Supplementary Materials

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Supplementary Table S1: Number of participants at each site

Research Centre	Number of individuals contributed			
	16p11.2 deletion	16p11.2 duplication	22q11.2 deletion	22q11.2 duplication
Cardiff University ECHO & IMAGINE-ID cohorts	8	8	67	11
Belgrade University Children's Hospital			8	
Children's Hospital of Philadelphia				18
16p11.2 European consortium	4	9		
Simons VIP	70	33		
University of California, Los Angeles			69	16
University Medical Center Utrecht			140	
The State University of New York			86	

Supplementary Table S2: Genotype information

CNV group	Genotype	Frequency
16p11.2 deletion	BP2-BP5	2
16p11.2 deletion	BP4-BP5	80
16p11.2 duplication	BP4-BP5	50
22q11.2 deletion	LCR A-B	23
22q11.2 deletion	LCR A-B + centromeric region	1
22q11.2 deletion	LCR A-C	2
22q11.2 deletion	LCR A-D	261
22q11.2 deletion	confirmed via FISH*	83
22q11.2 duplication	LCR A-B	6
22q11.2 duplication	LCR A-D	38
22q11.2 duplication	LCR A-F	1

BP, breakpoints; LCR, low copy repeat region; FISH, Fluorescence in situ hybridization.

*22q11.2 deletion confirmed by FISH, indicating deletion hits the critical region but exact LCRs could not be defined.

Supplementary Table S3: ADI-R assessors and sites of assessment

Site	Assessors	Sites of assessments
Cardiff University	Dr Samuel Chawner (postdoctoral research psychologist), Hayley Moss (psychology research assistant), Dr Joanne Doherty (Child and Adolescent Mental Health Services psychiatrist). Training and reliability by certified ADI-R trainer Dr Sarah Curran (Consultant Child and Adolescent Mental Health Services Psychiatrist).	Assessments administered in the patient's home, or at the Hadyn Ellis Building clinic at Cardiff University.
Belgrade University Children's Hospital	Milica Pejovic-Milovancevic (Child psychiatrist, Institute of Mental Health, Belgrade) Marina Mihaljevic (Psychiatrist, Clinic for Psychiatry, Clinical Center of Serbia). Assessors were trained by ADI-R trainer Prof Patrick Bolton Consultant Child and Adolescent Mental Health Services Psychiatrist	Assessments administered at the Institute of Mental Health, Belgrade.
Children's Hospital of Philadelphia	Research-reliable, Licensed Ph.D. or supervised M.A. clinical psychologists.	Assessments administered remotely from Children's Hospital of Philadelphia
16p11.2 European consortium	Trained and certified psychologists. ADI-R training provided by Professor Bernadette Rogé.	Assessments administered at Lausanne University hospital
Simons VIP	Research-reliable, Licensed Ph.D. or supervised M.A. clinical psychologists. Training and reliability were conducted by Catherine Lord's lab (UMACC/CADB) and/or independent certified ADI-R trainers.	Assessments administered at one of five Simons VIP sites (Baylor College of Medicine, Boston Children's Hospital, Children's Hospital of Philadelphia, the University of California San Francisco, and the University of Washington).
University of California, Los Angeles	Clinical psychologists and psychometrists trained I n the ADI-R to research reliability levels by the UCLA Center for Autism Research and Treatment (CART).	Assessments administered at University of California Los Angeles, Semel Institute for Neuroscience and Human Behavior.
University Medical Center Utrecht	M.D. PhD child/adolescent psychiatrist and M.Sc. psychologist, who were certified in ADI-R assessments. Training and reliability were conducted by an independent, certified ADI-R trainer.	Assessments administered took place at the psychiatry department of the University Medical Center Utrecht.
The State University of New York - Upstate Medical University	Research-reliable, licensed Ph.D. clinical child psychologist and M.D. child/adolescent psychiatrist.	Assessments administered at State University of New York, Upstate Department of Psychiatry.

ADI-R

Following previous studies[1-3] we only analysed the scores that contributed to the diagnostic algorithm, the majority of which are early developmental "ever/most abnormal" items[1]. The social domain comprises four domains: 'social interaction', 'peer relationships', 'shared enjoyment' and 'socioemotional reciprocity' subdomains. For the communication domain we excluded subdomains that were designed only for verbal individuals and only retained those available for both verbal and nonverbal individuals, which were 'gesture' and 'imitation and imagination' subdomains. This followed the approach of a previous study that examined subdomain scores[3]. The RRB (Restricted, Repetitive, and Stereotyped Behaviours) domain comprises 'repetitive behaviour', 'routines and rituals', 'motor mannerisms' (hand and finger mannerisms, and stereotyped body movements) and 'sensorimotor interest' (unusual sensory interests and repetitive use of objects) subdomains. All ADI-R assessors were extensively trained to research reliability standards and each site used consensus coding procedures.

