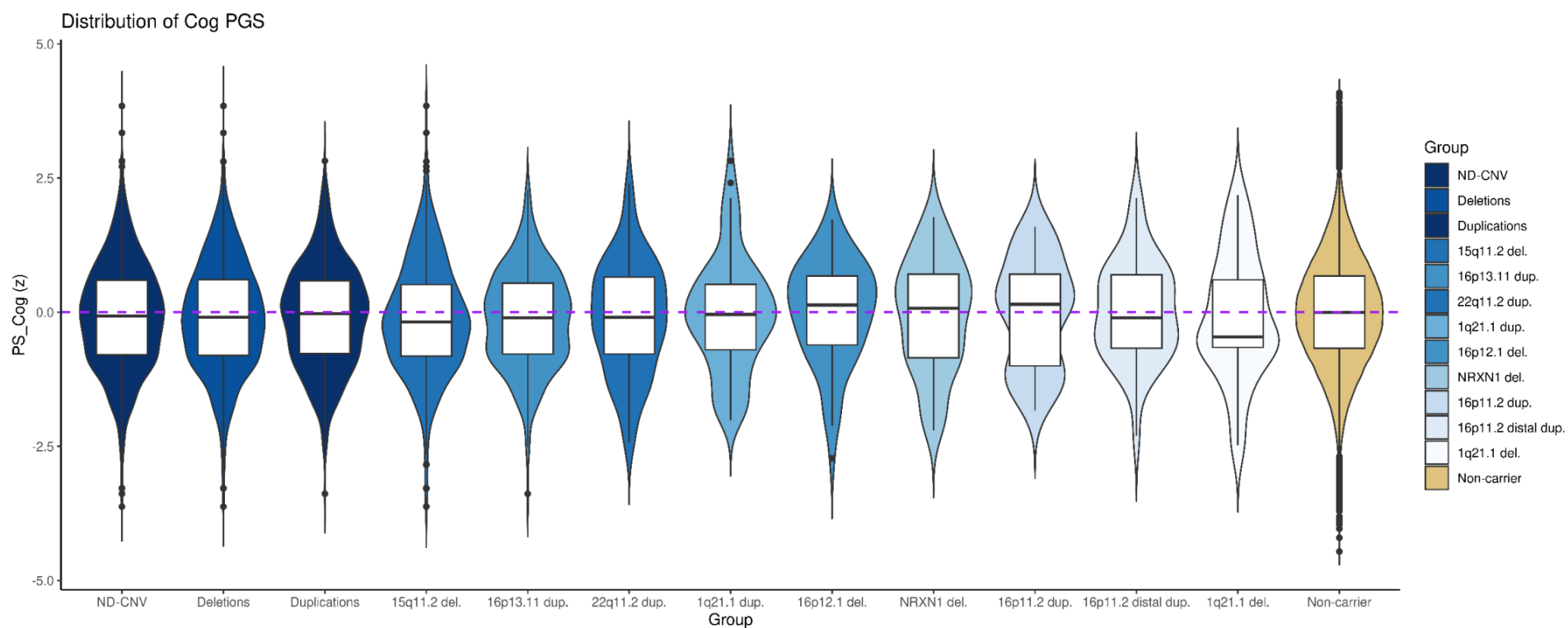
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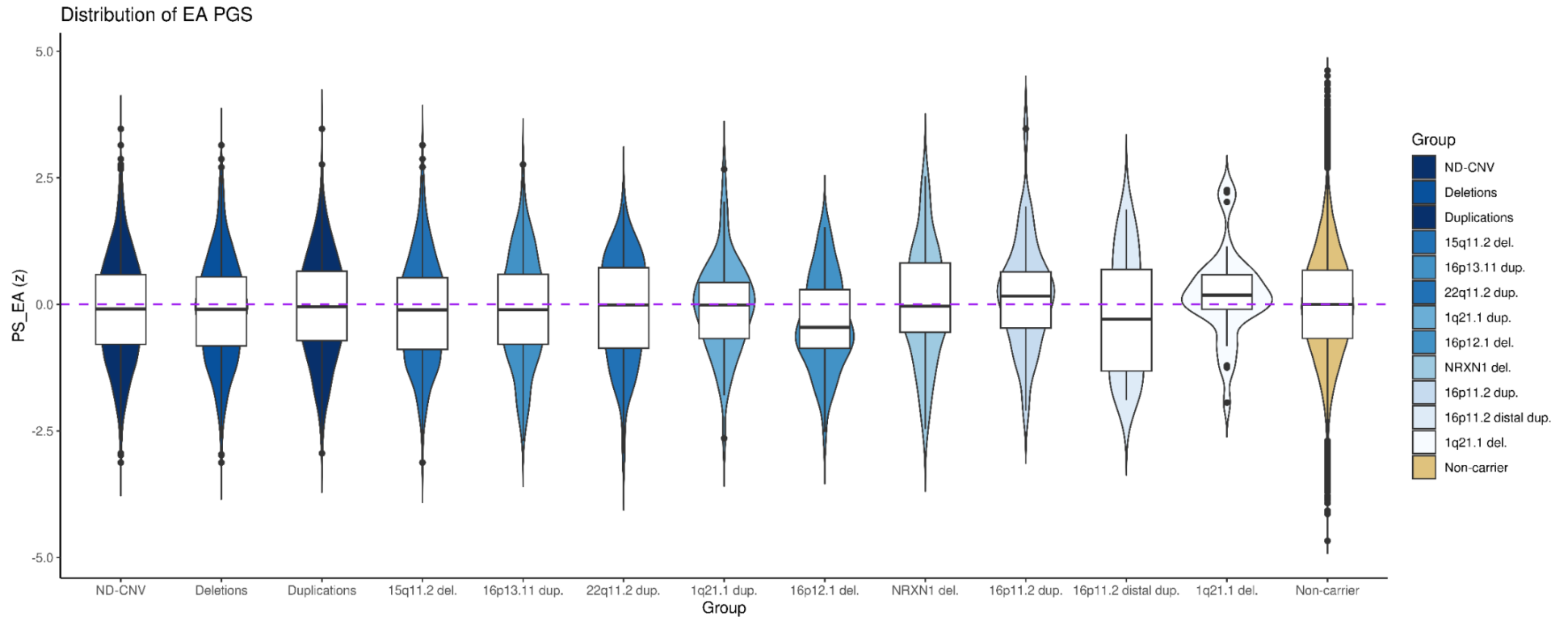
340 **Supplementary Figure 8. Forest plots of linear regression analyses of participant *FI* scores vs LOF variants.** The plots show the β coefficients
341 from linear regression analyses (Table 2.) testing the association of participant *FI* with normalised counts of LOF variants within all **a.** ND-CNV
342 carriers (n = 1,274), **b.** deletion carriers (n = 739), **c.** duplication carriers (n = 542), **d.** 15q11.2 del. carriers (n = 523), **e.** 16p13.11 dup. carriers (n
343 = 267), **f.** ND-CNV carriers (excluding 15q11.2 del. and 16p13.11 dup.) (n = 488), **g.** deletion carriers (excluding 15q11.2 del.) (n = 216), **h.**
344 duplications carriers (excluding 16p13.11 dup.) (n = 275), and **i.** non-carriers (n = 146,859). Significant principal components (PCs) were not
345 plotted for non-carriers visualisation purposes. *Red* = $\beta < 0$, *Blue* = $\beta > 0$. *Del.* = *deletion*; *Dup.* = *duplication*; *TDI* = *Townsend Deprivation Index*;
346 *LOF* = *Intolerant to loss-of-function brain expressed genes*; * = $p < 0.05$, ** = $p < 0.01$, *** = < 0.001 .

