SUPPLEMENTARY ONLINE CONTENT

This supplementary material has been provided by the authors to give readers additional information about their work.

FIGURES CONTENT

TABLES CONTENT

SUPPLEMENTARY METHODS

Definition of autism

Autism spectrum disorder (ASD) refers to autism as defined in DSM-V (1). As the participants involved in the current study were diagnosed following DSM-IV criteria which uses a subtyping strategy (autistic disorder, Asperger syndrome, and PDDNOS) (2), we will use the generic term ‘’autism” to avoid confusion.

CNV detection, annotation and filtering

Genotyping and whole genome sequencing

- *Genotyping data*

CNV detections and standard filtering strategies were previously published (3). CNV calling was performed using the same pipeline for individuals from the Simons Simplex Collection (SSC) (4), IMAGEN (5), and Saguenay Youth Study (SYS) (6) to obtain a harmonized dataset.
In the IMAGEN cohort (5), 2,090 individuals were genotyped using a combination of the Illumina 610Kq (N probes=620,901; N arrays=708) and 660Wq (N probes=657,366; N arrays=1,385). The genotyping was performed at the Centre National de Genotypage (CNG; Paris, France).
In SYS cohort (6), 1,994 Illumina SNP arrays were analyzed using Illumina 610Kq (N probes=620,901; N arrays=599) and the HumanOmniExpress BeadChip - V12 (HOE-V12) (N probes=730,525; N arrays=1,395). The genotyping was performed at CNG for 610Kq and at the Genome Analysis Centre of Helmholtz Zentrum München (Munich, Germany) for HOE-V12.
In the SSC (4), 10,032 individuals were genotyped at Yale University using Illumina SNP genotyping arrays 1Mv1, 1Mv3 Duo, or Omni2.5M.

- *Whole genome sequencing data*

In the MSSNG database (7), 7,233 individuals were sequenced at multiple sites using Illumina sequencing HiSeq, HiSeq 2,500, or HiSeqX.
Next generation sequencing data were analysed using Broadinstitute Genome Analysis Toolkit (GATK) best practice (8).

Call of CNVs

CNVs from SSC, IMAGEN and SYS were called using PennCNV (9) and QuantiSNP (10) with the following parameters:

- Number of consecutive probes for CNV detection ≥ 3
- CNV size ≥ 1Kb
- Confidence scores ≥ 15.

Then, we merged detected CNVs from both algorithms with CNVision (11).
For MSSNG, read alignment data were used to compute CNV calling following the workflow of Trost et al. (12).

Filtering of micro-array

To ensure good quality of CNVs, we kept only micro-arrays without too much noise.

- For IMAGEN and SYS cohorts:
  - Wave Factor (WF) < |0.05|
  - Standard deviation of the Log-R-Ratio (LRR-SD) < 0.35
  - Standard deviation of the B allele frequency (BAF-SD) < 0.08
  - Call Rate > 0.99
- For SSC cohort: all micro-array detecting ≥ 200 CNVs were considered as noisy and were removed from the analysis.

CNV coordinates

The CNVs coordinates were updated from hg18 to hg19 using Illumina information and the liftover tool from the genome browser (https://genome.ucsc.edu/cgi-bin/hgLiftOver and http://grch37.ensembl.org/Homo_sapiens/Tools/AssemblyConverter).

Concatenation of CNVs

In a subsequent step, using an in-house algorithm (Pasteur) followed by visual inspection (SnipPeep, http://snippeep.sourceforge.net), we stitched CNVs that appeared to be incorrectly split by the calling algorithms, and we removed any CNVs (size of ≥ 500Kb and ≥ 100 SNPs) that spanned known large assembly gaps (greater than 150Kb).

CNV filtering

CNVs with the following criteria were selected for analysis:

- Size ≥ 50 Kb
- Autosomal (Since deletions and duplications are not comparable between sex-linked and autosomal CNVs, we could not pool both types of CNVs. Sex-linked CNVs were therefore excluded from the analysis.)
- Unambiguous type: deletions or duplications.
- Confidence score ≥ 30 with at least one of both detection algorithms
- Cross array criteria: CNVs overlapping ≥ 10 probes in each of the array technologies used in the study.
- And additional filters were applied for CNVs which are not 40% overlapping with recurrent CNVs from TableS3: Overlap with Segmental duplicates or centromeric regions < 50%.

CNV annotation and scoring

The annotation of CNVs was performed with a R package developed by our team. This package was developed using RefSeq (https://genome.ucsc.edu/) and ANNOVAR (13) coding and non-coding genes. For these analyses, we excluded the pseudo-genes (UCSC site: https://genome.ucsc.edu/).

Deletions and duplication were annotated for size, number of genes, number of expression quantitative trait loci regulating genes expressed in the brain (14), and each coding gene with all isoforms fully encompassed in CNVs was annotated using 6 constraint scores. For each individual, we computed the sum of these annotations for deletions and for duplications.

Coding genes were annotated using the following constraint scores and transformations:

- the probability of being loss-of-function intolerant (pLI) (15) between 0 and 1 where 1 means that the gene is completely intolerant;
- the residual variation intolerance score (16) between 0 and 100 was transformed with 100-RVIS such as 100 represents the more intolerant;
- the ExAC CNV score for deletions (17) between -2.62 and 3.81 was transformed with deletion score + min(deletion score) such that it becomes between 0 and 6.43 where 6.43 represents the more intolerant.
- the ExAC CNV score for duplication (17) between -2.53 and 2.86 was transformed with duplication score + min(duplication score) such that it becomes between 0 and 5.39 where 5.39 represents the more intolerant.
- the number of protein-protein interactions defined as the number of proteins interacting with each protein coding gene according to STRINGs Protein v10 for Human database (18) (9606.protein.links.v10.txt.gz; http://string-db.org/) where protein networks were defined based on high confidence (> 0.7) interactions;
- the differential stability (DS) score (19), a correlation-based metric which assess reproducibility of regional patterns of gene expression in the brain between -0.057 and 0.97 was transformed with DS + min(DS) such that it becomes between 0 and 1.027 where a higher score means high specific expression in brain.

For the six scores detailed above, the default value associated to gene without available score was 0.

De novo CNVs identification

De novo CNVs in the SSC were identified in probands, unaffected siblings, and unselected population from SYS using two previously published datasets (11, 20), combined with our own algorithm developed in R. A CNV was considered as *de novo* only if it was defined as such by all three approaches.

Frequency

We used two sources to calculate the frequency. First frequency (DGV frequency) was annotated using the database of genomic variants (DGV) on the basis of a minimal overlap of 70% between the CNV of interest and its more closely resembling CNV displayed in DGV (DGV hg19, http://www.dgv.tcag.ca). If CNV was seen in several cohorts, we selected the maximal frequency conditionally to the fact that the sample size of the DGV cohort is ≥ 100; otherwise, frequency was considered as null.

Second frequency was computed on the CNVs of 1,804 adolescents in IMAGEN and 893 parents in SYS from the general population cohort (GP-Cohort frequency). It was computed on the basis of a minimal overlap of 70% between CNVs. Since CNVs with a frequency < 0.1% were visualized to ensure the CNVs veracity, the GP-Cohort frequency was recomputed after excluding false positive CNVs. This process was done iteratively until no more CNV is excluded. Then the CNVs of the entire database (SSC and general population cohorts) were annotated with GP-Cohort frequency on the basis of a minimal overlap of 70% between the CNV of interest and its more closely resembling CNV displayed in GP-Cohort. The frequency of a CNV that is not seen in GP-Cohort was considered as null.

Definition of a rare CNV

Throughout the paper, a rare CNV is either a known recurrent CNV (Table S3) with a DGV frequency < 0.1% or a non-recurrent CNVs with the following characteristics: (i) DGV frequency < 0.1%; (ii) < 50% of the CNV is contained in regions present at > 1% in DGV (11, 21, 22); (iii) unselected population frequency 1/1000. All CNVs annotated as rare were manually curated by visual inspection (SnipPeep, http://snippeep.sourceforge.net) and false positives were excluded.

Genetic analysis of pairwise ancestry and population stratification

Classical multidimensional scaling (MDS) was used to identify ancestry based on the identity by state (IBS) matrices of genetic distances (D) in the IMAGEN, the SYS and the SSC cohorts, based on the reference population HapMap3 (23) with 993 individuals (Hapmap Consortium 2003 (www.hapmap.ncbi.nlm.nih.gov). PLINK (24) (pngu.mgh.harvard.edu/purcell/plink/) was used to do these calculations. SNPs were filtered to keep only autosomal SNPs with minor allele frequency (MAF) > 5% and with good quality, significance threshold for a test of Hardy-Weinberg equilibrium < 1.10^{-6} and missing genotype rates < 10%. Related individuals were identified based on *D* defined by the following formula:

$$D = \frac{IBS2 + 0.5\,IBS1}{N\ SNP\ pairs}$$

with *IBS1* and *IBS2* being the number of loci at which a pair of individuals share either 1 or 2 alleles identical by state, respectively, and *N SNP pairs* is the number of loci tested. Pairs of individuals were defined as related when $D \geq 0.8$.

Ancestry was estimated using Admixture (25) (http://www.genetics.ucla.edu/software/admixture) with reference populations from HapMap3 (23) allowing for 4 ancestry components (Africa, Asia, European and India). Results show a strong European ancestry component in the three datasets. We then performed a principal components analysis based on the variance-standardized relationship matrix and displayed the 3 first ancestry dimensions and associated eigenvalues.

Clinical assessments

Non-verbal Intelligence Quotient (IQ)

Intellectual ability was measured using standardized tests according to the cognitive level of the participant (Table S2).

For SSC autistic probands, non-verbal intelligence quotient (NVIQ) scores were obtained from the Differential Ability Scales, 2nd Edition (DAS-II) (26) for early years (N=1,031) and school age children (N=1,213), the Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV) (27) (N=45), the Wechsler Abbreviated Scale of Intelligence – First Edition (WASI-I) (28) (N=63) or the Mullen Scales of Early Learning (MSEL) (29) (N=213) (see density distribution of NVIQ by test used in Figure S1B). Norm-referenced standard scores (deviation NVIQ) were available for most of the participants (85.10%). However, for individuals from SSC who were not able to obtain a deviation NVIQ due to their age and/or developmental level, ratio NVIQ were derived by dividing mental age by chronological age and multiplying by 100. See Bishop et al., 2011 for more details concerning convergence between ratio and deviation NVIQ (30).

For MSSNG autistic probands, NVIQ scores were obtained from the Leiter international performance scale – Original and revised (31, 32) (N=372), the raven progressive matrices (33) (N=214), the Stanford-Binet intelligence scale (N=281), the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) (27) (N=46), the Wechsler Abbreviated Scale of Intelligence – First and Second Editions (WASI-I, WASI-II) (28, 34) (N=338) or the Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV) (35) (N=128) (see density distribution of NVIQ by test used in Figure S1C). Deviation NVIQ were available for all participants.

Individuals in IMAGEN undertook the fourth edition of the Wechsler intelligence scale for children (WISC-IV) whereas SYS cohort used the third edition (WISC-III) to assess children. Deviation NVIQ were available for all participants.

As a preeminent test of fluid intelligence, the Raven's progressive matrices, has been reported as a better assessment of general cognitive abilities in autistic individuals than common NVIQ tests (36), we also investigated the matrices subtests measured in SSC probands using the Differential Ability Scales – second edition (DAS-II) (26).

Social Responsiveness Scale

For all the individuals from the SSC and for the unselected population from IMAGEN, severity of social deficits was ascertained with scores from the social responsiveness scale (SRS) (37, 38).

Severity of autism main domains

For probands from the SSC and MSSNG, the severity of autism main domains were assessed by domain-calibrated scores from the Autism Diagnostic Observation Schedule (ADOS) (39, 40) and the Autism Diagnostic Interview-Revised (ADI-R) (41).

Child behaviour Checklist

For SSC probands and their unaffected siblings, behavioural problems were assessed on the Total Problems Score, as well as the Internalizing and Externalizing domains of the Preschool and School-aged Child behaviour Checklist (CBCL) (42, 43).

Phenotypes only available for probands from the SSC

- *Language and phonology*

Phonological short-term memory was measured using scaled scores from the non-word repetition subtest of the Comprehensive Test of Phonological Processing (CTOPP) (44).

Language level was measured using age of first words, age of first phrases and the overall level of expressive language from the ADI-R (45) (question 09, question 10 and question 30 respectively).

Words and phrases delay variables in probands have been derived using both items of age of first words and age of first phrases from the ADI-R score as following:

We considered that autistic probands have word or phrase delay if parents reported an age of first words greater than 24 months on question 9 and the first phrases after 33 months on question 10.

Also, if autistic probands scored 993, 994, or 997 on question 9 or 10, they were considered as delayed in the corresponding variable. At the contrary, if they scored of 996 on question 9 or 10, they were considered as non-delayed in the corresponding variable.

- *Adaptative skills*

Standard scores of total adaptive skills, communication, interaction and daily living skills domains were measured using the Vineland Adaptive behaviour Rating Scales - Second Edition (VABS-II). (46)

- *Motor skills*

Motor skills were measured using the corresponding main domain of the VAB-II, as well as gross and fine motor skills subdomains.

We also used the age of onset for walking reported in the ADI-R (question 5) as continuous and categorical measures of gross motor skills. (45)

Walking delay variables in probands have been derived using item of age of onset for walking from the ADI-R score (question 5).

We considered that autistic probands have walking delay if parents reported an age of first walk greater than 18 months on question 5, as well as if they scored 997 at the same item. At the contrary, if they scored of 996 on question 5, they were considered as non-delayed.

Motor coordination was assessed by the Developmental Coordination Disorder Questionnaire (DCDQ).

- *Associated neurological condition*

Finally, the presence of non-febrile seizures was assessed from the ADI-R (question 85) and the Medical History Form.