Analysis of covariance models

Autism symptom severity: Analysis of covariance (ANCOVA) model with ADI-R total score as the phenotypic outcome. *Autism domain profile:* multivariate analysis of covariance (MANCOVA) with social, communication and repetitive behaviour ADI-R domain total scores as the phenotypic outcomes entered into the same model. *Autism subdomain profile:* MANCOVA model with ADI-R social subdomains (social interaction, peer relationships, shared enjoyment and socioemotional reciprocity), ADI-R communication subdomains (gestures, imagination and imitation), ADI-R repetitive behaviour subdomains (unusual interests, routines and rituals, motor mannerisms and sensorimotor mannerisms) as phenotypic outcomes entered into the same model. *Cognitive profile:* ANCOVA model with FSIQ as the phenotypic outcome, and a further MANCOVA model with PIQ and VIQ as phenotypic outcomes entered into the same model.

Supplementary Table S4: Proportion of CNV carriers who met clinical cut-offs for the three autism domains

	Social	Communication	RRB
16p11.2 deletion	60%	73%	59%
16p11.2 duplication	72%	74%	86%
22q11.2 deletion	47%	46%	32%
22q11.2 duplication	53%	64%	58%

RRB: Restricted, Repetitive, and Stereotyped Behaviours

Supplementary Table S5: Between group variance adjusted for FSIQ

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient ; ADI-R, Autism Diagnostic Interview ; RRB, Restricted, Repetitive, and Stereotyped Behaviours.

Score	Between group variation controlled for FSIQ	
ADI-R scores	p-value	eta-squared %
Total score	<0.001	8.1
Social domain	<0.001	6.0
subdomains:		
Social interaction	0.044	1.6
Peer relationships	<0.001	3.3
Shared enjoyment	<0.001	5.7
Socioemotional reciprocity	<0.001	8.5
Communication domain	<0.001	3.2
subdomains:		
Gestures	<0.001	3.5
Imagination & Imitation	0.011	2.0
RRB domain	<0.001	16.4
subdomains		
Unusual interests	<0.001	4.9
Routines & rituals	<0.001	3.5
Motor mannerisms	<0.001	23.4
Sensorimotor interests	<0.001	19.9

Supplementary Table S6: Effect of age in Aim 1 MANCOVA analyses

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient ; ADI-R, Autism Diagnostic Interview ; RRB, Restricted, Repetitive, and Stereotyped Behaviours.

Score	p-value	Eta-squared	Fixed effect slope coefficient
Cognitive scores			
FSIQ	0.009	1.2	-0.37
VIQ	0.088	0.6	-0.27
PIQ	<0.001	1.9	-0.54
ADI-R scores			
Total score	0.232	0.2	-0.18
Social domain	0.233	0.2	-0.11
subdomains:			
Social interaction	0.921	0.0	-0.01
Peer relationships	0.106	0.5	-0.05
Shared enjoyment	0.570	0.1	0.01
Socioemotional reciprocity	0.014	1.0	-0.07
Communication domain	0.766	0.0	-0.02
subdomains:			
Gestures	0.215	0.3	-0.03
Imagination & Imitation	0.348	0.2	0.01
RRB domain	0.055	0.6	-0.05
subdomains:			
Unusual interests	0.315	0.2	0.01
Routines & rituals	0.197	0.3	-0.01
Motor mannerisms	0.132	0.3	-0.01
Sensorimotor interests	<0.001	2.9	-0.03

Supplementary Table S7: Phenotypic post hoc contrasts between genetic variant groups

Arrows indicate the direction of effect of the difference between genetic variant groups; an upward arrow ↑ indicates that the first group mentioned in the pair has a higher value than the second group mentioned; a downward arrow ↓ indicates the opposite; no arrow indicates that the values were the same between groups. For example, for FSIQ, 16p11.2 duplication carriers have a lower FSIQ than 16p11.2 deletion carriers. Tukey's method was used to conduct post hoc contrasts between CNV groups, producing p-values adjusted for the number of contrasts. Green highlighted cells indicate a significant contrast.