347 Supplementary Figure 9.



348 **Supplementary Figure 9. Distribution of PS_Cog across ND-CNV carriers and non-carriers.** Depicted is the distribution (violin plot), interquartile
 349 range (black bars of violin plot), minimum (bottom of violin plot), maximum (top of violin plot), group mean (black horizontal line of boxplot)
 350 and cohort mean (purple dashed line) of PS_Cog across ND-CNV carriers and non-carriers. PS_Cog was converted to a z-score by normalising to
 351 the cohort mean. *ND-CNV* $n = 1,318$; *15q11.2 del.* $n = 543$; *16p13.11 dup.* $n = 275$; *22q11.2 dup.* $n = 83$; *1q21.1 dup.* $n = 73$; *16p12.1 del.* $n = 64$;
 352 *NRXN1 del.* $n = 56$; *16p11.2 dup.* $n = 46$; *16p11.2 distal dup.* $n = 38$; *1q21.1 del.* $n = 35$; *non-carriers* = 152,325. PS_Cog = cognition polygenic score.

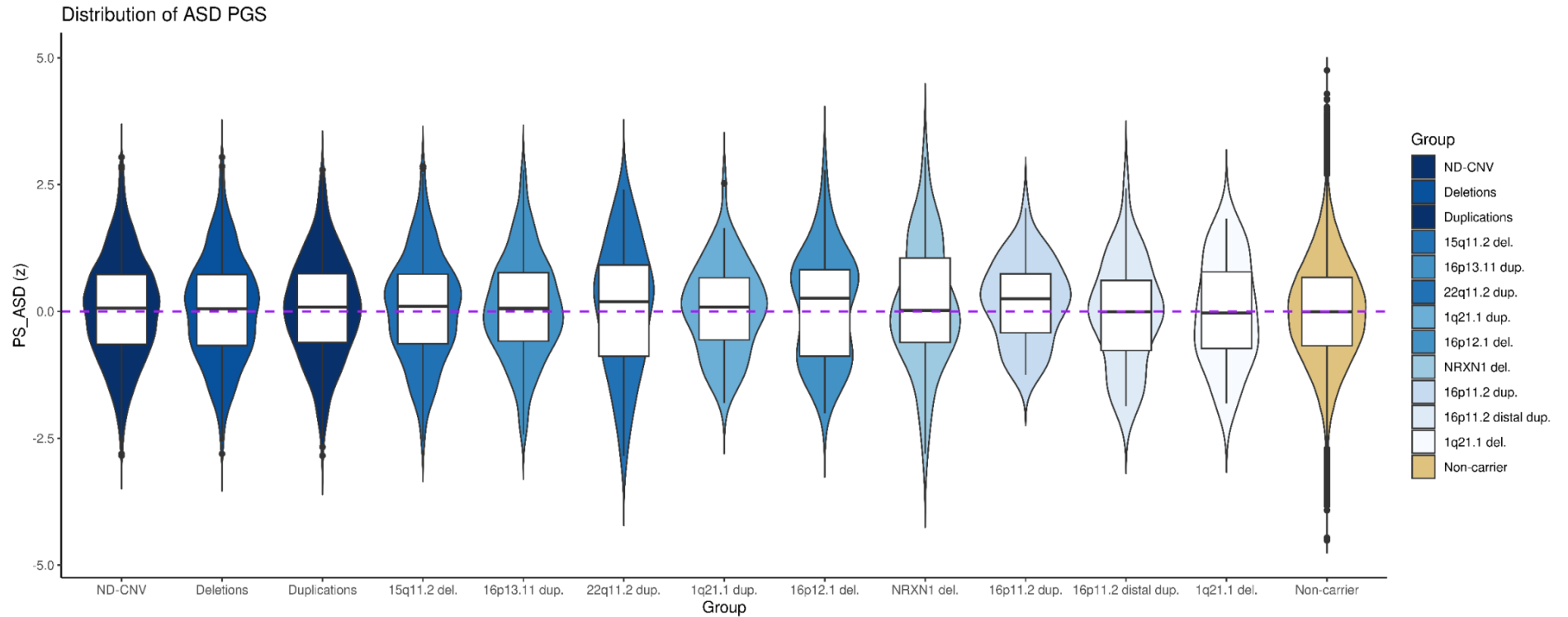
353 Supplementary Figure 10.