Statistical analyses

Stepwise variable selection procedure based on Bayesian information criteria

The stepwise variable selection procedure was used to choose the best model with the smallest Bayesian Information Criterion (BIC). We allowed pairwise interactions conditionally upon main effects to also be included in the model. Since variable selection and model fitting steps were performed on the same dataset, this could induce a selection bias in the estimates. We used a bootstrap (1,000 iterations) estimation of the bias in our final models to correct for this bias. (47)

Genetic variable selection procedure was performed using the boot.stepAIC() function from the R package 'bootStepAIC'. (48)

Effect of gene dosage on general intelligence

The model selected in SSC cohort was applied in the unselected population sample. Both were adjusted for NVIQ test used, sex and ancestry. Moreover, the unselected population sample includes related individuals, thus we included a random effect in the model to take into account the familial relationship.

The model adjusted for familial relationship with a random effect could be written as:

$NVIQ \sim \boldsymbol{\alpha}X + \gamma Z + \beta_1 CNV_{DEL} + \beta_2 CNV_{DUP}$

where X represents the adjustments covariates (NVIQ test used, sex and ancestry) and Z is the familial relatedness; $CNV_{DUP/DEL}$: CNV scoring selected as best genetic explanatory variable in SSC cohort; (α, β_1, β_2) and γ are respectively the vectors of coefficients for fixed and random effects. The mixed effect model was computed using lme() function from the 'nlme' R package. (49)

- *Replication in MSSNG*

The model selected in SSC cohort was applied in MSSNG cohort, except that the ancestry is not available for MSSNG dataset and therefore we could not adjust for it. The MSSNG dataset also includes related individuals, thus we included a random effect in the model to take into account the familial relationships.

- *Matching autistic probands from SSC and from MSSNG based on NVIQ*

We used a matching procedure to obtain identical NVIQ distributions in both cohorts (1MSSNG:2SSC) (Figure S2B). Matching was made by searching for the nearest neighbor within ± 5 points of NVIQ. We used the Match() function from the R package 'Matching'. (51) To avoid errors due to randomness, we performed the matching 500 times, obtaining 500 matched cohorts and 500 corresponding estimates.

- *Model with pooled dataset to test the interaction between CNV scoring and diagnosis*

NVIQ ~ $\boldsymbol{\alpha}X + \gamma Z + \beta_1$ CNV_{DEL} + β_2 CNV_{DUP} + β_3 CNV_{DEL} * diagnosis + β_4 CNV_{DUP} * diagnosis

where X represents the adjustments covariates (NVIQ test used, sex, and diagnosis) and Z is the familial relatedness; $CNV_{DUP/DEL}$: CNV scoring selected as best genetic explanatory variable is SSC cohort; (α, β_1, β_2, β_3, β_4) and γ are respectively the vectors of coefficients for fixed and random effects. The mixed effect model was computed using lme() function from the 'nlme' R package. (49)

Effect of gene dosage on autism risk

All enrichment analyses were performed by excluding related individuals of MSSNG and general population cohorts, i.e. only one subject by family was included in the analyses.

Conditional logistic regression was performed for the comparison of probands paired to their unaffected siblings using the clogit() function from the R package 'survival'. (50)

All models for this section included sex and ancestry as covariates when available.

- *Matching of autistic probands and general population regarding the NVIQ*

We used a matching procedure to pairs probands from the SSC with individuals from the unselected populations (ratio 1:1) with similar NVIQ (± 5 points of NVIQ). We used the Match() function from the R package 'Matching'. (51)

To avoid errors due to randomness, we performed the matching 500 times, obtaining 500 matched cohorts including 1,411 to 1,469 pairs, and 500 corresponding estimates. The Figure S1A and S1D represent the NVIQ distributions in initial cohorts and in an example of matched cohorts.

- *Contribution of NVIQ in autism risk effect*

To estimate the proportion of autism-risk potentially mediated by NVIQ for deletions and duplication, we performed a counterfactual-based mediation analysis on the pooled dataset. We used the neImpute(), neModel(), and neEffdecomp() functions from the R package 'medflex' (52) on two logistic regression including sum of pLI in deletions or duplications as the main explanatory variable. We also applied a logistic regression including sum of pLI in deletions and duplications as the two mains explanatory variables to estimate the autism risk conferred by deletions and duplications in both subgroups of individuals above and below median NVIQ.

Effect of gene dosage on phenotypic measures

- *SRS as a continuous variable in the SSC probands, unaffected siblings and parents, and in the unselected population from IMAGEN*

We used a linear mixed effect model to quantify the effect of gene dosage measured by pLI scores on SRS total raw score after pooling probands and their unaffected relatives (siblings and parents). A kinship matrix was generated to model the genetic covariance between related individuals using the kinship() function from the R package 'kinship2' (53) and this covariance was used as a random effect in the model performed with the function lmekin() from the R package 'coxme' (54). We further explored a potential effect of gene dosage on the SRS within the autism group, unaffected siblings, parents and unselected population from IMAGEN using a linear regression and adjusting for the abnormal distributions with a square root transformation of the SRS scores when necessary (Table S8). All models used were adjusted for age, sex, ancestry, and in a second time for NVIQ and/or for the diagnosis of autism.

- *SRS as a categorical variable in the SSC probands, unaffected siblings and unselected population from IMAGEN*

We also investigated the SRS scores based on the previously published *T*-score categorization (55) as follow:

- ***T*-scores of 76 or higher**: Clinically significant deficits in social functioning that interfere with interactions with others;
- **66 <*T*-scores< 75**: Moderate, signaling some clinically significant social deficits;
- **60 <*T*-scores< 65** : Mild to moderate deficiencies in social behaviour;
- ***T*-scores< 59**: Indicate an individual probably does not have social difficulties indicative of a possible autism diagnosis.

A logistic regression was applied in this pooled dataset (autistic probands; unaffected siblings and unselected population) to investigate the effect of gene dosage on binary categorical SRS: clinical (obtained after merging the moderate, mild and

clinically significant categories) and normal (Table S8, Figure S5C and S5D). This logistic regression model took into account the family relatedness as random factor using the glmer() function from the R package 'lme4'.(56)
A cumulative ordinal regression model was also performed on SRS coding for 4 different levels of social deficits (normal, moderate, mild and clinically significant) (Table S8, Figure S5E and S5F). This model was applied using the function vglm() from the R package 'VGAM'. (57) All models used were adjusted for age, ancestry, and in a second time for the diagnosis of autism.

- *Autism core symptoms in probands from the SSC and MSSNG*

A cumulative ordinal regression model was used to assess the effect of gene dosage on ADOS and ADI-R domains in autistic probands from the SSC and MSSNG separately, and in the pooled dataset (probands from the SSC and MSSNG). Ordinal regression (cumulative, parallel slopes):
$ln(P(Y>k)/P(Y<=k)) \sim \alpha_k X+\beta_1 pLI_{DEL} + \beta_2 pLI_{DUP}$
Models assessing the ADI-R were adjusted for age, sex and in a second time for NVIQ. When exploring the ADOS, models were corrected for sex and in a second time for NVIQ (Table S9). Additional correction for the population was applied when the model was run on the pooled dataset.

- *CBCL in probands and unaffected siblings from the SSC*

Early analysis using T scores generated by the CBCL demonstrated that despite T scores being normed for sex and age, sex and age emerged as significant factors affecting scores on the school-aged tests. For all analysis afterwards, raw scores were used and corrected for age and sex in the analysis. Several possible models, including an ordinal model testing binning based on "pre-clinical" and "clinical" thresholds based on T-scores, were discarded with the switch to raw scores. Pre-school and school-aged tests were analyzed separately.
Since raw scores have an oversampling of zeros and are overdispersed, it was necessary to use a negative binomial distribution function to adequately assess the relationship between CBCL scores and gene dosage measured by pLI. Probands and unaffected siblings were assessed separately and together. In the pooled sample, a negative binomial mixed effects model was used, with family as a random variable to account for familial relatedness. The function used for probands and siblings alone was glm.nb() from the R package 'MASS' (58), and for pooled samples, glmmTMB() was used from the package 'glmmTMB'. (59) All models used were adjusted for age, sex, ancestry, and in a second time for NVIQ and/or for the diagnosis of autism (Table S10).

See Table S7 for detail of the models used for the other phenotypical measures.

- *Computation of significance threshold*

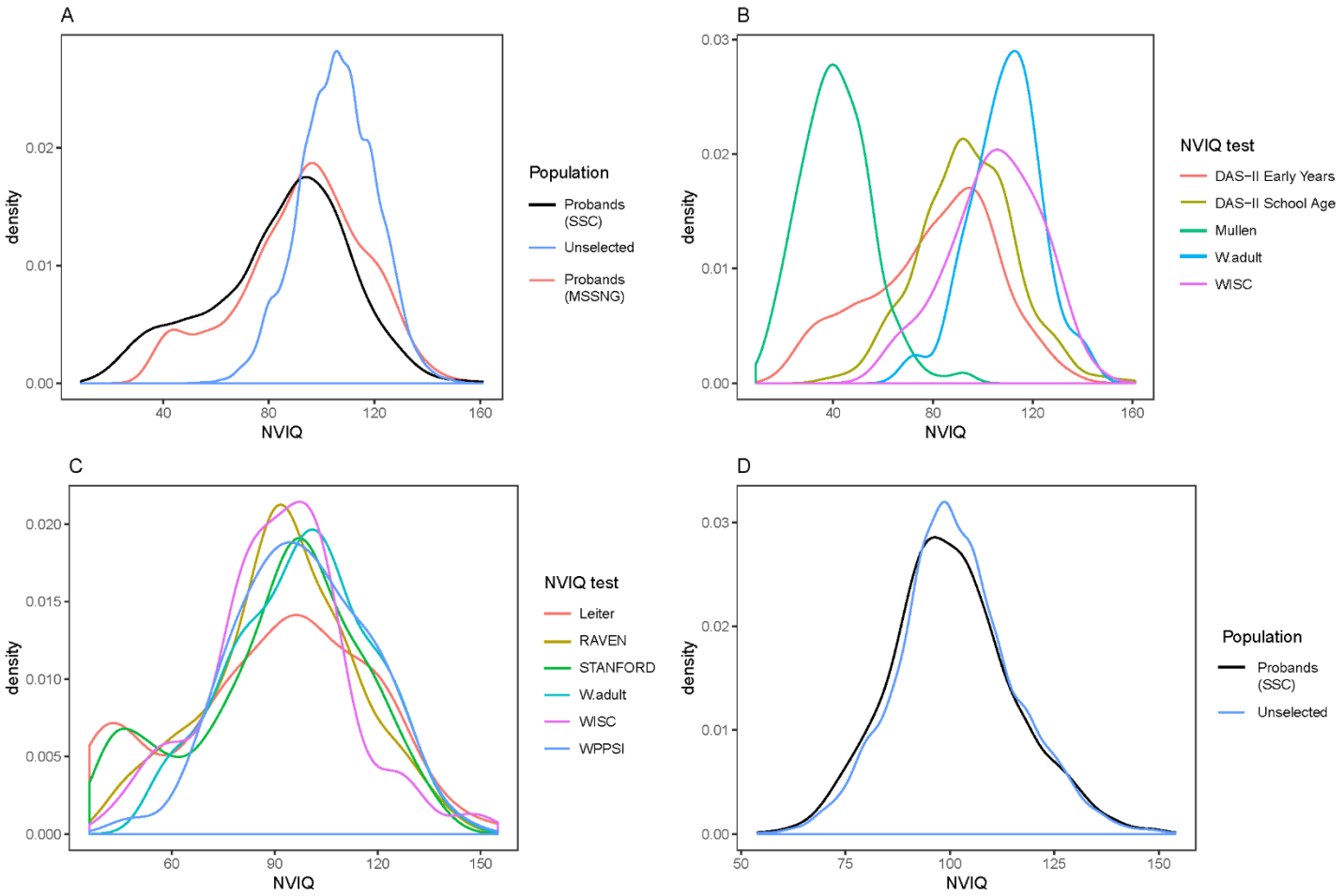
To control for multiple testing, we computed our significance threshold by adapting the methodology of Cheverud (2001) previously applied to control the FWER when analyzing many SNPs (60). When computing the matrix of correlations between phenotypes, Cheverud argued that the eigenvalues of this matrix could be used to estimate the effective number of independent tests. Thus, we calculated an effective number of independent tests, m_e, and then used this number in a Bonferroni-style correction.
m_e was calculated as follow:

$$m_e = 1 + (m - 1)\left(1 - \frac{1}{m}\,\mathrm{Var}(\lambda)\right)$$

$$Var(\lambda) = \frac{1}{m-1}\sum_{i=1}^{m}(\lambda_i - 1)^2$$

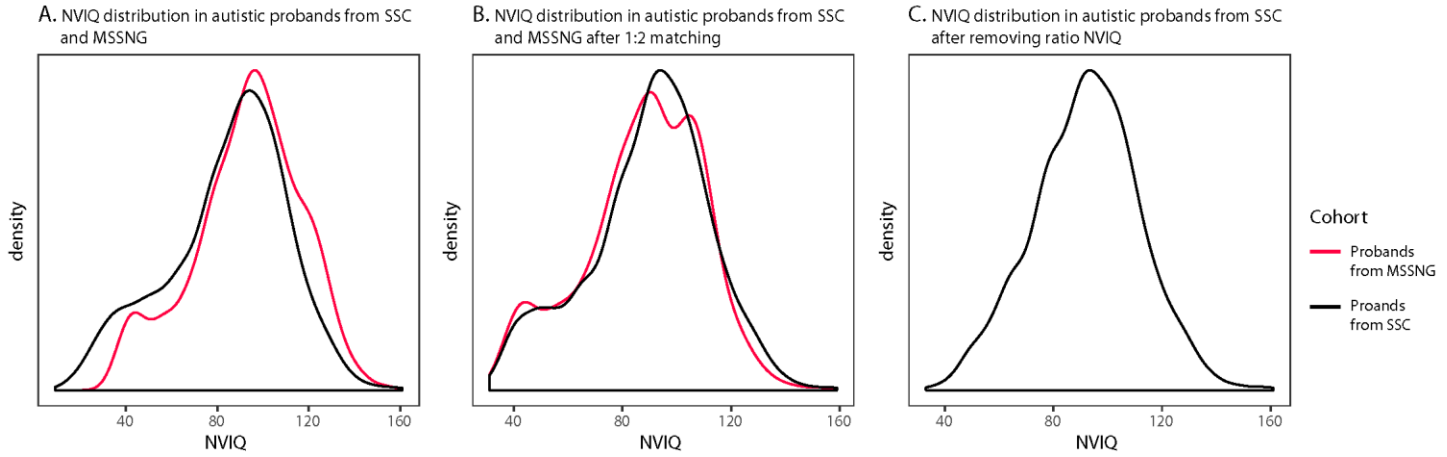
SUPPLEMENTARY FIGURES

Figure S1: NVIQ distributions.