Phenotypic trait	16p11.2 duplication-16p11.2 deletion	22q11.2 deletion-16p11.2 deletion	22q11.2 duplication-16p11.2 deletion	22q11.2 deletion-16p11.2 duplication	22q11.2 duplication-16p11.2 duplication	22q11.2 duplication-22q11.2 deletion
FSIQ	→ 6.71E-04	→ 3.10E-08	← 1.33E-01	→ 9.94E-01	← 2.93E-06	← 1.69E-09
VIQ	→ 3.90E-01	→ 3.80E-02	← 2.78E-01	→ 9.90E-01	← 1.96E-02	← 8.37E-04
PIQ	→ 7.80E-06	→ 1.90E-10	← 9.78E-01	→ 9.98E-01	← 1.42E-04	← 3.47E-06
Total ADI-R score	← 4.94E-02	→ 2.18E-03	→ 9.80E-01	→ 2.65E-08	→ 4.62E-02	← 9.88E-02
Social domain	← 1.39E-01	→ 1.25E-02	→ 9.86E-01	→ 3.88E-06	→ 1.29E-01	← 2.03E-01
Social interaction	← 4.15E-01	→ 9.24E-01	← 9.90E-01	→ 9.05E-02	→ 7.10E-01	← 8.33E-01
Peer relationships	← 3.60E-01	→ 9.18E-02	→ 8.08E-01	→ 8.01E-04	→ 1.16E-01	← 8.75E-01
Shared enjoyment	← 2.20E-01	→ 5.51E-03	1.00E+00	→ 5.40E-06	→ 2.93E-01	← 6.96E-02
Socioemotional reciprocity	← 1.17E-01	→ 4.00E-04	→ 9.87E-01	→ 3.82E-08	→ 1.13E-01	← 3.47E-02
Communication domain	← 7.26E-01	→ 3.21E-02	→ 9.38E-01	→ 3.28E-03	→ 4.80E-01	← 4.77E-01
Gestures	← 3.05E-01	→ 1.52E-01	← 8.68E-01	→ 1.01E-03	→ 8.44E-01	← 5.59E-02
Imagination & Imitation	→ 1.00E+00	→ 2.75E-02	→ 1.60E-01	→ 1.36E-01	→ 2.73E-01	→ 9.92E-01
RRB domain	← 1.04E-05	→ 1.34E-04	1.00E+00	→ 3.60E-10	→ 1.77E-04	← 5.30E-03
Unusual interests	← 7.71E-05	9.53E-01	← 9.16E-01	→ 1.14E-05	→ 6.56E-03	← 9.84E-01
Routines & rituals	← 1.52E-03	9.34E-01	← 3.72E-01	→ 6.54E-04	→ 3.01E-01	← 4.76E-01
Motor mannerisms	← 8.21E-02	→ 3.60E-10	→ 8.90E-01	→ 3.60E-10	→ 3.34E-02	← 6.84E-07
Sensorimotor interests	← 9.67E-02	→ 3.60E-10	→ 5.78E-02	→ 3.60E-10	→ 1.22E-04	← 4.80E-03

Supplementary Table S8: Comparison of autism in the genetic variant groups to the heterogeneous autism group in terms of IQ and symptom domains

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient ; ADI-R, Autism Diagnostic Interview; RRB, Restricted, Repetitive, and Stereotyped Behaviours.

Separate MANCOVA analyses were ran for domain and subdomain scores to avoid including mathematically related scores in the same analysis. Total ADI-R score was analysed separately using an ANCOVA model. Age, gender and site were included as covariates.

Score	Heterogeneous autism N	mean	sd	16p11.2 deletion N	mean	sd	differ from hetereogenous autism p-value	16p11.2 duplication N	mean	sd	differ from hetereogenous autism p-value	22q11.2 deletion N	mean	sd	differ from hetereogenous autism p-value	22q11.2 duplication N	mean	sd	differ from hetereogenous autism p-value	5-Group difference MANCOVA p-value
Cognitive scores																					
FSIQ	948	76.0	25.3	33	78.9	16.0	0.948	29	66.2	21.8	0.153	72	68.9	14.1	0.085	15	80.5	22.6	0.939	**0.013**
VIQ	1135	78.4	27.5	33	75.9	19.7	0.982	29	68.7	23.6	0.266	71	69.8	14.0	**0.049**	15	77.8	17.4	0.999	0.084
PIQ	1297	83.5	24.9	34	82.6	16.1	0.999	29	68.2	23.0	**0.006**	72	72.9	16.6	**0.002**	15	83.4	20.5	0.999	**<0.001**
ADI-R scores																					
Total score	2027	39.1	8.2	35	31.5	8.6	**<0.001**	29	36.7	9.6	0.505	85	31.8	7.5	**<0.001**	20	35.3	8.6	0.226	**<0.001**
Social domain	2027	22.2	5.1	35	18.5	5.8	**<0.001**	29	20.7	5.5	0.490	85	18.2	4.7	**<0.001**	20	21.0	4.9	0.800	**<0.001**
subdomains:																					
Social interaction	2027	4.2	1.6	35	3.4	1.7	**0.017**	29	3.7	2.0	0.345	85	4.0	1.7	0.635	20	4.4	1.3	0.975	**0.005**
Peer relationships	2027	6.6	1.6	35	5.6	1.8	**0.003**	29	6.6	1.2	0.999	85	5.8	1.5	**<0.001**	20	6.0	1.6	0.492	**<0.001**
Shared enjoyment	2027	4.8	1.5	35	3.7	2.0	**<0.001**	29	4.3	1.6	0.493	85	3.4	1.7	**<0.001**	20	4.5	1.6	0.847	**<0.001**
Socioemotional reciprocity	2027	6.7	2.1	35	5.9	2.1	0.147	29	6.1	2.1	0.587	85	5.1	1.9	**<0.001**	20	6.1	1.8	0.737	**<0.001**
Communication domain	2027	10.4	3.1	35	7.9	3.4	**<0.001**	29	9.3	3.9	0.365	85	8.4	3.0	**<0.001**	20	8.7	3.7	0.090	**<0.001**
subdomains:																					
Gestures	2027	5.5	2.4	35	3.7	2.5	**<0.001**	29	4.4	2.9	0.137	85	3.6	2.6	**<0.001**	20	4.5	2.4	0.351	**<0.001**
Imagination & Imitation	2027	4.9	1.3	35	4.2	1.5	**0.009**	29	4.9	1.5	0.999	85	4.8	1.3	0.845	20	4.2	1.6	0.060	**0.001**
RRB domain	2027	6.5	2.3	35	5.1	1.7	**0.005**	29	6.7	2.3	0.992	85	5.2	2.2	**<0.001**	20	5.7	1.9	0.541	**<0.001**
subdomains:																					
Unusual interests	2027	1.9	1.3	35	1.2	1.1	**0.012**	29	2.0	1.0	0.990	85	1.9	1.1	0.999	20	1.7	1.0	0.977	**0.030**
Routines & rituals	2027	1.5	1.3	35	1.0	1.2	0.097	29	1.6	1.4	0.999	85	1.5	1.3	0.999	20	1.4	1.1	0.994	0.178
Motor mannerisms	2027	1.5	0.7	35	1.3	0.9	0.593	29	1.4	0.8	0.996	85	0.7	0.8	**<0.001**	20	1.2	0.9	0.384	**<0.001**
Sensorimotor interests	2027	1.6	0.6	35	1.7	0.5	0.964	29	1.7	0.5	0.901	85	1.2	0.8	**<0.001**	20	1.4	0.8	0.641	**<0.001**