354 **Supplementary Figure 10. Distribution of PS_EA across ND-CNV carriers and non-carriers.** Depicted is the distribution (violin plot), interquartile
355 range (black bars of violin plot), minimum (bottom of violin plot), maximum (top of violin plot), group mean (black horizontal line of boxplot)
356 and cohort mean (purple dashed line) of PS_EA across ND-CNV carriers and non-carriers. PS_Cog was converted to a z-score by normalising to
357 the cohort mean. *ND-CNV* $n = 1,318$; *15q11.2 del.* $n = 543$; *16p13.11 dup.* $n = 275$; *22q11.2 dup.* $n = 83$; *1q21.1 dup.* $n = 73$; *16p12.1 del.* $n = 64$;

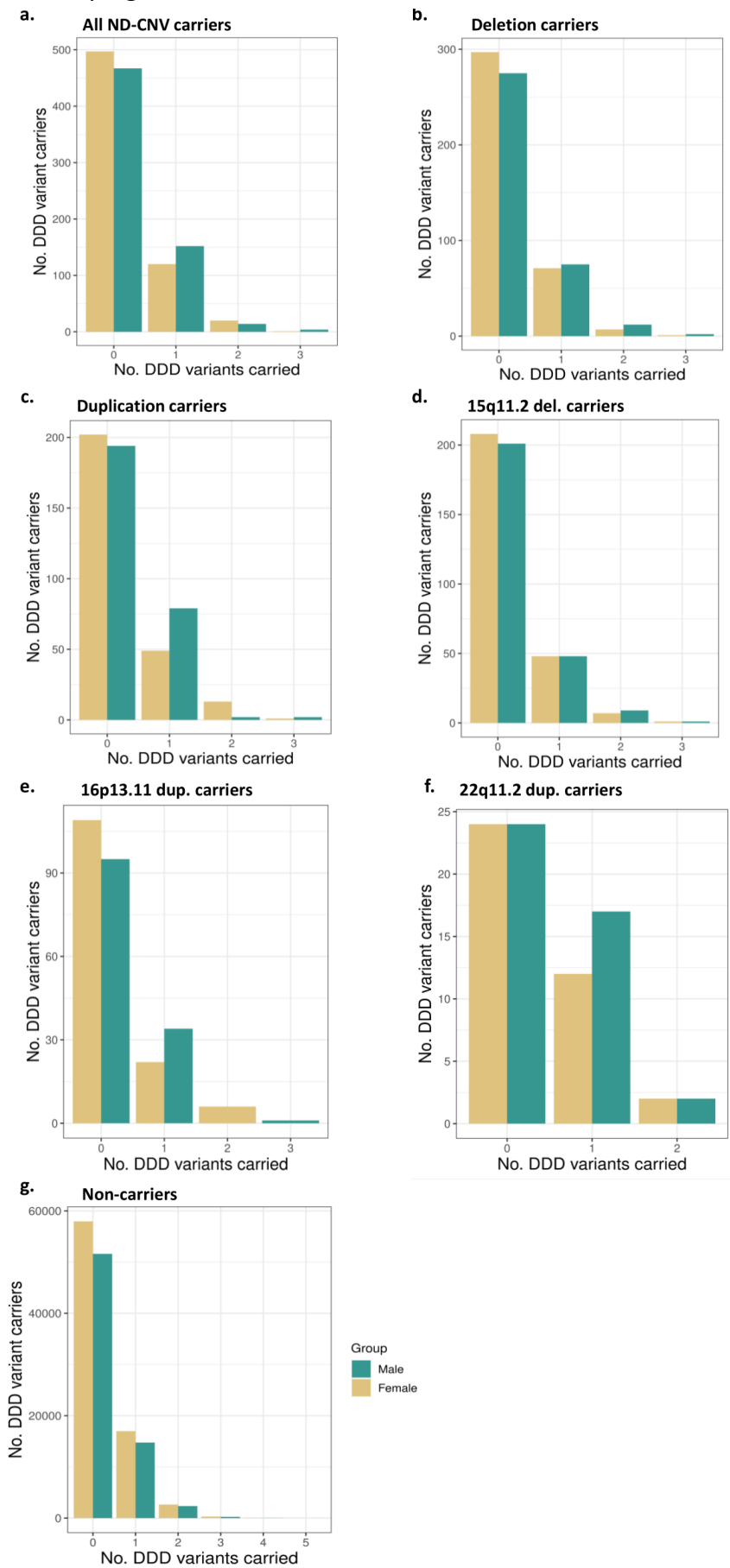
358 *NRXN1 del. n = 56; 16p11.2 dup. n = 46; 16p11.2 distal dup. n = 38; 1q21.1 del. n = 35; non-carriers = 152,325. PS_EA = educational attainment*
359 *polygenic score.*