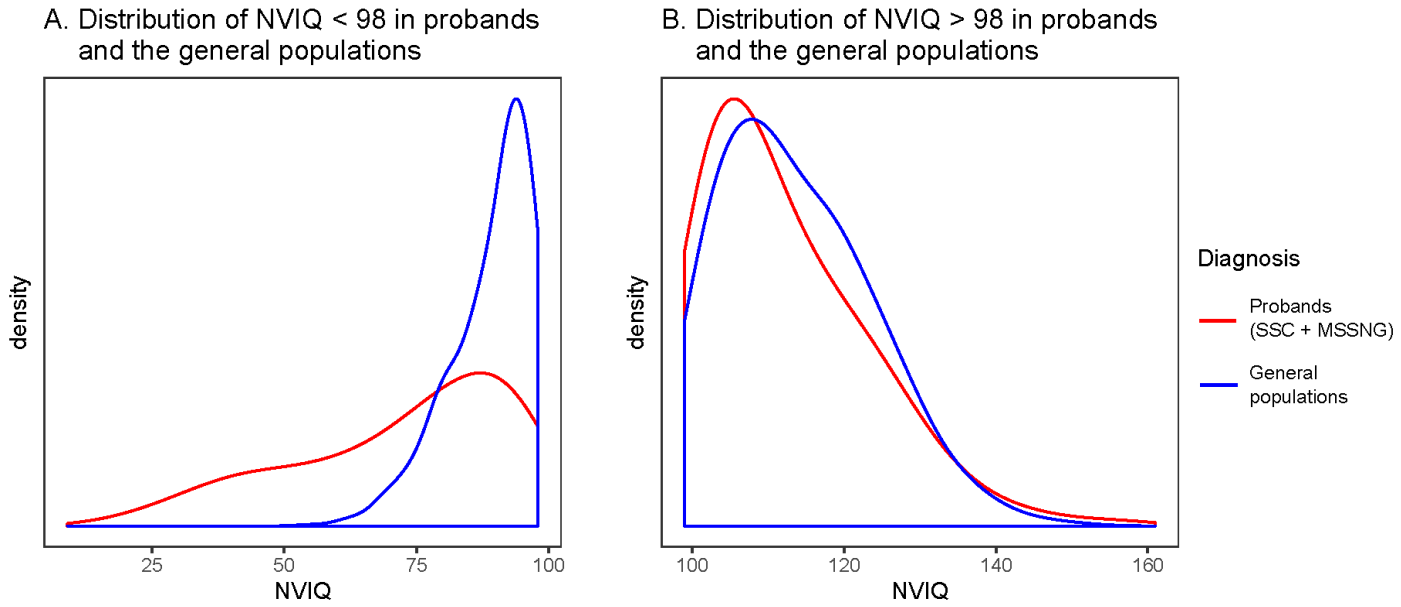
A) Density distribution of NVIQ in the autistic probands from SSC (black) and MSSNG (red), and from the unselected population (green: IMAGEN and SYS pooled). B) Density distribution of NVIQ in the autistic probands from SSC in function of the test used. C) Density distribution of NVIQ in the autistic probands from MSSNG in function of the test used. D) Density distribution of NVIQ in the autistic probands from SSC (black) and from the unselected population (green: IMAGEN and SYS pooled) after 1:1 matching procedure. NVIQ: Non-verbal IQ; DAS-II: Differential Ability Scales, 2nd Edition; WASI: Wechsler Abbreviated Scale Intelligence, WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Preschool and Primary Scale of Intelligence.

Figure S2: NVIQ distributions after selection for sensitivity analyses.



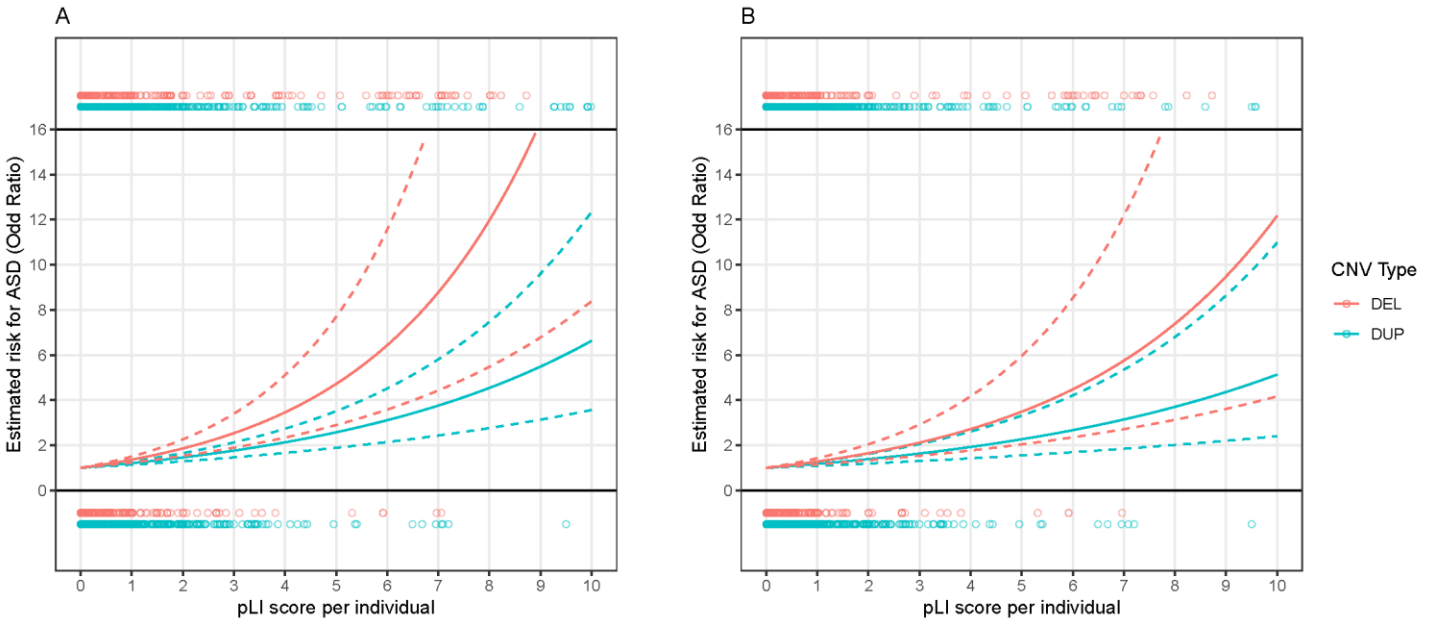
A) NVIQ distribution of autistic probands from SSC (black) and MSSNG (red) before matching. B) NVIQ distribution of autistic probands from SSC (black) and MSSNG (red) after 1:2 matching on NVIQ (example of 1 among 500 iterations). C) NVIQ distribution of autistic probands from SSC (black) after removing 382 individuals with a ratio NVIQ.

Figure S3: NVIQ distributions of individual below or above the median (98), using probands from SSC and MSSNG, and the unselected populations.



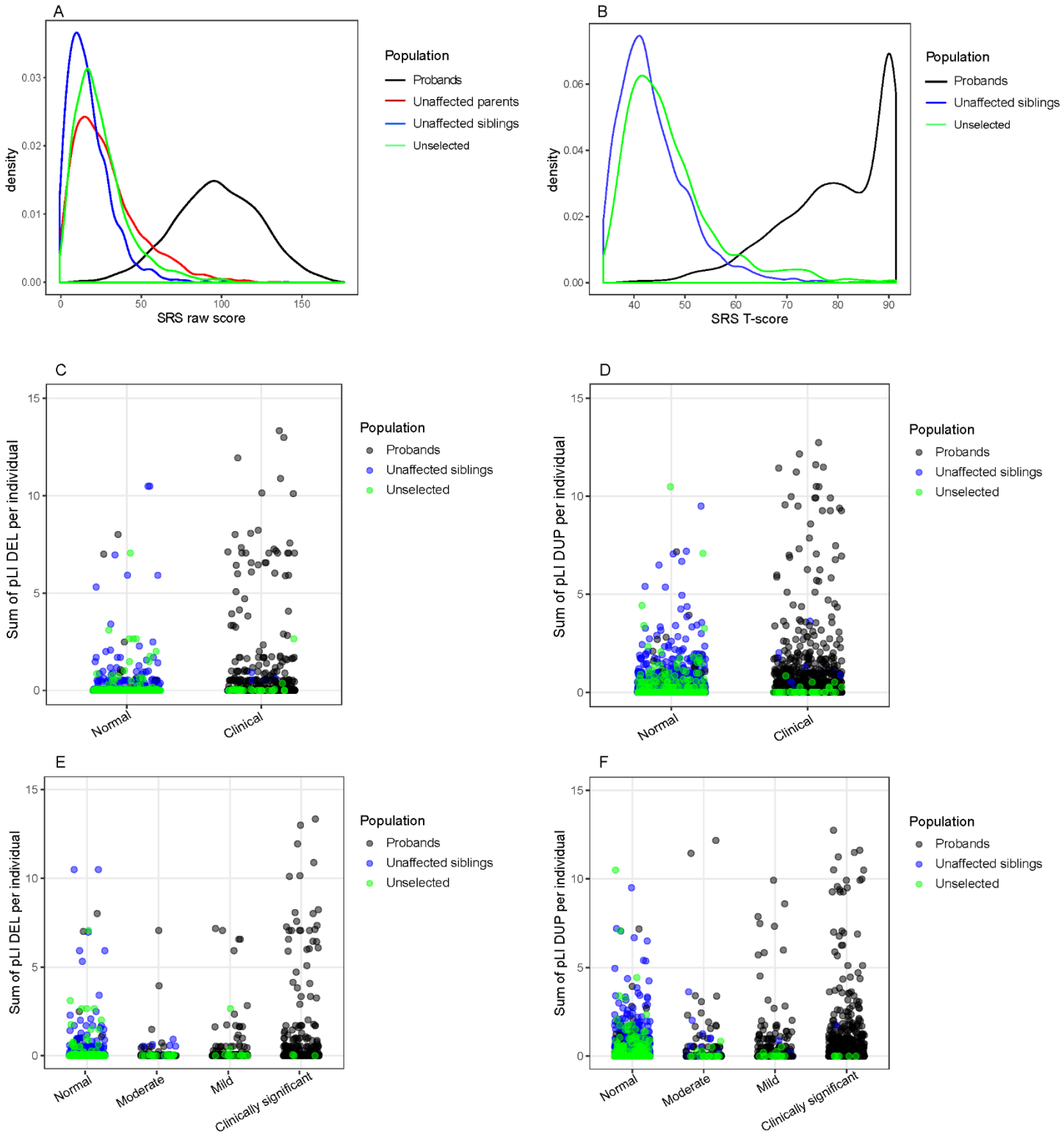
A) NVIQ distribution of autistic probands from SSC and MSSNG (red) and unselected populations (blue) with a NVIQ bellow 98. B) NVIQ distribution of autistic probands from SSC and MSSNG (red) and unselected populations (blue) with a NVIQ over 98.

Figure S4: Effect of gene dosage measured by pLI on autism risk.



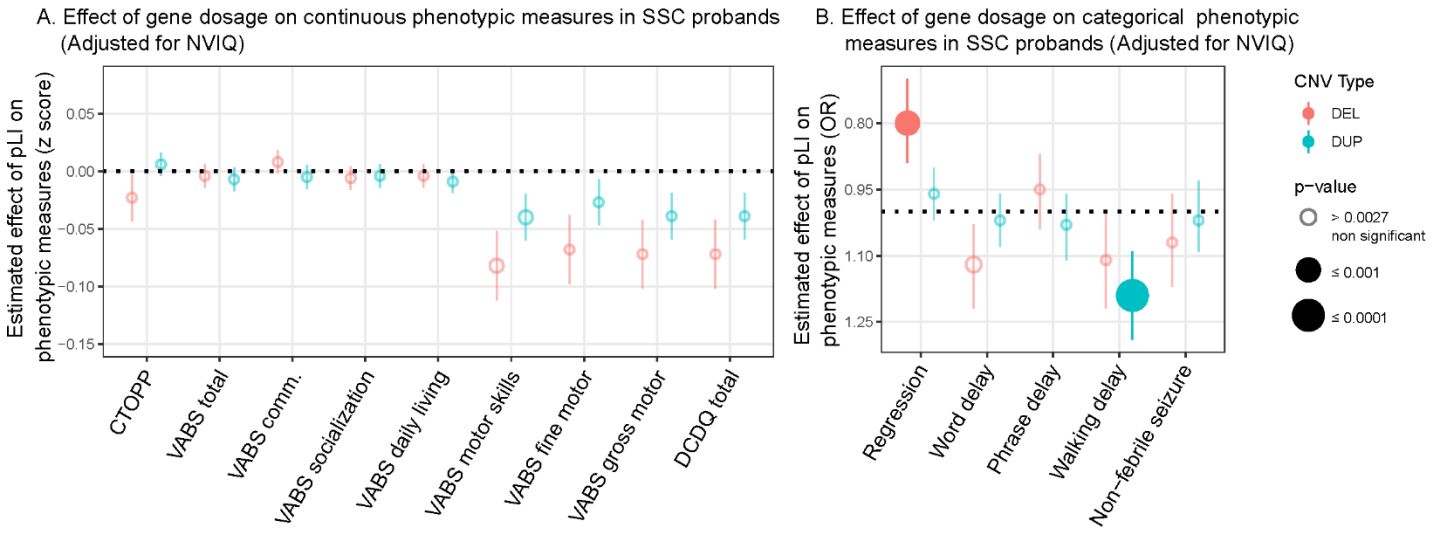
Representation of the non-linear effect of deleted (red) or duplicated (blue) point of pLI on autism risk estimated by logistic regression model when including (A) or excluding (B) the 16 recurrent CNVs detailed in Table S6. X-axis represents the sum of pLI score per individual and y-axis represents the risk of autism diagnosis estimated by our model in odds ratio.