Supplementary Table S9: Effect of age in Aim 2 MANCOVA analyses

FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient ; ADI-R, Autism Diagnostic Interview ; RRB, Restricted, Repetitive, and Stereotyped Behaviours.

Score	p-value	Eta-squared	Fixed effect slope coefficient
Cognitive scores			
FSIQ	**<0.001**	1.8	0.31
VIQ	**<0.001**	3.6	0.88
PIQ	0.568	0.0	-0.22
ADI-R scores			
Total score	**<0.001**	2.1	0.24
Social domain	**<0.001**	1.9	0.14
subdomains:			
Social interaction	**<0.001**	5.3	0.07
Peer relationships	**0.007**	0.3	0.02
Shared enjoyment	**<0.001**	1.5	0.04
Socioemotional reciprocity	0.114	0.1	0.01
Communication domain	**<0.001**	1.0	0.06
subdomains:			
Gestures	**0.008**	0.3	0.03
Imagination & Imitation	**<0.001**	1.7	0.04
RRB domain	**<0.001**	0.6	0.03
subdomains:			
Unusual interests	**<0.001**	1.7	0.03
Routines & rituals	**<0.001**	1.0	0.03
Motor mannerisms	**<0.001**	0.8	-0.01
Sensorimotor interests	**<0.001**	0.6	-0.01

Supplementary Figure S1: Proportion of CNV carriers who met clinical cut-offs for the three autism domains
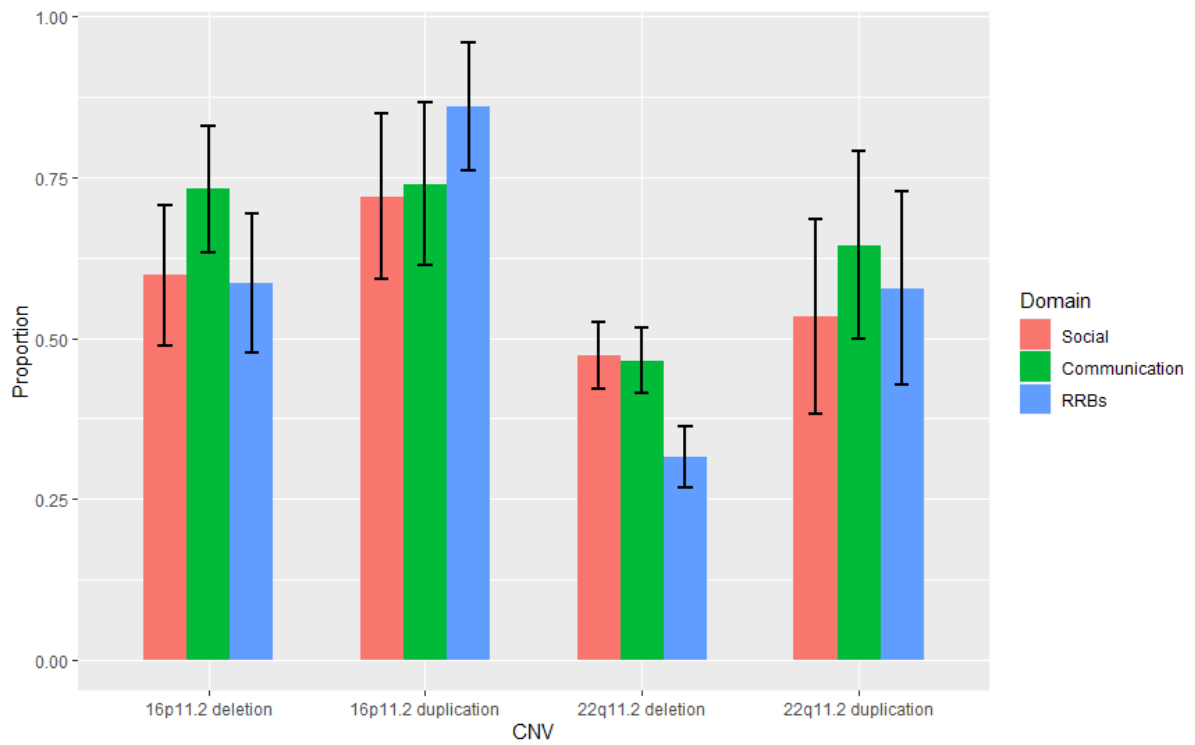
Error bars indicate 95% confidence intervals. RRB: Restricted, Repetitive, and Stereotyped Behaviours.