360 Supplementary Figure 11.



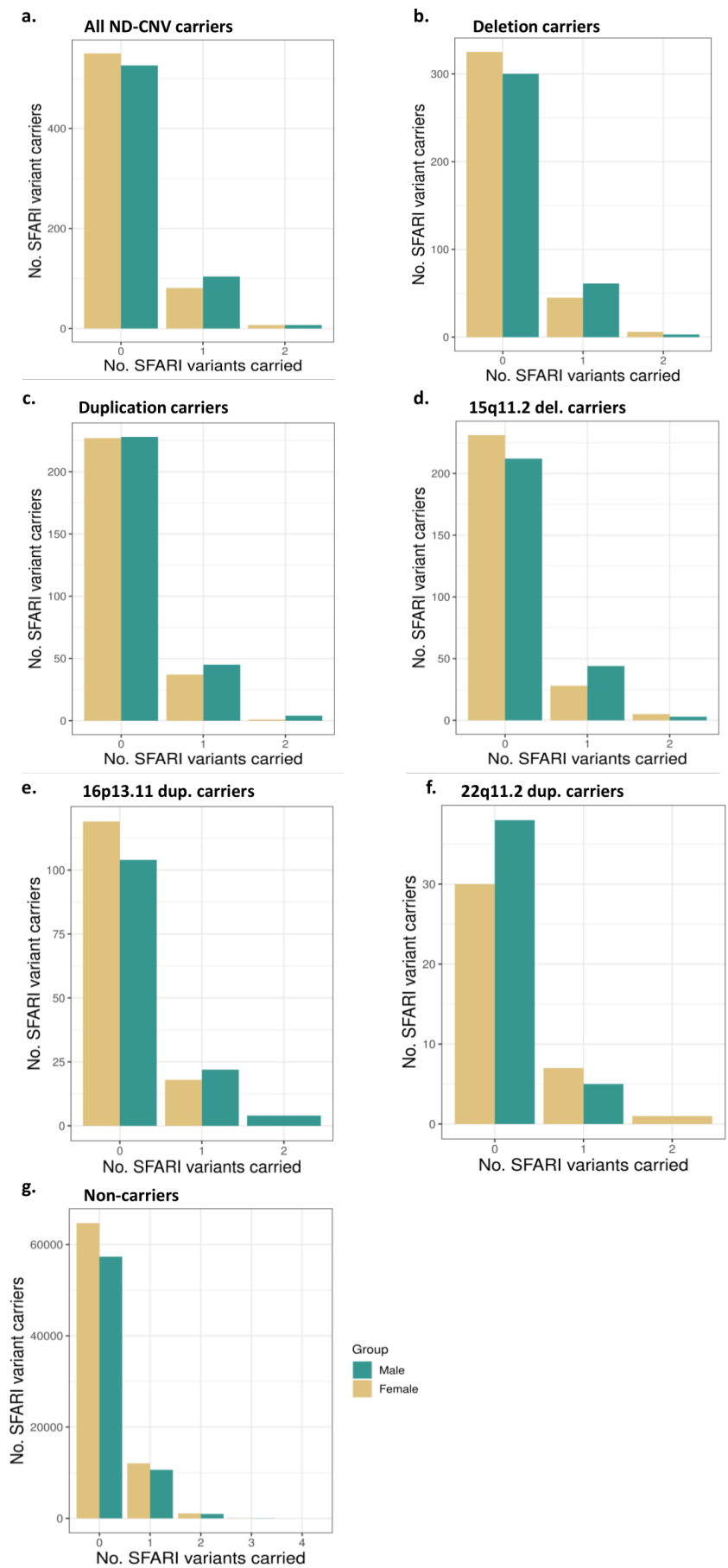
361 **Supplementary Figure 11. Distribution of PS_ASF across ND-CNV carriers and non-carriers.** Depicted is the distribution (violin plot),
362 interquartile range (black bars of violin plot), minimum (bottom of violin plot), maximum (top of violin plot), group mean (black horizontal line
363 of boxplot) and cohort mean (purple dashed line) of PS_ASF across ND-CNV carriers and non-carriers. PS_ASF was converted to a z-score by
364 normalising to the cohort mean. *ND-CNV* $n = 1,318$; *15q11.2 del.* $n = 543$; *16p13.11 dup.* $n = 275$; *22q11.2 dup.* $n = 83$; *1q21.1 dup.* $n = 73$; *16p12.1*