Figure S5: Effect of gene dosage measured by pLI on SRS score.



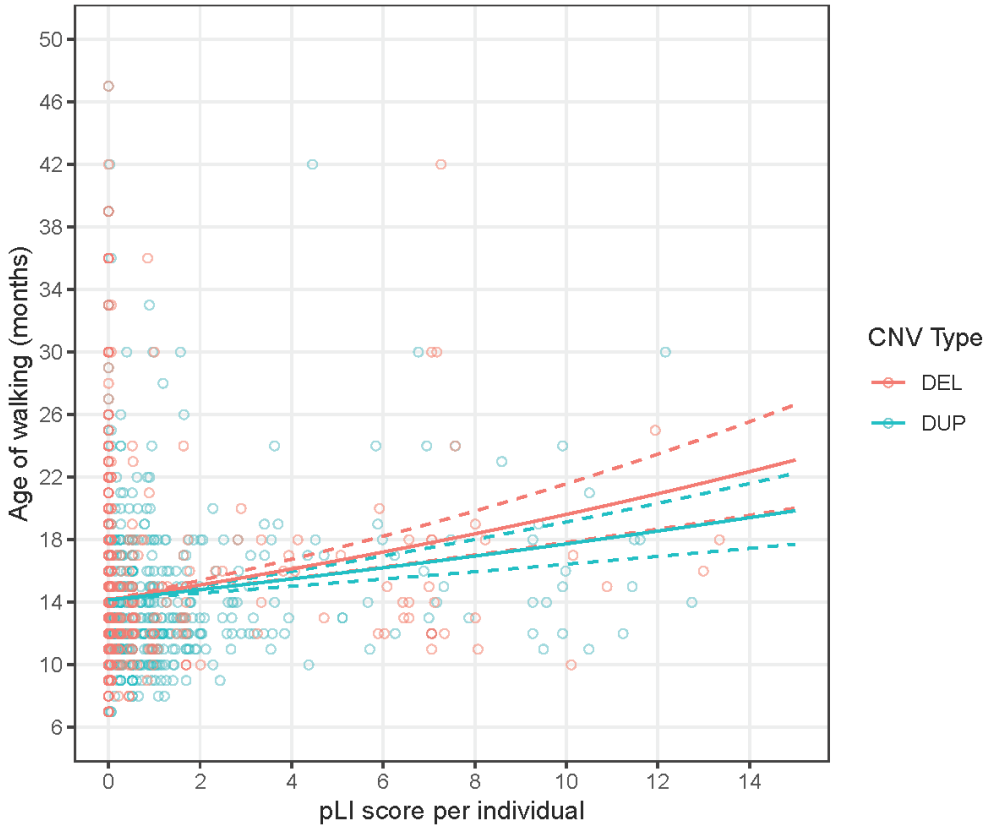
A) SRS raw score distribution in the autistic probands from SSC (black), their unaffected siblings (blue), their parents (red) and the unselected population from IMAGEN (green). B) SRS T-scores distribution in the autistic probands from SSC (black), their unaffected siblings (blue), and from the unselected population from IMAGEN (green). C to F) Representation of the distribution of Sum of pLI deleted (C,E) or duplicated (D,F) per individual in function of SRS categories (binary (C,D) or all assessed categories (E,F)) in the autistic probands from SSC (black), their unaffected siblings (blue) or unselected population from IMAGEN (green).

Figure S6: Effect of gene dosage measured by pLI on phenotypic measures adjusted for NVIQ in SSC probands.



(A, B) Effect-size of a deleted (red) or duplicated (blue) point of pLI on continuous (A) and categorical (B) phenotypes in autistic probands from the SSC adjusted for NVIQ. Y-axis values of panel (A) are measures z-scored using normative data (Table S7) except for DCDQ which was z-scored using the SSC autistic proband group. Y-axis values of panel (B) are odds ratios computed by logistic regression. The significance threshold was computed (60) to account for multiple testing: 0.0027. CTOPP: Comprehensive Test of Phonological Processing; VABS-II: Vineland Adaptive behaviour Rating Scales - Second Edition; DCDQ: Developmental Coordination Disorder Questionnaire.

Figure S7: Effect of gene dosage measured by pLI on age of onset for walking.



Representation of the non-linear effect of deleted (red: OR, 1.03 [95% CI, 1.02-1.04]; P=5×10^{-12}) or duplicated (blue: OR, 1.02 [95% CI, 1.02-1.03]; P=2×10^{-9}) point of pLI on age of onset for walking estimated using quasi-Poisson model adjusted for sex. X-axis represents the sum of pLI score per individual and y-axis represents the age of onset for walking in month.

SUPPLEMENTARY TABLES

Table S1: Description of cohorts for demographic, genotypical characteristics and phenotypical measures.

Variables	IMAGEN	SYS	SSC probands	SSC siblings	SSC parents	MSSNG
Demographic characteristics						
N individuals	1,802	967	2,569	2,092	5,138	1,381
Age, mean (SD)[(b)]	14.45 (0.37)	14.99 (1.84)	9.03 (3.58)	10.06 (4.33)	41.48 (6.18)	9.21 (4.44)
N male (%)	880 (48.91)	462 (47.72)	2,227 (86.66)	969 (46.31)	2,569 (50.00)	1,106 (80.09)
Genotypical characteristics (Chr 1-22)						
Detection technology	Illumina 610Kq or 660Wq array	Illumina 610Kq or HumanOmniExpress12 array	Illumina 1Mv1, 1Mv3 or Omni 2.5 array			Illumina HiSeq, HiSeq 2,500 or HiSeqX sequencing
N carriers of CNVs	855	610	1,835	1,490	2,040	932
N carriers of documented CNVs[(a)]	26	22	77	33	82	40
N total CNVs	2,712	2,213	6,597	5,159	12,689	4,075
N deletions (total)	1,574	1,212	3,323	2,562	6,410	2,435
N deletions, mean (SD)	0.87 (0.91)	1.25 (1.06)	1.29 (1.05)	1.22 (1.05)	1.24 (1.04)	1.76 (1.39)
N duplications (total)	1,138	1,001	3,274	2,597	6,279	1,640
N duplications, mean (SD)	0.63 (0.79)	1.03 (1.04)	1.27 (1.13)	1.24 (1.12)	1.22 (1.11)	1.19 (1,15)
pLI deletions, sum	94.97	55.16	416.00	118.08	232.37	171.61
pLI deletions per individual, mean (SD)	0.05 (0.34)	0.06 (0.46)	0.16 (1.00)	0.06 (0.46)	0.04 (0.39)	0.12 (0.63)
pLI duplications, sum	226.27	248.75	816.38	375.74	891.78	350.23
pLI duplications per individual, mean (SD)	0.13 (0.53)	0.26 (0.73)	0.32 (1.44)	0.18 (0.63)	0.17 (0.60)	0.25 (1.12)
Phenotypical measures						
N NVIQ	1,744	966	2,569	-	-	1,381
NVIQ, mean (SD)	106.62 (14.77)	104.50 (13.09)	84.47 (26.27)	-	-	92.97 (23.72)
Autism related symptoms						
N DAWBA DSM	1,303	-	-	-	-	-
N SRS	977	-	2,556	2,078	4,838	598
SRS raw score, mean (SD)	25.42 (16.99)	-	97.98 (26.97)	18.36 (13.82)	29.53 (21.34)	-
SRS T-score, mean (SD)	49.86 (36.51)	-	79.52 (10.45)	43.80 (7.04)	-	-
N ADOS-overall css	-	-	2,498	-	-	679
ADOS-overall css, mean (SD)	-	-	7.45 (1.68)	-	-	7.30 (2.11)

N ADOS-social affect css	-	-	2,372	-	-	325
ADOS-social css, mean (SD)	-	-	7.25 (1.76)	-	-	6.86 (2.00)
N ADOS-rrsb css	-	-	2,449	-	-	330
ADOS-rrsb css, mean (SD)	-	-	7.78 (1.92)	-	-	8.52 (1.51)
N ADIR reciprocal social interactions	-	-	2,567	-	-	403
ADIR reciprocal social interactions, mean (SD)	-	-	20.35 (5.69)	-	-	18.26 (7.98)
N ADIR rrb	-	-	2,567	-	-	696
ADIR rrb, mean (SD)	-	-	6.52 (2.50)	-	-	6.43 (2.50)
N ADIR verbal communication	-	-	2,254	-	-	374
ADIR verbal communication, mean (SD)	-	-	16.48 (4.29)	-	-	14.42 (5.82)
N ADIR non-verbal communication	-	-	2,567	-	-	71
ADIR non-verbal communication, mean (SD)	-	-	9.26 (3.45)	-	-	10.76 (3.03)
N with/without regression	-	-	911/1,657	-	-	-
Language and phonology						
N ADIR overall level of language	-	-	2,568	-	-	1,039
N age of first word	-	-	2,467	-	-	-
age of first word in months, mean (SD)	-	-	24.38 (14.97)	-	-	-
N with/without word delay	-	-	935/1,632	-	-	-
N age of first phrase	-	-	2,311	-	-	-
age of first phrase in months, mean (SD)	-	-	39.18 (18.52)	-	-	-
N with/without phrase delay	-	-	1,567/1,000	-	-	-
N CTOPP	-	-	1,988	-	-	-
CTOPP, mean (SD)	-	-	7.76 (2.86)	-	-	-
behavioural problems						
N CBCL total score	-	-	1,945	1,596	-	-
CBCL total score, mean (SD)	-	-	50.77 (23.93)	17.99 (15.18)	-	-
N CBCL internalizing	-	-	1,945	1,596	-	-
CBCL internalizing, mean (SD)	-	-	11.06 (8.46)	4.71 (5.25)	-	-
N CBCL externalizing	-	-	1,945	1,596	-	-

CBCL externalizing, mean (SD)	-	-	11.56 (7.91)	5.06 (5.05)	-	-
Adaptative skills						
N VABS-II total	-	-	2,569	-	-	-
VABS-II total, mean (SD)	-	-	73.08 (12.13)	-	-	-
N VABS-II daily living	-	-	2,569	-	-	-
VABS-II daily living, mean (SD)	-	-	76.33 (13.92)	-	-	-
N VABS-II communication	-	-	2,569	-	-	-
VABS-II communication, mean (SD)	-	-	76.98 (14.63)	-	-	-
N VABS-II socialization	-	-	2,569	-	-	-
VABS-II socialization, mean (SD)	-	-	70.91 (12.59)	-	-	-
Motor skills						
N VABS-II motor	-	-	919	-	-	-
VABS-II motor, mean (SD)	-	-	81.75 (12.60)	-	-	-
N VABS-II gross motor	-	-	926	-	-	-
VABS-II gross motor, mean (SD)	-	-	12.25 (2.23)	-	-	-
N VABS-II fine motor	-	-	923	-	-	-
VABS-II fine motor, mean (SD)	-	-	11.78 (2.69)	-	-	-
N age of onset of walking	-	-	2,550	-	-	-
age of onset of walking in months, mean (SD)	-	-	13.56 (4.00)	-	-	-
N with/without onset of walking delay	-	-	159/2,405	-	-	-
N DCDQ	-	-	2,209	-	-	-
DCDQ, mean (SD)	-	-	38.50 (12.44)	-	-	-
Associated neurological condition						
N with/without non-febrile seizure	-	-	233/2,333	-	-	-

(a) Number of carriers of a CNV which overlap ≥ 30% with a documented CNV from the Table S6; SD: Standard deviation; Sum pLI deletions or duplications: sum of score of pLI for the entire population; NVIQ: Non-verbal intelligence quotient; DAWBA: Development and Well-Being Assessment; SRS: Social Responsiveness Scale; ADOS: Autism Diagnostic Observation Schedule; css: calibrated severity score; rrsb: repetitive, restricted and stereotyped behaviours; ADI-R: Autism Diagnostic Interview-Revised; CTOPP: Comprehensive Test of Phonological Processing; CBCL: Child behaviour Checklist; VABS-II: Vineland Adaptive behaviour Rating Scales - Second Edition; DCDQ: Developmental Coordination Disorder Questionnaire.

Table S2: NVIQ available in autistic probands from SSC and MSSNG, and individuals from unselected population.

Cohorts	N available NVIQ	Age		Males		NVIQ		
		mean	SD	N	%	Test used	Mean	SD
IMAGEN	1,744	14.45	0.37	880	48.91	WISC-IV	106.62	14.77
SYS	966	14.99	1.84	462	47.72	WISC-III	104.50	13.09
SSC autistic probands	2,564	9.03	3.58	2,227	86.66	DAS-II, MSEL, WASI-I, WISC-IV	84.47	26.27
MSSNG autistic probands	1,381	9.21	4.44	1,106	80.09	Leiter, Raven, Stanford-Binet, WASI-I, WASI-II, WISC-IV, WPPSI-IV	92.97	23.72

SD: Standard deviation; NVIQ: Non-verbal intelligence quotient; DAS-II: Differential Ability Scales - Second Edition; MSEL: Mullen Scale of Early Learning; WASI-I or II: Wechsler Abbreviated Scale of Intelligence – First or Second Edition; WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition.