**Supplementary Figure S2:** Distribution of total ADI-R score, autism domain scores, and FSIQ by genetic variant group

The range of scores for total ADI-R scores is highly overlapping between groups (16p11.2 deletion, 3 to 48; 16p11.2 duplication, 0 to 53; 22q11.2 deletion, 0 to 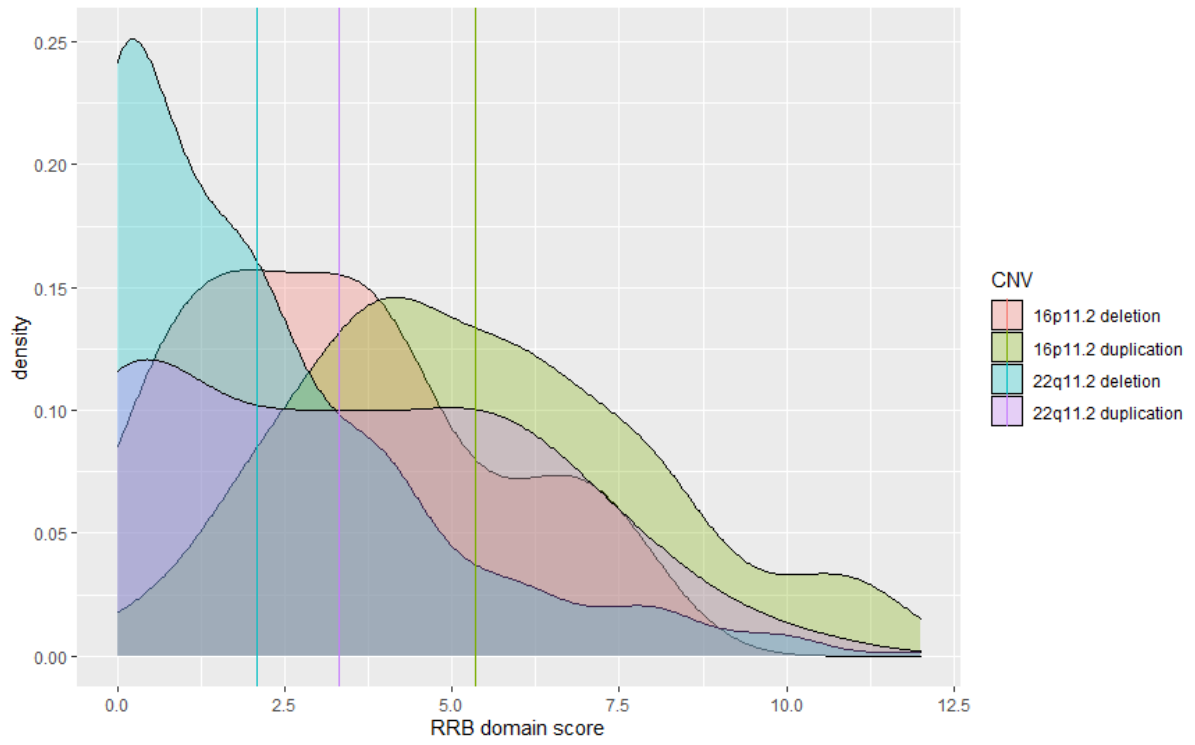48; 22q11.2 duplication, 0 to 48). Similarly, the IQ ranges overlap (16p11.2 deletion, 42 - 122; 16p11.2 duplication, 28 - 108; 22q11.2 deletion, 42 - 117; 22q11.2 duplication, 30 - 119).

The 4 vertical lines indicate group means.