365 *del. n = 64; NRXN1 del. n = 56; 16p11.2 dup. n = 46; 16p11.2 distal dup. n = 38; 1q21.1 del. n = 35; non-carriers = 152,325. PS_ASD = autism*
366 *polygenic score.*



368 **Supplementary Figure 12. Distribution of DDD rare variants in ND-CNV carriers and non-**
369 **carriers.** Here is shown the distribution of deleterious DDD rare variants in ND-CNV carriers
370 and non-carriers. The plots show the number of DDD variants (x-axis) vs the number of DDD
371 variant carriers (y-axis) for **a.** ND-CNV carriers ($n = 1,275$), **b.** deletion carriers ($n = 740$), **c.**
372 duplication carriers ($n = 542$), **d.** 15q11.2 del. carriers ($n = 523$), **e.** 16p13.11 dup. carriers ($n =$
373 267), **f.** 22q11.2 dup. ($n = 81$), **g.** non-carriers ($n = 146,894$). *DDD = Deciphering Developmental*
374 *Disorders.*

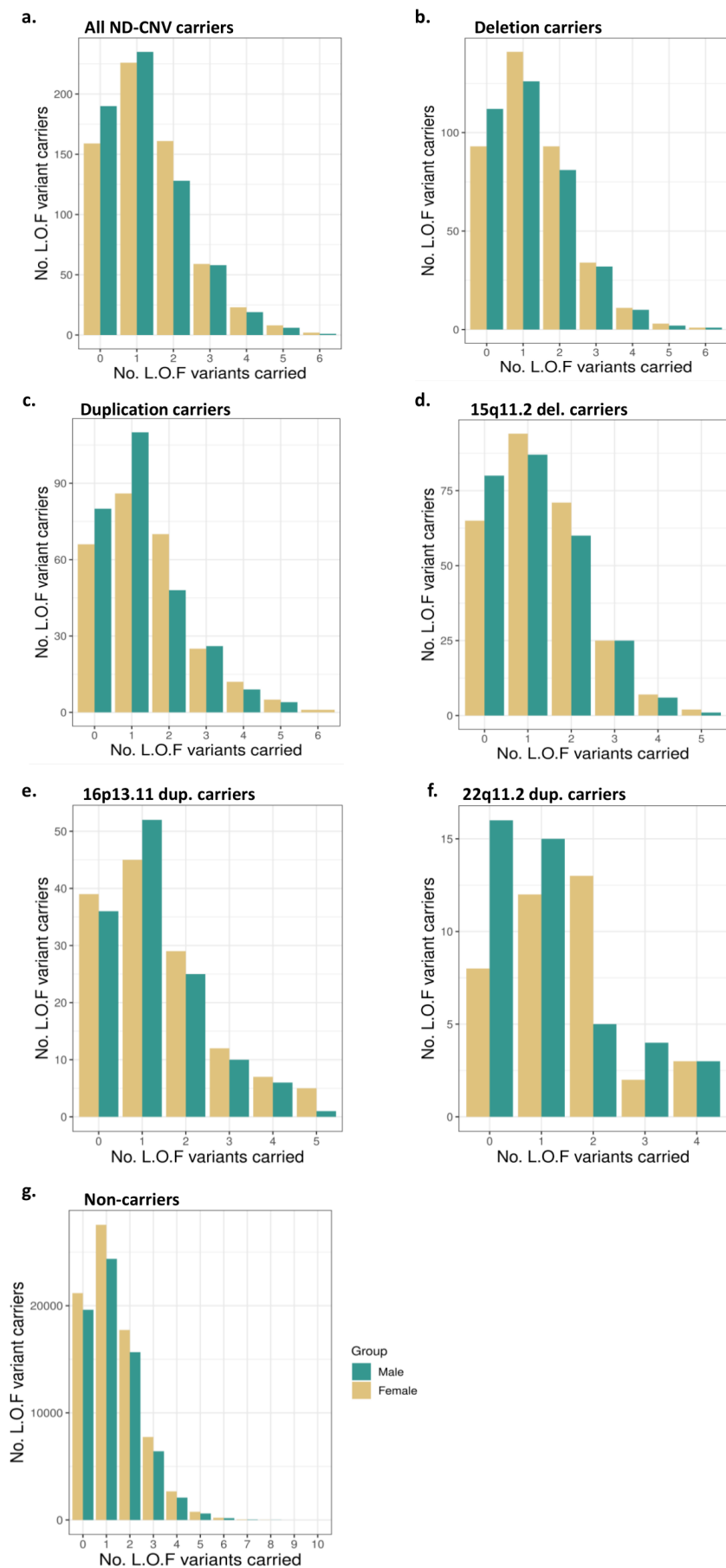
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377 **Supplementary Figure 13. Distribution of SFARI rare variants in ND-CNV carriers and non-**
378 **carriers.** Here is shown the distribution of deleterious SFARI rare variants in ND-CNV carriers