Table S3: Breakpoints used to detect recurrent CNVs associated to neurodevelopmental disorders.

Reference	Chr	Start hg19	Stop hg19	Type	Note protective CNV
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	1	10077413	DEL	*GABRD*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	710137	9977413	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	860137	3660140	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	145288643	145628643	DEL	*HFE2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	145338643	149783376	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	145338643	147883376	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	146573376	147393376	DEL	*GJA5*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	146573376	147393376	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	168733376	173733377	DEL	*FMO* and *DNM3*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr1	245033377	248833377	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	50146496	51256496	DEL	*NRXN1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	57746496	61736496	DEL	*VRK2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	59646496	63146496	DUP	*PEX13* to *AHSA2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	96726273	97676273	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	100693568	108443568	DEL	*NCK2* and *FHL2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	111333937	113233529	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	111383531	113093529	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	111383531	113093529	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	200161755	200511755	DEL	*SATB2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	235735261	243102476	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr2	239705243	242471327	DEL	*HDAC4*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	9525000	11025000	DUP	*JAGN1* to *TATDN2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	87237310	87557310	DEL	*CHMP2B* to *POU1F1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	115237310	115647310	DEL	*GAP43*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	191517306	193017306	DEL	*FGF12*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	195715603	197355603	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	195715603	197355603	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	195745603	197355603	DEL	*DLG1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr3	195745603	197355603	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr4	110000	7049099	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr4	1870202	2010202	DEL	*WHSC1* and *WHSC2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr4	80780976	83280976	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr5	1	11727000	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr5	87964244	88224244	DEL	*MEF2C*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr5	175717394	177057394	DEL	*NSD1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr5	180117394	180817394	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr6	92043279	104693307	DEL	*FOXP1* and *SIM1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr6	100813279	100943279	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr6	165330010	170908075	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	10239	3833474	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	66482565	72272064	DEL	*AUTS2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	66482565	72272064	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	72662064	74262064	DUP	

Table S3 continued

Reference	Chr	Start hg19	Stop hg19	Type	Note protective CNV
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	72662064	74262064	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	72742064	74142064	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	72742064	74142064	DEL	*ELN* and *GTF2I*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	74962064	76662064	DEL	*RHBDD2* and *HIP1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr7	74962064	76662064	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr8	160000	11912591	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr8	8092590	11892591	DEL	*SOX7* and *CLDN23*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr8	8092590	11892591	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr8	8212590	11912591	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr9	32010000	39010000	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr9	131060179	141080179	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr9	137810179	141080179	DEL	*EHMT1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr9	137810179	141080179	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr9	137860179	141080179	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr9	137860179	141080179	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr10	46929994	48429994	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr10	49389994	52389994	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr10	81690020	88940020	DEL	*SFTPD* to *GLUD1*, *NRG3*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr10	81960020	88800020	DEL	*NRG3* and *GRID1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr10	127760010	135400010	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr11	310000	3443424	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr11	43983424	46063424	DEL	*EXT2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr11	67753424	71282352	DEL	*SHANK2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr11	128044790	134844790	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr12	6469739	6809739	DUP	*SCNN1A* to *PIANP*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr12	65073733	68643733	DEL	*GRIP1* and *HMGA2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr14	104480247	106378955	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	22648636	28626405	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	22648636	31912708	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	22798636	23088559	DEL	*NIPA1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	24818907	28426405	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	24818907	28426405	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	30862708	32962708	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	31132708	32482708	DEL	*CHRNA7*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	72912946	75792945	DEL	*PML*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	72912946	74412947	DEL	*BBS4, NPTN, NEO1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	72962947	75532947	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	72962947	76012945	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	74012947	75532947	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	74012947	76012945	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	74012947	78132945	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	74012947	75532947	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	74412947	75592947	DEL	*CLK3, CSK*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	75592947	75792945	DEL	*SIN3A*

Table S3 continued

Reference	Chr	Start hg19	Stop hg19	Type	Note protective CNV
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	75972945	78202945	DEL	*FBXO22* and *TPSAN3*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	83182945	84738996	DEL	*HOMER2* and *BNC1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	85138996	85698996	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	99362477	102521392	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr15	99362477	102521392	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	160000	5159999	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	3779999	3859999	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	14892499	16892499	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	14892499	18292499	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	15502499	16292499	DEL	*MYH11*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	15502499	16292499	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	21352499	29442499	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	21612499	29042499	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	21892499	22492499	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	21942499	22462499	DEL	*EEF2K* and *CDR2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	28442499	30342499	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	28442499	30342499	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	28772499	29112499	DEL	*SH2B1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	29652499	30202499	DEL	*TBX6*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	29652499	30202499	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr16	83792499	90222499	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	50000	2593250	DEL	*YWHAE* and *PAFAH1B1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	50000	2593250	DUP	*YWHAE* and *PAFAH1B1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	100000	4153251	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	553250	1353250	DEL	*PAFAH1B1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	553250	1353250	DUP	*PAFAH1B1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	2363250	2923250	DEL	*YWHAE*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	2363250	2923250	DUP	*YWHAE*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	16709275	20479408	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	16709275	20309408	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	16709275	20479408	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	29165874	30215887	DEL	*NF1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	34815887	36205887	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	34815887	36205887	DEL	*TCF2*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	43644217	44144178	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	43704217	44184217	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	43704217	44184217	DEL	*MAPT*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	57655218	58075218	DEL	*TUBD1* and *TMEM49*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	58065218	60305218	DEL	*TBX2* and *TBX4*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr17	72088405	81060000	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr18	110000	5310000	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr18	70949020	77899009	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr19	199000	5899000	DUP	

Table S3 continued

Reference	Chr	Start hg19	Stop hg19	Type	Note protective CNV
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr19	199000	8789000	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr21	42478130	47975572	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	17470000	25020000	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	18820000	22270000	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	19020000	20290000	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	19020000	20290000	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	21910000	23650000	DEL	*BCR* and *MAPK1*
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	21910000	23650000	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	44268667	51244566	DEL	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	47021336	51244566	DUP	
Cooper et al. 2012 (61) and Coe et al. 2014 (62)	chr22	51113134	51173134	DEL	*SHANK3*
Marshall et al 2017 (63)	chr1	145430996	148237104	DEL	
Marshall et al 2017 (63)	chr1	145430996	148237104	DUP	
Marshall et al 2017 (63)	chr2	49920350	51032536	DEL	*NRXN1*
Marshall et al 2017 (63)	chr3	196018732	197628732	DEL	
Marshall et al 2017 (63)	chr7	65373855	65401085	DEL	*ZNF92,* Protective
Marshall et al 2017 (63)	chr7	65373855	65401085	DUP	*ZNF92,* Protective
Marshall et al 2017 (63)	chr7	73328061	74727726	DUP	
Marshall et al 2017 (63)	chr7	158660506	159179546	DEL	*WDR60* and *VIPR2*
Marshall et al 2017 (63)	chr7	158660506	159179546	DUP	*WDR60* and *VIPR2*
Marshall et al 2017 (63)	chr8	100025494	100889814	DEL	*VPS13B*
Marshall et al 2017 (63)	chr9	841690	969090	DEL	*DMRT1*
Marshall et al 2017 (63)	chr9	841690	969090	DUP	*DMRT1*
Marshall et al 2017 (63)	chr13	20397624	20437776	DUP	*ZMYM5,* Protective
Marshall et al 2017 (63)	chr15	22784509	23074432	DEL	
Marshall et al 2017 (63)	chr15	30840505	32190507	DEL	
Marshall et al 2017 (63)	chr16	28811178	29041178	DEL	
Marshall et al 2017 (63)	chr16	29641178	30191178	DUP	
Marshall et al 2017 (63)	chr22	19032487	21065711	DEL	
Marshall et al 2017 (63)	chr22	19032487	21065711	DUP	Protective
Marshall et al 2017 (63)	chrX	148793685	148798928	DUP	*MAGEA11*, Protective
Marshall et al 2017 (63)	chrX	154918531	155342497	DUP	
Moreno del luca et al 2013 (64)	chr1	144000000	144340000	DUP	
Moreno del luca et al 2013 (64)	chr1	144000000	144340000	DEL	
Moreno del luca et al 2013 (64)	chr1	145040000	145860000	DEL	
Moreno del luca et al 2013 (64)	chr1	145040000	145860000	DUP	
Moreno del luca et al 2013 (64)	chr1	145040000	145860000	DEL	
Moreno del luca et al 2013 (64)	chr1	145040000	145860000	DUP	
Moreno del luca et al 2013 (64)	chr3	197230000	198840000	DUP	
Moreno del luca et al 2013 (64)	chr3	197230000	198840000	DEL	
Moreno del luca et al 2013 (64)	chr5	175650000	176990000	DUP	
Moreno del luca et al 2013 (64)	chr5	175650000	176990000	DEL	
Moreno del luca et al 2013 (64)	chr7	72380000	73780000	DEL	
Moreno del luca et al 2013 (64)	chr7	72380000	73780000	DUP	

Table S3 continued

Reference	Chr	Start hg19	Stop hg19	Type	Note protective CNV
Moreno del luca et al 2013 (64)	chr8	8130000	11930000	DEL	
Moreno del luca et al 2013 (64)	chr8	8130000	11930000	DUP	
Moreno del luca et al 2013 (64)	chr10	81950000	88790000	DUP	
Moreno del luca et al 2013 (64)	chr15	22370000	26100000	DEL	
Moreno del luca et al 2013 (64)	chr15	22370000	26100000	DUP	
Moreno del luca et al 2013 (64)	chr15	22370000	26100000	DUP	
Moreno del luca et al 2013 (64)	chr15	28920000	30270000	DEL	
Moreno del luca et al 2013 (64)	chr15	28920000	30270000	DUP	
Moreno del luca et al 2013 (64)	chr15	28920000	30270000	DEL	
Moreno del luca et al 2013 (64)	chr15	28920000	30270000	DUP	
Moreno del luca et al 2013 (64)	chr16	15410000	16200000	DUP	
Moreno del luca et al 2013 (64)	chr16	15410000	16200000	DEL	
Moreno del luca et al 2013 (64)	chr16	21850000	22370000	DUP	
Moreno del luca et al 2013 (64)	chr16	21850000	22370000	DEL	
Moreno del luca et al 2013 (64)	chr16	28680000	29020000	DEL	
Moreno del luca et al 2013 (64)	chr16	28680000	29020000	DUP	
Moreno del luca et al 2013 (64)	chr16	28680000	29020000	DEL	
Moreno del luca et al 2013 (64)	chr16	28680000	29020000	DUP	
Moreno del luca et al 2013 (64)	chr16	29560000	30110000	DEL	
Moreno del luca et al 2013 (64)	chr16	29560000	30110000	DUP	
Moreno del luca et al 2013 (64)	chr16	29560000	30110000	DEL	
Moreno del luca et al 2013 (64)	chr16	29560000	30110000	DUP	
Moreno del luca et al 2013 (64)	chr17	16650000	20420000	DEL	
Moreno del luca et al 2013 (64)	chr17	16650000	20420000	DUP	
Moreno del luca et al 2013 (64)	chr17	26190000	27240000	DUP	
Moreno del luca et al 2013 (64)	chr17	31890000	33280000	DEL	
Moreno del luca et al 2013 (64)	chr17	31890000	33280000	DUP	
Moreno del luca et al 2013 (64)	chr17	31890000	33280000	DEL	
Moreno del luca et al 2013 (64)	chr17	41060000	41540000	DUP	
Moreno del luca et al 2013 (64)	chr22	17400000	18670000	DEL	
Moreno del luca et al 2013 (64)	chr22	17400000	18670000	DUP	
Moreno del luca et al 2013 (64)	chr22	17400000	18670000	DEL	
Moreno del luca et al 2013 (64)	chr22	17400000	18670000	DUP	
Moreno del luca et al 2013 (64)	chr22	20240000	21980000	DEL	
Moreno del luca et al 2013 (64)	chr22	20240000	21980000	DUP	
Stefansson et al. (65)	chr1	146089254	147859944	DEL	
Stefansson et al. (65)	chr1	146089254	147858944	DUP	
Stefansson et al. (65)	chr2	1792885	2335045	DUP	*MYT1L*
Stefansson et al. (65)	chr2	50145643	51259674	DEL	*NRXN1*
Stefansson et al. (65)	chr3	195766737	197216349	DEL	
Stefansson et al. (65)	chr7	157860945	159119486	DEL	*WDR60* and *VIPR2*
Stefansson et al. (65)	chr7	158726462	158947294	DUP	*WDR60* and *VIPR2*
Stefansson et al. (65)	chr10	46508694	51912781	DEL	

Table S3 continued

Reference	Chr	Start hg19	Stop hg19	Type	Note protective CNV
Stefansson et al. (65)	chr10	47543322	51912781	DUP	
Stefansson et al. (65)	chr13	93879078	95060273	DUP	*GPC6*
Stefansson et al. (65)	chr15	22750305	23272733	DEL	
Stefansson et al. (65)	chr15	22770994	28535266	DUP	
Stefansson et al. (65)	chr15	28973396	30556183	DUP	
Stefansson et al. (65)	chr15	29562640	30689724	DEL	
Stefansson et al. (65)	chr15	30936285	32515849	DEL	
Stefansson et al. (65)	chr15	32018731	32620127	DEL	*CHRNA7*
Stefansson et al. (65)	chr16	14989844	16291983	DUP	
Stefansson et al. (65)	chr16	15125441	16291983	DEL	
Stefansson et al. (65)	chr16	21947230	22423698	DEL	
Stefansson et al. (65)	chr16	28814098	29043450	DEL	
Stefansson et al. (65)	chr16	29595483	30192561	DEL	
Stefansson et al. (65)	chr16	29624247	30198151	DUP	
Stefansson et al. (65)	chr17	14101029	15471179	DEL	
Stefansson et al. (65)	chr17	34815551	36249430	DEL	
Stefansson et al. (65)	chr17	34815551	36249430	DUP	
Stefansson et al. (65)	chr22	20718116	21465780	DUP	
Stefansson et al. (65)	chr22	20733495	21465780	DEL	
Huguet et al. (3)	chr1	145430996	148237104	DEL	
Huguet et al. (3)	chr1	145430996	148237104	DUP	
Huguet et al. (3)	chr2	49920350	51032536	DEL	*NRXN1*
Huguet et al. (3)	chr3	196018732	197628732	DEL	
Huguet et al. (3)	chr7	73328061	74727726	DUP	
Huguet et al. (3)	chr7	65373855	65401085	DEL	*ZNF92*
Huguet et al. (3)	chr7	65373855	65401085	DUP	*ZNF92*
Huguet et al. (3)	chr7	158660506	159179546	DEL	*VIPR2* and *WDR60*
Huguet et al. (3)	chr7	158660506	159179546	DUP	*VIPR2* and *WDR60*
Huguet et al. (3)	chr8	99013266	99877580	DEL	*VPS13B*
Huguet et al. (3)	chr9	841690	969090	DEL	*DMRT1*
Huguet et al. (3)	chr9	841690	969090	DUP	*DMRT1*
Huguet et al. (3)	chr13	19837453	19863633	DUP	*ZMYM5*
Huguet et al. (3)	chr15	30840505	32190507	DEL	
Huguet et al. (3)	chr15	22784509	23074432	DEL	
Huguet et al. (3)	chr16	29641178	30191178	DUP	
Huguet et al. (3)	chr16	28811178	29041178	DEL	
Huguet et al. (3)	chr22	19032487	21065711	DEL	
Huguet et al. (3)	chr22	19032487	21065711	DUP	

Chr: Chromosome; hg19: Homo sapiens (human) genome assembly GRCh37 (hg19) from Genome Reference Consortium; DEL: deletion; DUP: duplication.