ADI-R, Autism Diagnostic Interview ; RRB, Restricted, Repetitive, and Stereotyped Behaviours.
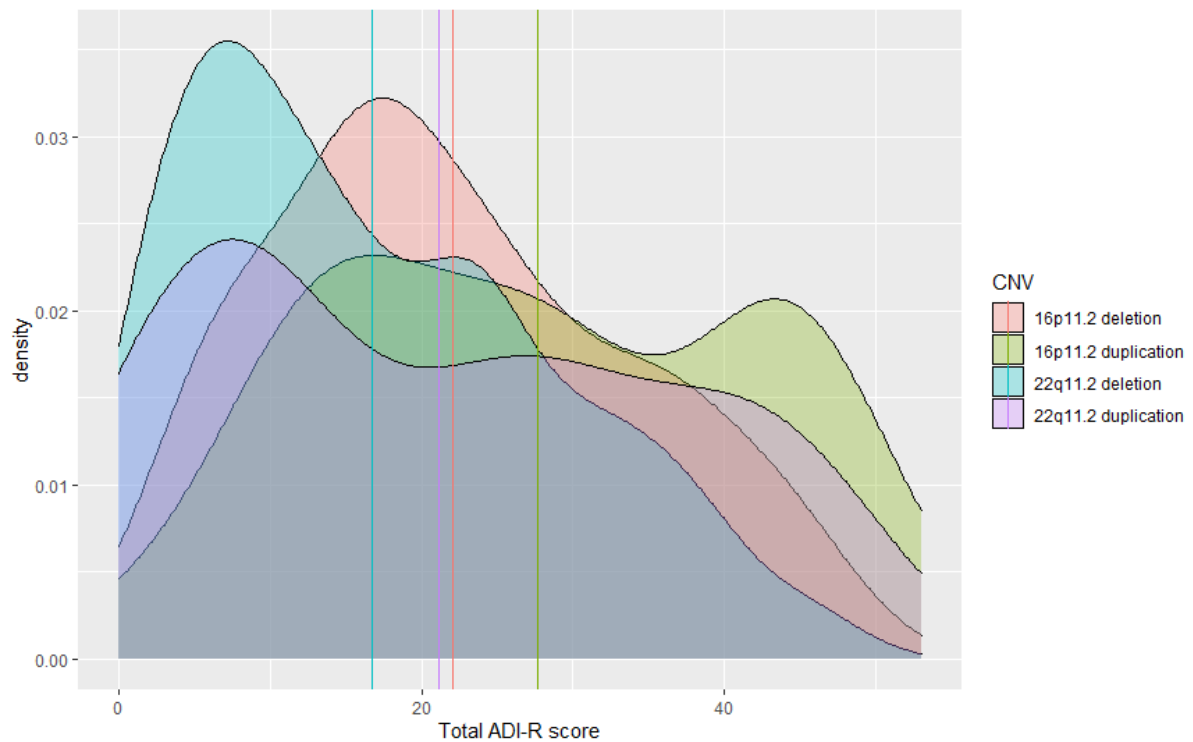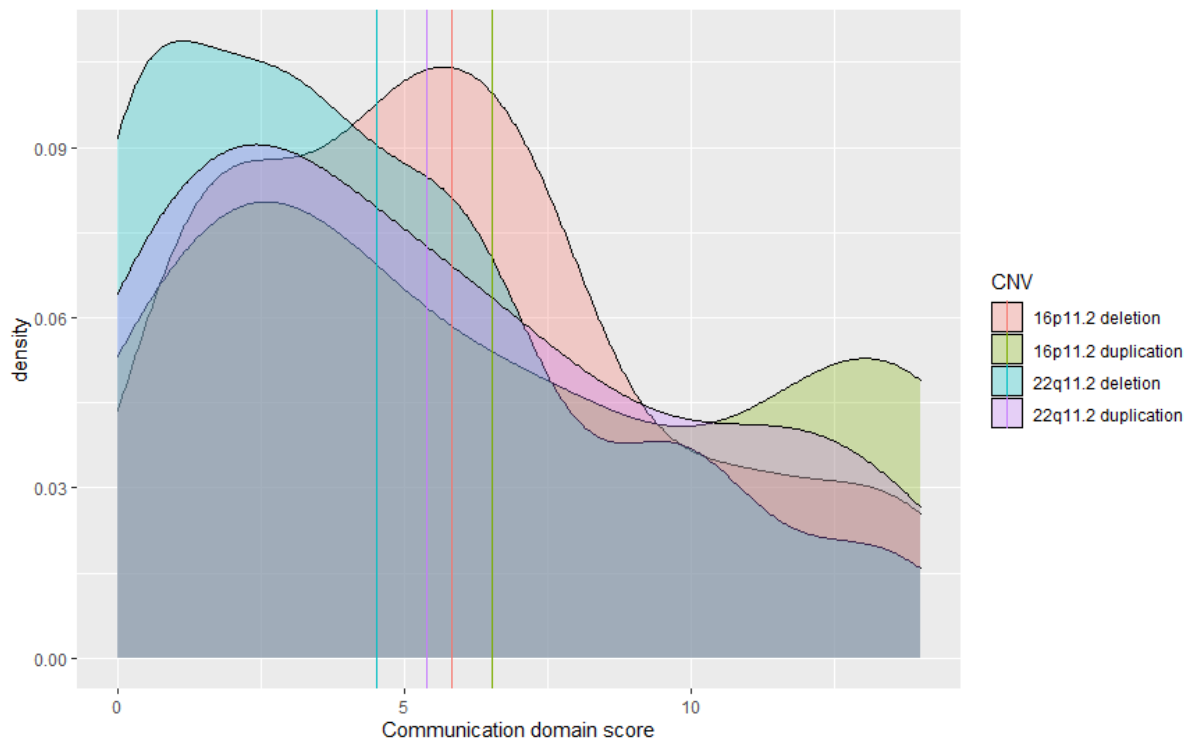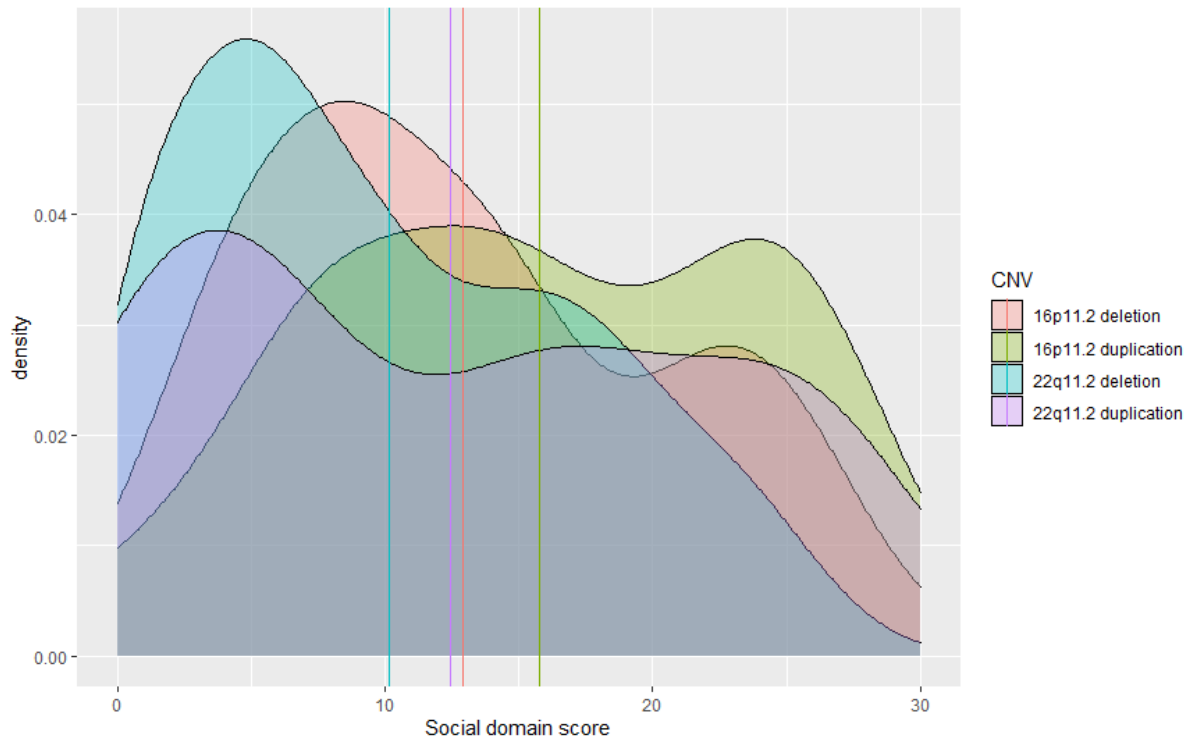