379 and non-carriers. The plots show the number of SFARI variants (x-axis) vs the number of SFARI
380 variant carriers (y-axis) for **a.** ND-CNV carriers ($n = 1,275$), **b.** deletion carriers ($n = 740$), **c.**
381 duplication carriers ($n = 542$), **d.** 15q11.2 del. carriers ($n = 523$), **e.** 16p13.11 dup. carriers ($n =$
382 267), **f.** 22q11.2 dup. ($n = 81$), **g.** non-carriers ($n = 146,894$). *SFARI = Simons Foundation Autism*
383 *Research Initiative.*

384

385 Supplementary Figure 14.



386 **Supplementary Figure 14. Distribution of LOF rare variants across SFARI, DDD and L.O.F**
387 **gene-sets in ND-CNV carriers and non-carriers.** Here is shown the distribution of deleterious
388 LOF rare variants in ND-CNV carriers and non-carriers. The plots show the number of LOF
389 variants (x-axis) vs the number of LOF variant carriers (y-axis) for **a.** ND-CNV carriers ($n =$
390 1,275), **b.** deletion carriers ($n = 740$), **c.** duplication carriers ($n = 542$), **d.** 15q11.2 del. carriers
391 ($n = 523$), **e.** 16p13.11 dup. carriers ($n = 267$), **f.** 22q11.2 dup. ($n = 81$), **g.** non-carriers ($n =$
392 146,894). *LOF = Intolerant to loss-of-function brain-expressed genes.*