Table S4: Sensitivity analysis of the effect of gene dosage measured by pLI on NVIQ in autistic probands from SSC and MSSNG, and in the unselected population.

Phenotype	Models	N	pLI DEL			pLI DUP		
			β	SE	p	β	SE	p
NVIQ	All SSC probands	2,564	**-0.17**	**0.03**	**8.29×10^{-10}**	**-0.06**	**0.02**	**1.50×10^{-3}**
			No significant interaction with the type of NVIQ test			No significant interaction with the type of NVIQ test		
	SSC probands after 1:2 matching with MSSNG probands	2,245	**-0.14**	**0.03**	**100%***	**-0.06**	**0.02**	**96.8%***
	SSC probands after removing ratio NVIQ[(a)]	2,182	**-0.15**	**0.03**	**2.08×10^{-6}**	**-0.07**	**0.02**	**2.10×10^{-3}**
	All individuals (SSC probands + MSSNG probands + unselected population)	6,656	**-0.18**	**0.02**	**1.44×10^{-16}**	**-0.04**	**0.01**	**3.20×10^{-3}**
			Interaction pLI deletions and diagnosis p=0.86			Interaction pLI duplications and diagnosis p=0.16		
			Interaction pLI deletions and sex p=0.62			Interaction pLI duplications and sex p=0.51		
	Remove carriers of CNVs with a pLI > 10	6,629	**-0.18**	**0.03**	**2.43×10^{-11}**	-0.02	0.02	0.31
	Remove carriers of recurrent CNVs previously associated with NDD	6,484	**-0.20**	**0.03**	**3.42×10^{-11}**	**-0.05**	0.02	**9.53×10^{-3}**
	Remove carriers of rare *de novo* CNVs[(b)]	4,126	**-0.11**	**0.05**	**0.04**	-0.04	0.02	0.23

[(a)] Ratio NVIQ were provided for 382 very impaired probands (see supplementary Methods). [(b)] Information about the transmission of each CNV is not available in IMAGEN, the selection of rare CNVs are described in supplementary Methods. *percentage of the 500 matched samples providing an estimate with a p-value ≤ 0.05. Significative p-values are in bold (≤ 0.05). SE: Standard error; NVIQ: Non-verbal intelligence quotient; NDD: Neurodevelopmental disorders; pLI: probability of being Loss-of-function Intolerant; pLI DEL or pLI DUP: deleted or duplicated point of pLI score; CNV: Copy number variants.

Table S5: Sensitivity analysis of the effect of gene dosage measured by pLI on autism risk using autistic probands from SSC and MSSNG, unaffected siblings from SSC, and the unselected population.

Populations	Models	N individuals		CNV score	Not adjusted for NVIQ			Adjusted for NVIQ		
		Probands	Controls		OR	95%CI	p	OR	95%CI	p
Probands (SSC-MSSNG) Vs. Unselected population	All individuals	3,703	2,224	pLI DEL	**1.43**	**1.26-1.67**	**6.38×10^{-7}**	**1.28**	**1.11-1.53**	**2.14×10^{-3}**
				pLI DUP	**1.23**	**1.14-1.34**	**7.19×10^{-7}**	**1.21**	**1.11-1.34**	**3.56×10^{-5}**
				pLI DEL*sex	1.01	0.76-1.37	0.96	1.02	0.74-1.44	0.89
				pLI DUP*sex	1.06	0.90-1.26	0.51	1.07	0.89-1.29	0.50
	Remove carriers of CNVs with a pLI >10	3,680	2,222	pLI DEL	**1.42**	**1.24-1.66**	**2.05×10^{-6}**	**1.28**	**1.10-1.52**	**2.95×10^{-3}**
				pLI DUP	**1.26**	**1.15-1.39**	**3.01×10^{-6}**	**1.24**	**1.12-1.39**	**8.43×10^{-5}**
	Remove carriers of recurrent CNVs associated with NDD	3,578	2,193	pLI DEL	**1.40**	**1.19-1.73**	**4.19×10^{-4}**	1.21	0.99-1.56	0.10
				pLI DUP	**1.23**	**1.11-1.38**	**2.41×10^{-4}**	**1.21**	**1.08-1.38**	**2.09×10^{-3}**
	Remove carriers of rare *de novo* CNVs[a,b]	3,070	480	pLI DEL	1.22	0.91-1.84	0.26	1.20	0.86-1.90	0.34
				pLI DUP	0.92	0.82-1.05	0.22	0.89	0.78-1.02	0.08
	Removing the 10 individuals with autism risk from Imagen[c]	3,703	2,091	pLI DEL	**1.41**	**1.24-1.64**	**1.49×10^{-6}**	**1.26**	**1.09-1.50**	**3.46×10^{-3}**
				pLI DUP	**1.22**	**1.13-1.33**	**1.98×10^{-6}**	**1.20**	**1.10-1.33**	**7.99×10^{-5}**
SSC probands Vs. Siblings	Remove carriers of rare *de novo* CNVs[b,d]	1,950	1,950	pLI DEL	**1.44**	**1.03-2.01**	**0.03**	N.A.	N.A.	N.A.
				pLI DUP	**1.21**	**1.03-1.41**	**0.02**	N.A.	N.A.	N.A.
		Unaffected siblings	Imagen + SYS							
SSC unaffected siblings vs. Unselected population	All individuals	2,074	2,224	pLI DEL	1.03	0.88-1.21	0.69	N.A.	N.A.	N.A.
				pLI DUP	1.09	0.98-1.21	0.10	N.A.	N.A.	N.A.

[a] Information about the transmission of each CNV was not available in IMAGEN, this analysis was underpowered because of the lack of information on *de novo* CNVs in the unselected population; [b] the selection of rare CNVs are described in supplementary Methods, [c] 10 individuals from IMAGEN met criteria for Autism as estimated by the DAWBA (Development and Well-Being Assessment), we also excluded 124 individual without diagnostic information (DAWBA), [d] NVIQ was not available in unaffected siblings for the adjustment. OR: Odds ratio; 95%CI: 95% Confidence interval; CNV: Copy number variant; NVIQ: Non-verbal IQ; NDD: Neurodevelopmental disorders; pLI: probability of being Loss-of-function Intolerant; pLI DEL or pLI DUP: deleted or duplicated point of pLI score; pLI DEL*sex or DUP*sex: interaction between pLI and sex; N.A.: Not applicable.

Table S6: Breakpoints used to detect recurrent CNVs associated to autism and corresponding empirical and estimated odds ratios in autistic population.

Locus	Type	Chr	Start - Stop hg19 (Mb)	Sum of pLI	N autism cases[(a)]	N Controls [(a)]	Published autism risk [(a)]		Ref	Estimated autism risk[(b)]		Estimated loss of NVIQ points		Estimated gain of SRS points	
							OR	95%CI		OR	95%CI		95%CI		95%CI
1q21.1 (class I)	DEL	1	146.57-147.50	2.49	1/3,032	16/75,505	**1.56**	**0.21-11.74**	(66)	**2.15**	**1.57-2.93**	6.72	6.13-7.31	9.27	8.16-10.38
1q21.1 (class I)	DUP	1	146.57-147.50	2.49	8/3,032	19/57,730	8.03	3.51-18.37	(66)	1.44	1.19-1.74	1.49	1.20-1.78	4.65	3.81-5.49
3q29	DEL	3	195.73-197.34	6.56	1/2,120	1/63,649	**30.04**	**1.88-480.40**	(66)	**7.50**	**3.31-17.01**	17.71	17.12-18.30	24.42	23.31-25.53
5q35	DEL	5	175.65-176.99	11.92	1/3,955	0/13,696	∞	N.S.	(64)	38.91	8.79-172.24	32.18	31.59-32.77	44.38	43.27-45.49
7q11.23 (WBS)	DUP	7	72.72-74.15	10.27	4/2,120	1/16,257	**30.73**	**3.43-275.07**	(66)	**4.45**	**2.03-9.72**	6.16	5.87-6.45	19.16	18.32-20.00
15q11.2 (BP1-BP2)	DEL	15	22.75-23.27	1.70	8/2,525	19/7,086	**1.30**	**0.42-3.96**	(67)	**1.69**	**1.36-2.08**	4.59	4.00-5.18	6.33	5.22-7.44
15q11.2 (BP1-BP2)	DUP	15	22.75-23.27	1.70	20/2,525	38/7,086	**1.80**	**0.82-3.97**	(67)	**1.28**	**1.12-1.46**	1.02	0.73-1.31	3.17	2.33-4.01
15q13.3 (BP4-BP5)	DEL	15	30.92-32.51	1.71	4/2,120	13/74,106	10.77	3.51-33.07	(66)	1.69	1.37-2.09	4.62	4.03-5.21	6.37	5.26-7.48
15q13.3 (BP4-BP5)	DUP	15	30.92-32.51	1.71	2/3,955	5/13,696	**1.39**	**0.27-7.14**	(64)	**1.28**	**1.13-1.46**	1.03	0.74-1.32	3.19	2.35-4.03
16p11.2 (BP4-BP5)	DEL	16	29.60-30.30	9.92	18/4,315	25/56,752	**9.50**	**5.18-17.43**	(66)	**21.05**	**6.10-72.26**	26.78	26.19-27.37	36.93	35.82-38.04
16p11.2 (BP4-BP5)	DUP	16	29.60-30.30	9.92	17/4,315	19/56,752	**11.81**	**6.13-22.74**	(66)	**4.23**	**1.99-9.00**	5.95	5.66-6.24	18.51	17.67-19.35
16p11.2 distal	DEL	16	28.81-29.04	3.82	1/3,955	2/13,696	**1.73**	**0.16-19.10**	(64)	**3.23**	**2.01-5.21**	10.31	9.72-10.90	14.22	13.11-15.33
16p11.2 distal	DUP	16	28.81-29.04	3.82	1/3,955	3/13,696	**1.15**	**0.12-11.10**	(64)	**1.74**	**1.30-2.33**	2.29	2.00-2.58	7.13	6.29-7.97
16p13.11	DEL	16	15.12-16.29	2.84	5/3,955	4/13,696	**4.34**	**1.16-16.14**	(64)	**2.39**	**1.68-3.41**	7.67	7.08-8.26	10.57	9.46-11.68
16p13.11	DUP	16	15.12-16.29	2.84	4/2,120	81/62,973	**1.47**	**0.54-4.01**	(66)	**1.51**	**1.22-1.88**	1.70	1.41-1.99	5.30	4.46-6.14
17p11.2 (SMS)	DEL	17	16.58-20.33	12.21	2/4,687	0/151,619	∞	N.S.	(68)	42.54	9.27-195.22	32.97	32.38-33.56	45.46	44.35-46.57
17p11.2 (SMS)	DUP	17	16.58-20.33	12.21	1/4,687	1/151,619	**32.30**	**2.02-517.39**	(68)	**5.90**	**2.33-14.94**	7.33	7.04-7.62	22.79	21.95-23.63
17p12	DEL	17	14.04-15.41	1.17	2/2,120	14/59,086	**4.00**	**0.9-17.5**	(66)	**1.43**	**1.24-1.66**	3.16	2.57-3.75	4.36	3.25-5.47
17q12	DEL	17	34.81-36.25	5.07	2/2,120	4/68,131	**16.08**	**2.94-87.86**	(66)	**4.75**	**2.52-8.94**	13.69	13.10-14.28	18.87	17.76-19.98
22q11.2	DEL	22	18.89-21.90	11.44	5/4,687	5/151,619	**32.37**	**9.37-111.87**	(68)	**33.58**	**8.05-139.99**	30.89	30.30-31.48	42.59	41.48-43.70
22q11.2	DUP	22	18.89-21.90	11.44	12/4,315	23/27,133	**3.28**	**1.63-6.61**	(66)	**5.27**	**2.21-12.60**	6.86	6.57-7.15	21.35	20.51-22.19

[(a)]Based on number of carriers in autistic probands and controls reported in Malhotra et al. (2012) (66) Moreno DeLuca et al. (2013) (64), Chaste et al. (2014) (67), and Sanders et al. (2019) (68). In bold: CNVs for which previously published data and our estimation are overlapping. BP: Break points; WBS: William Beuren Syndrome; SMS: Smith Magenis Syndrome; DEL: deletion; DUP: duplication; chr: chromosome; hg19: Homo sapiens (human) genome assembly GRCh37 (hg19) from Genome Reference Consortium; pLI: probability of being Loss-of-function Intolerant; Sum of pLI: sum of score of pLI for the corresponding region; OR: Odds ratio; 95% CI: 95% confidence intervals; N.S.: Non-significant; Ref: reference.