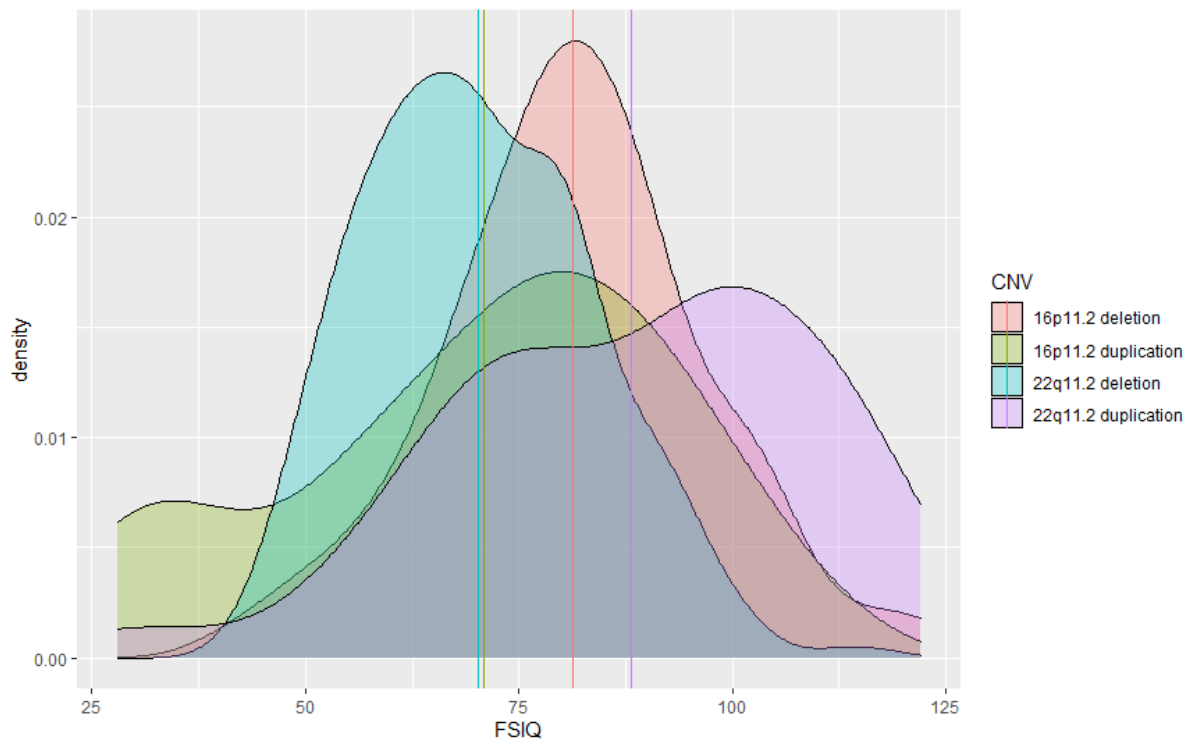
Supplementary Figure S3: Hypothetical plots of "non-specific", "partially specific" and "highly specific" models of genotype-phenotype relationships within autism