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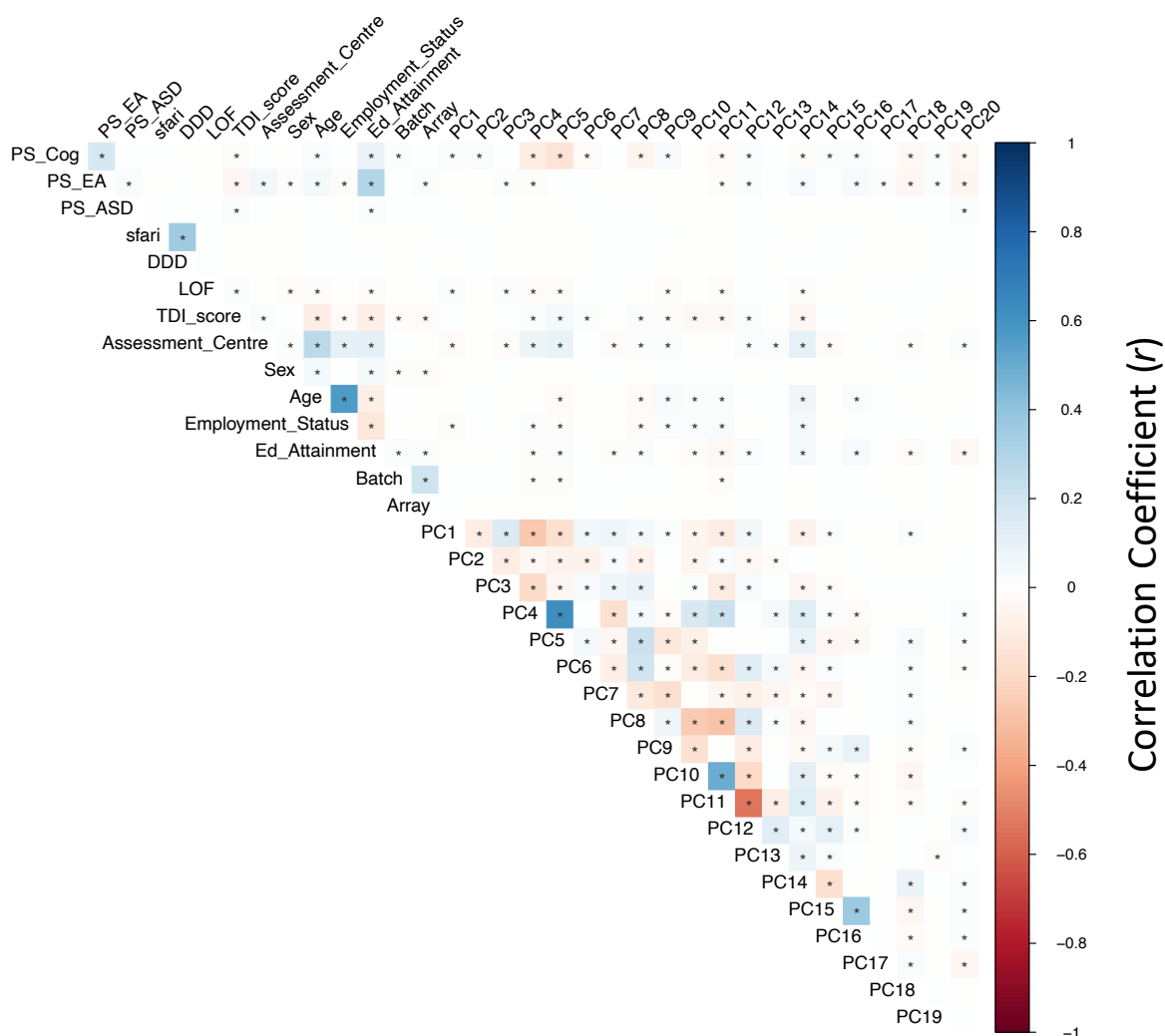
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406 Supplementary Figure. 15



407 **Supplementary Figure 15. Correlation plot of predictor in linear regression analyses.**

408 Displayed is a correlation matrix of all predictors considered for linear regression analyses. No
 409 strong correlation was observed between any pair of predictors ($r > 0.7$). Bonferroni
 410 correction was applied to all tests ($p = 0.0001$). This figure was generated using the *corrplot*
 411 package in R. * = $p < 0.0001$. *PS_Cog* = cognition polygenic score; *PS_EA* = educational
 412 attainment polygenic score; *PS_ASD* = autism polygenic score; *TDI_score* = townsend
 413 deprivation index score; *sfari* = autism associated rare variants; *DDD* = intellectual
 414 disability/developmental delay associated rare variants; *LOF* = intolerant to loss-of-function,
 415 *brain expressed rare variants*; *PC* = principal component.

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