Table S7: Description of models used for the investigation of the effect of gene dosage on phenotypical measures of autistic probands from SSC.

Phenotype	N	Type of normalization	Regression model	covariates
Autism related symptoms				
Regression	2,568	N.A.	Logistic	Sex, ancestry
Language and phonology				
CTOPP	1,988	z-scored with normative data: mean=10, SD=3	Linear	Sex, ancestry
Word delay	2,567	N.A.	Logistic	Sex, ancestry
Phrase delay	2,567	N.A.	Logistic	Sex, ancestry
Adaptive skills (VABS-II)				
Total score	2,569	z-scored with normative data: mean=100, SD=15	Linear	Ancestry
Daily living	2,569	z-scored with normative data: mean=100, SD=15	Linear	Ancestry
Communication	2,569	z-scored with normative data: mean=100, SD=15	Linear	Ancestry
Socialization	2,569	z-scored with normative data: mean=100, SD=15	Linear	Ancestry
Motor skills				
Motor VABS-II	919	z-scored with normative data: mean=100, SD=15	Linear	Ancestry
Gross motor VABS-II	926	z-scored with normative data: mean=15, SD=3	Linear	Ancestry
Fine motor VABS-II	923	z-scored with normative data: mean=15, SD=3	Linear	Ancestry
Delayed onset for walking	2,564	N.A.	Logistic	Sex, ancestry
Age of onset for walking	2,564	N.A.	Quasi-Poisson	Sex, ancestry
DCDQ score	2,209	z-scored with probands data: mean=38.5, SD=12.4	Linear	Age, sex, ancestry
Associated neurological condition				
Non-febrile seizure	2,566	N.A.	Logistic	Sex, ancestry

SD: Standard deviation; N.A.: Not applicable; CTOPP: Comprehensive Test of Phonological Processing; VABS-II: Vineland Adaptive behaviour Rating Scales - Second Edition; DCDQ: Developmental Coordination Disorder Questionnaire.

Table S8: Effect of gene dosage measured by pLI on SRS using autistic probands from SSC, their unaffected siblings and parents and the unselected population from IMAGEN.

Population	N	SRS-score	Model	CNV score	Effect size (β or OR)	SE or 95%CI	p
SSC probands	2,556	Total-raw	Linear not adjusted for NVIQ	pLI DEL	-0.21	0.40	0.60
				pLI DUP	-0.28	0.36	0.42
			Linear adjusted for NVIQ	pLI DEL	-0.31	0.41	0.45
				pLI DUP	-0.32	0.36	0.36
SSC unaffected siblings	2,078	√Total-raw[(a)]	Linear not adjusted for NVIQ	pLI DEL	0.05	0.08	0.47
				pLI DUP	0.001	0.06	0.99
SSC parents	4,838	√Total-raw[(a)]	Linear not adjusted for NVIQ	pLI DEL	0.07	0.09	0.43
				pLI DUP	0.01	0.04	0.83
MSSNG probands	598	Total-raw	Linear not adjusted for NVIQ	pLI DEL	0.71	1.78	0.69
				pLI DUP	-0.33	1.37	0.81
			Linear adjusted for NVIQ	pLI DEL	-0.70	1.76	0.69
				pLI DUP	-0.45	1.34	0.73
				NVIQ	**-0.30**	**0.06**	**1.32×10^{-7}**
IMAGEN	977	√Total-raw[(a)]	Linear not adjusted for NVIQ	pLI DEL	-0.06	0.15	0.66
				pLI DUP	0.03	0.09	0.71
			Linear adjusted for NVIQ	pLI DEL	-0.09	0.15	0.56
				pLI DUP	0.02	0.09	0.81
SSC probands + MSSNG probands	3,154	Total-raw	Linear not adjusted for NVIQ	pLI DEL	0.44	0.51	0.39
				pLI DUP	-0.27	0.45	0.54
			Linear adjusted for NVIQ	pLI DEL	-0.41	0.50	0.41
				pLI DUP	-0.52	0.43	0.23
				NVIQ	**-0.27**	**0.02**	**1.40×10^{-46}**
SSC probands + MSSNG probands + IMAGEN	4,131	Total-raw	Linear not adjusted for NVIQ or autism diagnosis	pLI DEL	**3.66**	**0.56**	**5.53×10^{-11}**
				pLI DUP	**1.64**	**0.42**	**1.12×10^{-3}**
			Linear adjusted for autism diagnosis	pLI DEL	0.56	0.35	0.11
				pLI DUP	-0.12	0.27	0.66
			Linear adjusted for NVIQ	pLI DEL	0.42	0.59	0.46
				pLI DUP	0.17	0.49	0.75
				NVIQ	**-0.52**	**0.02**	**1.26×10^{-135}**
			Linear adjusted for autism diagnosis and NVIQ	pLI DEL	-0.35	0.46	0.45
				pLI DUP	-0.45	0.39	0.25
				NVIQ	**-0.26**	**0.02**	**2.63×10^{-52}**
Unaffected siblings + Unaffected Parents + IMAGEN	7,926	Total-raw	Linear mixed-effect	pLI DEL	0.62	0.62	0.32
				pLI DUP	0.08	0.36	0.82
SSC probands + Unaffected siblings + Unaffected Parents	9,473	Total-raw	Linear mixed-effect not adjusted for autism diagnosis	pLI DEL	**3.47**	**0.58**	**2.40×10^{-9}**
				pLI DUP	**1.54**	**0.44**	**5.20×10^{-4}**
			Linear mixed-effect adjusted for autism diagnosis	pLI DEL	0.75	0.37	4.30×10^{-2}
				pLI DUP	-0.003	0.29	0.99
All SSC + IMAGEN	10,483	Total-raw	Linear mixed-effect not adjusted for autism diagnosis	pLI DEL	**3.72**	**0.57**	**5.10×10^{-11}**
				pLI DUP	**1.87**	**0.43**	**1.40×10^{-5}**
			Linear mixed-effect adjusted for autism diagnosis	pLI DEL	0.55	0.36	0.13
				pLI DUP	-0.10	0.27	0.72

All SSC + MSSNG + IMAGEN	11,081	Total-raw	Linear mixed-effect not adjusted for autism diagnosis	pLI DEL	**3.68**	**0.56**	**4.30×10^{-11}**
				pLI DUP	**1.63**	**0.42**	**1.20×10^{-4}**
			Linear mixed-effect adjusted for autism diagnosis	pLI DEL	0.56	0.35	0.11
				pLI DUP	-0.12	0.27	0.66
Probands + Unaffected siblings + IMAGEN	5,189	SRS categories (normal, clinical) [(b)]	Logistic regression not adjusted for autism diagnosis	pLI DEL	**1.20**	**1.10-1.33**	**8.46×10^{-5}**
				pLI DUP	**1.13**	**1.06-1.22**	**2.00×10^{-4}**
			Logistic regression adjusted for autism diagnosis	pLI DEL	0.96	0.84- 1.15	0.59
				pLI DUP	0.97	0.86-1.12	0.66
Probands + Unaffected siblings + IMAGEN	5,189	SRS categories (normal, moderate, mild, clinically significant) [(b)]	Ordinal cumulative not adjusted for autism diagnosis	pLI DEL	**1.20**	**1.11- 1.30**	**3.92×10^{-6}**
				pLI DUP	**1.11**	**1.05-1.18**	**3.00×10^{-4}**
			Ordinal cumulative adjusted for autism diagnosis	pLI DEL	1.05	0.96-1.15	0.26
				pLI DUP	0.99	0.93- 1.06	0.87

All linear, logistic, or ordinal regression models used were adjusted for age, sex and ancestry. Models take into account family as random-effect when including related individuals (Methods). Effect size are presented as β for linear regression models and as odds ratio for logistic and ordinal regression models. [(a)]Square root transformation of the total SRS raw score was performed to adjust for the non-gaussian distribution or bimodality of SRS distribution (Figure S5); [(b)] Based on the previously published *T*-score categorization (55) (Methods). The statistical threshold after correction for multiple testing is $p \leq 2.7.10^{-3}$. Significant results are in bold. SE: Standard error; OR: Odds ratio; 95%CI: 95% Confidence interval; NVIQ: Non-verbal intelligence quotient; DEL: deletion; DUP: duplication; pLI: probability of being Loss-of-function Intolerant; pLI DEL or pLI DUP: deleted or duplicated point of pLI score; √Total-raw: square root transformation of the total SRS raw.

Table S9: Effect of gene dosage measured by pLI on autism severity scores (main domains of ADI-R and ADOS-calibrated severity scores) using autistic probands from SSC and MSSNG.

Phenotype	N	CNV score	Not adjusted for NVIQ			Adjusted for NVIQ		
			OR	95%CI	p	OR	95%CI	p
Probands from SSC								
ADI-R reciprocal social interactions	2,567	pLI DEL	1.00	0.94-1.07	0.89	0.93	0.87-0.99	0.04
		pLI DUP	1.06	1.01-1.11	0.02	1.03	0.98-1.08	0.20
ADI-R rrsb	2,567	pLI DEL	0.95	0.89-1.02	0.14	0.94	0.88-1.01	0.10
		pLI DUP	1.01	0.97-1.06	0.54	1.01	0.97-1.06	0.61
ADI-R verbal communication	2,254	pLI DEL	1.00	0.93-1.08	0.91	0.95	0.88-1.02	0.18
		pLI DUP	1.06	1.00-1.12	0.05	1.04	0.98-1.10	0.17
ADI-R non-verbal communication	2,567	pLI DEL	1.01	0.95-1.08	0.73	0.94	0.88-1.00	0.07
		pLI DUP	1.04	0.99-1.09	0.09	1.01	0.97-1.06	0.55
ADOS overall css[(a)]	2,499	pLI DEL	0.94	0.88-1.01	0.09	0.92	0.86-0.98	0.02
		pLI DUP	1.02	0.97-1.07	0.41	1.01	0.96-1.06	0.73
ADOS social affect css[(a)]	2,371	pLI DEL	0.96	0.92-1.03	0.25	0.94	0.87-1.01	0.08
		pLI DUP	1.04	0.99-1.10	0.08	1.03	0.98-1.08	0.19
ADOS rrsb css[(a)]	2,450	pLI DEL	0.98	0.91-1.05	0.55	0.95	0.88-1.02	0.12
		pLI DUP	1.01	0.96-1.06	0.67	0.99	0.98-1.10	0.85
ADI-R Overall level of language	2,568	pLI DEL	1.08	0.98-1.19	0.13	0.93	0.83-1.04	0.18
		pLI DUP	1.06	1.00-1.13	0.04	1.03	0.97-1.10	0.36
Probands from MSSNG								
ADI-R reciprocal social interactions	397	pLI DEL	1.26	0.85-1.85	0.25	1.20	0.82-1.77	0.35
		pLI DUP	0.98	0.77-1.25	0.85	0.99	0.77-1.26	0.93
ADI-R rrsb	695	pLI DEL	1.15	0.98-1.37	0.09	1.15	0.97-1.36	0.11
		pLI DUP	1.00	0.86-1.13	0.87	0.99	0.86-1.13	0.83
ADI-R verbal communication	370	pLI DEL	1.08	0.82-1.42	0.59	1.04	0.79-1.37	0.77
		pLI DUP	1.01	0.79-1.29	0.95	0.97	0.76-1.24	0.80
ADI-R non-verbal communication	73	pLI DEL	1.12	0.77-1.64	0.49	1.10	0.75-1.61	0.63
		pLI DUP	0.90	0.75-1.07	0.27	0.89	0.74-1.07	0.21
ADOS overall css[(a)]	733	pLI DEL	0.94	0.75-1.18	0.58	0.92	0.73-1.16	0.50
		pLI DUP	0.86	0.75-0.99	0.04	0.86	0.75-0.99	0.04
ADOS social affect css[(a)]	373	pLI DEL	0.74	0.50-1.11	0.15	0.74	0.50-1.11	0.15
		pLI DUP	0.90	0.76-1.07	0.23	0.90	0.76-1.07	0.23
ADOS rrsb css[(a)]	388	pLI DEL	0.91	0.61-1.36	0.64	0.91	0.61-1.36	0.63
		pLI DUP	0.95	0.83-1.12	0.60	0.96	0.82-1.11	0.57
ADI-R Overall level of language	1,267	pLI DEL	1.27	1.03-1.21	$7.19.10^{-3}$	1.13	0.94-1.37	0.19
		pLI DUP	1.05	1.03-1.21	0.49	1.05	0.92-1.20	0.44
Pooled probands (SSC + MSSNG)								
ADI-R	2,966	pLI DEL	1.01	0.95-1.08	0.69	0.94	0.88-1.01	0.08

reciprocal social interactions		pLI DUP	1.05	1.00-1.10	0.03	1.03	0.98-1.08	0.24
ADI-R rrsb	3,264	pLI DEL	0.98	0.92-1.04	0.52	0.97	0.91-1.04	0.40
		pLI DUP	1.01	0.97-1.06	0.58	1.01	0.97-1.06	0.66
ADI-R verbal communication	2,626	pLI DEL	1.01	0.94-1.08	0.80	0.95	0.89-1.03	0.20
		pLI DUP	1.06	0.99-1.12	0.05	1.04	0.98-1.10	0.20
ADI-R non-verbal communication	2,642	pLI DEL	1.02	0.95-1.09	0.65	0.94	0.88-1.01	0.09
		pLI DUP	1.03	0.99-1.08	0.18	1.01	0.96-1.05	0.82
ADOS overall css[(a)]	3,122	pLI DEL	0.94	0.88-1.01	0.08	0.92	0.86-0.98	0.01
		pLI DUP	0.99	0.95-1.04	0.88	0.99	0.94-1.03	0.56
ADOS social affect css[(a)]	2,675	pLI DEL	0.95	0.89-1.02	0.16	0.93	0.87-1.00	0.05
		pLI DUP	1.03	0.98-1.08	0.25	1.02	0.97-1.07	0.44
ADOS rrsb css[(a)]	2,766	pLI DEL	0.98	0.91-1.05	0.50	0.94	0.88-1.01	0.11
		pLI DUP	1.00	0.96-1.05	0.91	0.99	0.95-1.04	0.67
ADI-R Overall level of language	3,607	pLI DEL	1.11	1.02-1.21	0.01	0.97	0.88-1.06	0.50
		pLI DUP	1.06	1.00-1.12	0.03	1.04	0.98-1.10	0.23

All ordinal regression models used for each severity score were adjusted for age and sex, and ancestry when available (for autistic probands from SSC only). [(a)]Calibrated severity score were computed based on previously published methodology from Hus et al. (2014) (40). The statistical threshold after correction for multiple testing is $p \leq 2.7.10^{-3}$. NVIQ: Non-verbal intelligence quotient; OR: Odds ratio; 95%CI: 95% Confidence interval; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; css: calibrated severity score; rrsb: repetitive, restricted and stereotyped behaviours; DEL: deletion; DUP: duplication; pLI: probability of being Loss-of-function Intolerant; pLI DEL or pLI DUP: deleted or duplicated point of pLI score.