We conceptualise three possible models (Figure 1); the "nonspecific effect" model whereby all genotypes lead to similar autism phenotypes; the "highly specific" model whereby each genotype leads to a unique autism phenotype; and the "partially specific model" whereby autism profiles are distinct but overlapping.

Non-specific model: for Trait A, genotype does not explain any of the variance in phenotype, indicating that phenotypic variability is explained by within group factors. Highly specific model: for Trait C genotype explains all the variability in phenotypic outcome, indicating that there is no within group variability. Partially specific model: where both between genotype and within genotype variability exist.
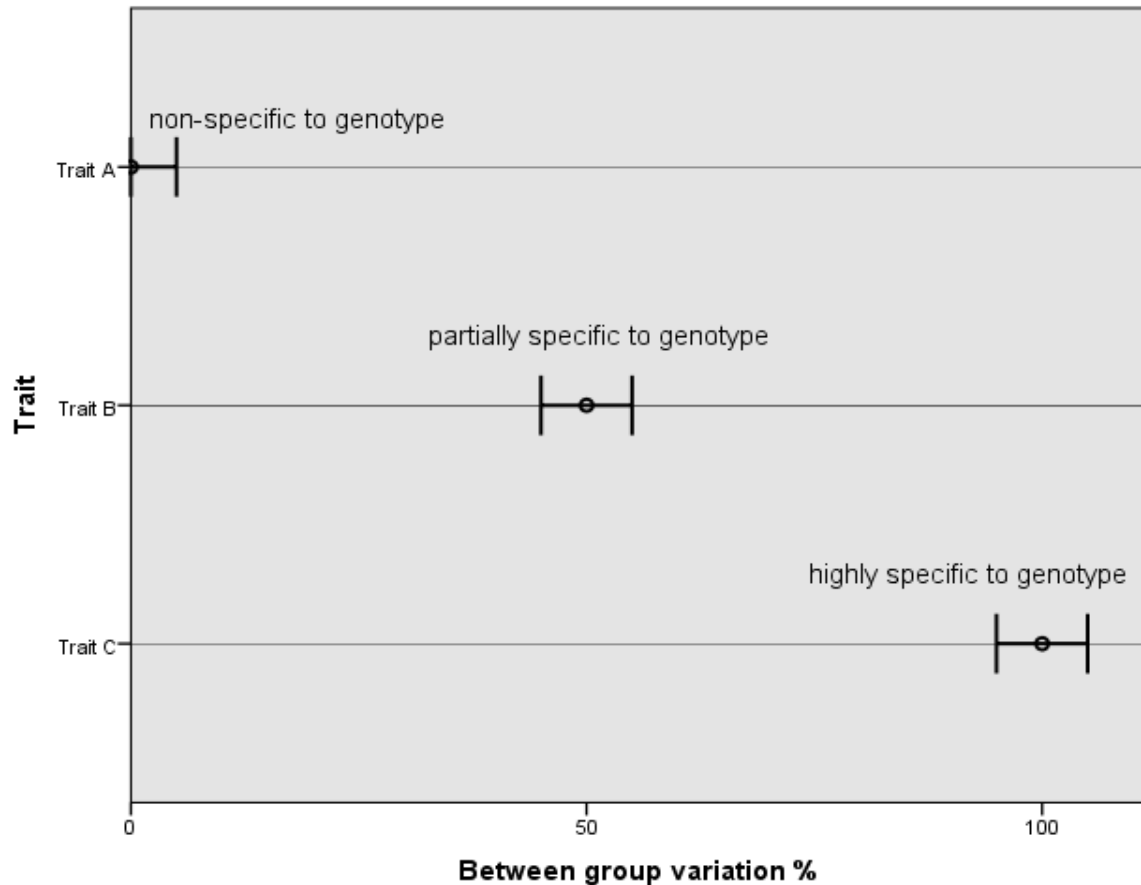
Supplementary Materials References

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