Table S10: Effect of gene dosage measured by pLI on CBCL using autistic probands from SSC and unaffected siblings.

Population	N	Model	CNV score	OR	95%CI	p
CBCL total Problems raw score						
Probands	1,945	Negative Binomial not adjusted for NVIQ	pLI DEL	1.01	0.99-1.03	0.43
			pLI DUP	1.00	0.98-1.01	0.64
		Negative Binomial adjusted for NVIQ	pLI DEL	1.01	0.99-1.03	0.40
			pLI DUP	1.00	0.98-1.01	0.67
Unaffected Siblings	1,596	Negative Binomial not adjusted for NVIQ	pLI DEL	1.07	0.98-1.20	0.13
			pLI DUP	1.05	0.99-1.13	0.10
Probands + Unaffected siblings	3,541	Negative Binomial mixed-effect not adjusted for autism diagnosis	pLI DEL	**1.05**	**1.03-1.08**	**$1.94x10^{-6}$**
			pLI DUP	1.02	1.01-1.04	$3.04x10^{-3}$
		Negative Binomial mixed-effect adjusted for autism diagnosis	pLI DEL	1.01	1.00-1.03	0.11
			pLI DUP	1.00	1.00-1.02	0.53
CBCL externalizing Problems raw score						
Probands	1,945	Negative Binomial not adjusted for NVIQ	pLI DEL	1.01	0.98-1.05	0.37
			pLI DUP	1.00	0.97-1.02	0.91
		Negative Binomial adjusted for NVIQ	pLI DEL	1.01	0.98-1.05	0.41
			pLI DUP	1.00	0.97-1.02	0.87
Unaffected Siblings	1,596	Negative Binomial not adjusted for NVIQ	pLI DEL	1.10	0.97-1.28	0.12
			pLI DUP	1.04	0.95-1.13	0.40
Probands + Unaffected siblings	3,541	Negative Binomial mixed-effect not adjusted for autism diagnosis	pLI DEL	**1.05**	**1.02-1.09**	**$4.94x10^{-4}$**
			pLI DUP	1.02	1.00-1.05	0.02
		Negative Binomial mixed-effect adjusted for autism diagnosis	pLI DEL	1.02	0.99-1.05	0.14
			pLI DUP	1.01	0.98-1.03	0.56
CBCL internalizing Problems raw score						
Probands	1,945	Negative Binomial not adjusted for NVIQ	pLI DEL	0.99	0.97-1.02	0.63
			pLI DUP	0.98	0.96-1.00	0.07
		Negative Binomial adjusted for NVIQ	pLI DEL	1.01	0.98-1.04	0.57
			pLI DUP	0.99	0.96-1.01	0.19
Unaffected Siblings	1,596	Negative Binomial not adjusted for NVIQ	pLI DEL	1.08	0.97-1.22	0.15
			pLI DUP	1.06	0.99-1.14	0.10
Probands + Unaffected siblings	3,541	Negative Binomial mixed-effect not adjusted for autism diagnosis	pLI DEL	**1.04**	**1.01-1.07**	**$2.12x10^{-3}$**
			pLI DUP	1.01	0.99-1.03	0.19
		Negative Binomial mixed-effect adjusted for autism diagnosis	pLI DEL	1.01	0.98-1.03	0.61
			pLI DUP	0.99	0.97-1.01	0.52

All negative binomial models used were adjusted for age, sex and ancestry. Models take into account family as random-effect when including related individuals (Methods). Effect size are presented as odds ratio. The statistical threshold after correction for multiple testing is $p \leq 2.7.10^{-3}$. Significant results are in bold. OR: Odds ratio; 95%CI: 95% Confidence interval; CBCL: Child behaviour Checklist; NVIQ: Non-verbal intelligence quotient; DEL: deletion; DUP: duplication; pLI: probability of being Loss-of-function Intolerant; pLI DEL or pLI DUP: deleted or duplicated point of pLI score.

Table S11: Effect of gene dosage measured by pLI on general intelligence in autistic probands from SSC and MSSNG, and in the unselected population.

Population	Measure	N	Covariates	CNV score	β	SE	p
Probands (SSC)	NVIQ	2,564	Sex, type of test used, ancestry	pLI DEL	**-0.17**	**0.03**	**8.29×10^{-10}**
				pLI DUP	**-0.06**	**0.02**	**1.50×10^{-3}**
	NVIQ-DAS	2,244	Sex, ancestry	pLI DEL	**-0.16**	**0.03**	**1.20×10^{-7}**
				pLI DUP	**-0.07**	**0.02**	**1.10×10^{-3}**
	NVR	1,958	Sex, ancestry	pLI DEL	**-0.10**	**0.03**	**4.60×10^{-4}**
				pLI DUP	**-0.06**	**0.02**	**5.90×10^{-3}**
	Matrices	1,958	Sex, ancestry	pLI DEL	**-0.09**	**0.03**	**9.30×10^{-4}**
				pLI DUP	**-0.04**	**0.02**	**4.80×10^{-2}**
Unselected	NVIQ	2,710	Sex, type of test used, ancestry	pLI DEL	**-0.19**	**0.04**	**6.90×10^{-5}**
				pLI DUP	0.02	0.03	0.52
Probands (MSSNG)	NVIQ	1,381	Sex, type of test used	**pLI DEL**	**-0.20**	**0.07**	**3.10×10^{-3}**
				pLI DUP	-0.02	0.04	0.61

All linear regression models were performed using a z-scored dependant variable. These z-scores are computed using normative data (e.g. mean NVIQ=100, SD NVIQ=15). CNV: Copy number variant; SE: Standard error; NVIQ: Non-verbal IQ; DAS: Differential Ability Scales; NVR: Non-verbal reasoning; pLI DEL or pLI DUP: deleted or duplicated point of pLI score.

Table S12: Effect of gene dosage measured by pLI on autism risk.

Group comparison	N		pLI DEL					pLI DUP				
	probands	controls	Sum pLI in probands	Sum pLI in controls	OR	95%CI	p	Sum pLI in probands	Sum pLI in controls	OR	95%CI	p
Not adjusted for NVIQ												
Probands vs. Unaffected Siblings	2,074	2,074	346.58	117.67	**1.43**	**1.23-1.66**	**3.78×10^{-6}**	640.32	371.62	**1.32**	**1.17-1.49**	**4.63×10^{-6}**
Probands vs. Unselected population	2,569	2,223	416.00	114.11	**1.40**	**1.23-1.64**	**2.33×10^{-6}**	816.99	330.31	**1.30**	**1.19-1.42**	**1.88×10^{-8}**
Adjusted for NVIQ												
Probands vs. unselected population	2,569	2,223	416.00	114.11	**1.22**	**1.05-1.45**	**0.01**	816.99	330.31	**1.27**	**1.15-1.42**	**4.89×10^{-6}**
Probands vs. unselected population	1,438	1,438	153.80	93.51	1.21	1.01-1.45	60.4 %*	357.01	219.40	**1.25**	**1.09-1.43**	**98.2 %***
Replication with probands from MSSNG												
Not adjusted												
Probands vs. Unselected population	1,139	2,223	156.41	114.11	**1.54**	**1.30-1.88**	**4.56×10^{-6}**	298.32	330.31	**1.19**	**1.08-1.33**	**8.30×10^{-4}**
Adjusted for NVIQ												
Probands vs. unselected population	1,139	2,223	156.41	114.11	**1.39**	**1.15-1.72**	**1.44×10^{-3}**	298.32	330.31	**1.20**	**1.08-1.35**	**1.44×10^{-3}**

Odds ratios are computed using a logistic regression including sum of pLI in deletions and duplications as the two main explanatory variables. OR represents the autism risk conferred for each deleted or duplicated point of pLI. Sum of pLI represents the sum of all genes deleted or duplicated in all individuals for the group. *percentage of the 500 matched samples providing an estimate with a p-value ≤ 0.05. Significative Significative p-values are in bold (≤ 0.05). pLI: probability of being Loss-of-function Intolerant; sum of pLI: sum of score of pLI in the entire population; pLI DEL or pLI DUP: deleted or duplicated point of pLI; NVIQ: Non-verbal intelligence quotient; OR: Odds ratio; 95%CI: 95% Confidence interval.

Table S13: Autism risk potentially mediated by NVIQ in the pooled dataset (SSC, MSSNG, unselected populations).

Populations	N individuals probands	N individuals controls	Effect	Variable	OR	95% CI	p
Probands (SSC-MSSNG) *vs.* Unselected populations	3,703	2,224	Direct effect	pLI DEL	**1.23**	**[1.08-1.41]**	**2.28×10^{-3}**
				pLI DUP	**1.18**	**[1.10-1.26]**	**1.00×10^{-6}**
			Indirect effect	pLI DEL	**1.17**	**[1.13-1.21]**	**2.00×10^{-16}**
				pLI DUP	**1.06**	**[1.03-1.08]**	**6.56×10^{-7}**
			Total effect	pLI DEL	**1.45**	**[1.26-1.65]**	**7.33×10^{-8}**
				pLI DUP	**1.25**	**[1.16-1.34]**	**2.92×10^{-9}**

Odds ratios are computed using a counterfactual-based mediation analysis on two different logistic regression including sum of pLI in deletions and duplications as the main explanatory variables. OR represents the autism risk conferred for each deleted or duplicated point of pLI. Direct effects of CNVs are those not mediated by NVIQ. Indirect are those potentially mediated by NVIQ. Total effects are those computed without adjusting for NVIQ. Significative p-values are in bold (≤ 0.05). pLI: probability of being Loss-of-function Intolerant. pLI DEL or pLI DUP: deleted or duplicated point of pLI. NVIQ: Non-verbal intelligence quotient; OR: Odds ratio; 95%CI: 95% Confidence interval.

Table S14: Autism risk measured by pLI in subgroups of individual below or above the median (98) in the pooled dataset (SSC, MSSNG, unselected populations).

Populations	N individuals probands	N individuals controls	IQ subgroup	Variable	OR	95% CI	p
Probands (SSC-MSSNG) *vs*. Unselected populations	2,363	667	Below median NVIQ	pLI DEL	**1.27**	**[1.10-1.53]**	**3.41×10^{-3}**
				pLI DUP	**1.34**	**[1.16-1.61]**	**5.57×10^{-4}**
	1,340	1,557	Above median NVIQ	pLI DEL	**1.53**	**[1.19-2.07]**	**2.17×10^{-3}**
				pLI DUP	**1.16**	**[1.04-1.31]**	**1.10×10^{-2}**

Odds ratios are computed using a logistic regression including sum of pLI in deletions and duplications as the two main explanatory variables. OR represents the autism risk conferred for each deleted or duplicated point of pLI. Significative p-values are in bold (≤ 0.05). pLI: probability of being Loss-of-function Intolerant. pLI DEL or pLI DUP: deleted or duplicated point of pLI. NVIQ: Non-verbal intelligence quotient; OR: Odds ratio; 95%CI: 95% Confidence interval.

Table S15: Estimated Genome wide effects of gene dosage on autism risk.

	ALL CNVs (including pLI=0)				CNVs with pLI > 0			
	>50Kb in autistic sample		1MB genome wide		>50Kb in autistic sample		1MB genome wide	
	OR DEL	OR DUP	OR DEL	OR DUP	OR DEL	OR DUP	OR DEL	OR DUP
N CNVs	5,319	4,614	5,586	5,586	2,136	2,045	4,377	4,377
Median	1.00	1.00	1.36	1.21	1.02	1.05	1.58	1.32
Mean	1.15	1.13	3.05	1.58	1.36	1.31	3.62	1.75
70%	1.00	1.00	1.85	1.45	1.02	1.17	2.13	1.58
75%	1.01	1.02	2.04	1.54	1.09	1.2	2.38	1.69
80%	1.02	1.05	2.35	1.68	1.09	1.21	2.66	1.82
90%	1.09	1.21	3.72	2.23	1.35	1.33	4.43	2.48
95%	1.31	1.33	6.65	3.17	1.60	1.63	8.28	3.63

pLI: probability of being Loss-of-function Intolerant; NVIQ: Non-verbal intelligence quotient; OR DEL/DUP: Estimated odds ratio for deletions or duplications based on pLI score. Odds ratio represents the estimated autism risk conferred by deleted or duplicated points of pLI in the autistic sample (probands from SSC and MSSNG) and in a genome of reference (Human Gene Nomenclature) (69) partitioned in CNV of 1Mb.

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