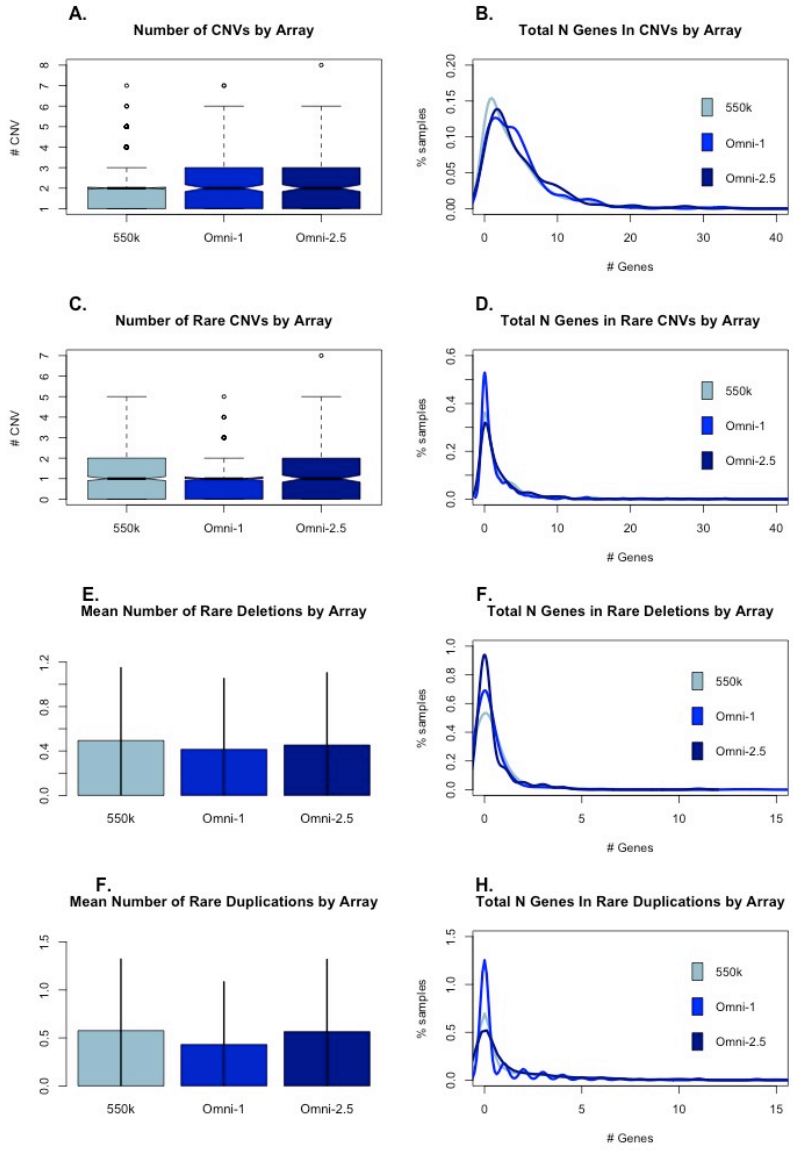
The American Journal of Human Genetics, Volume *99*

Supplemental Data

Rare Inherited and De Novo CNVs Reveal Complex Contributions to ASD Risk in Multiplex Families

Virpi M. Leppa, Stephanie N. Kravitz, Christa Lese Martin, Joris Andrieux, Cedric Le Caignec, Dominique Martin-Coignard, Christina DyBuncio, Stephan J. Sanders, Jennifer K. Lowe, Rita M. Cantor, and Daniel H. Geschwind

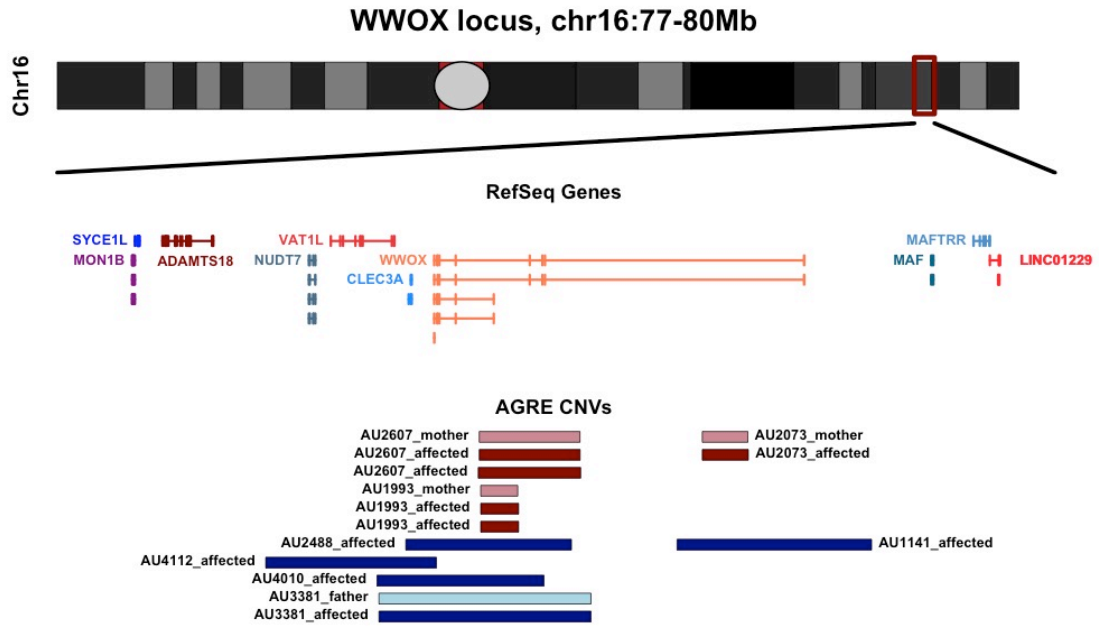
Figure S1. CNV Characteristics by Array



The overall number of CNVs and rare CNVs per individual differs between arrays, and there are subtle differences in the number of genes that overlap CNVs in each category. The differences can be due to multiple different reasons, including array probe density and location, batch effects from reagents, ethnicity and population structures that are

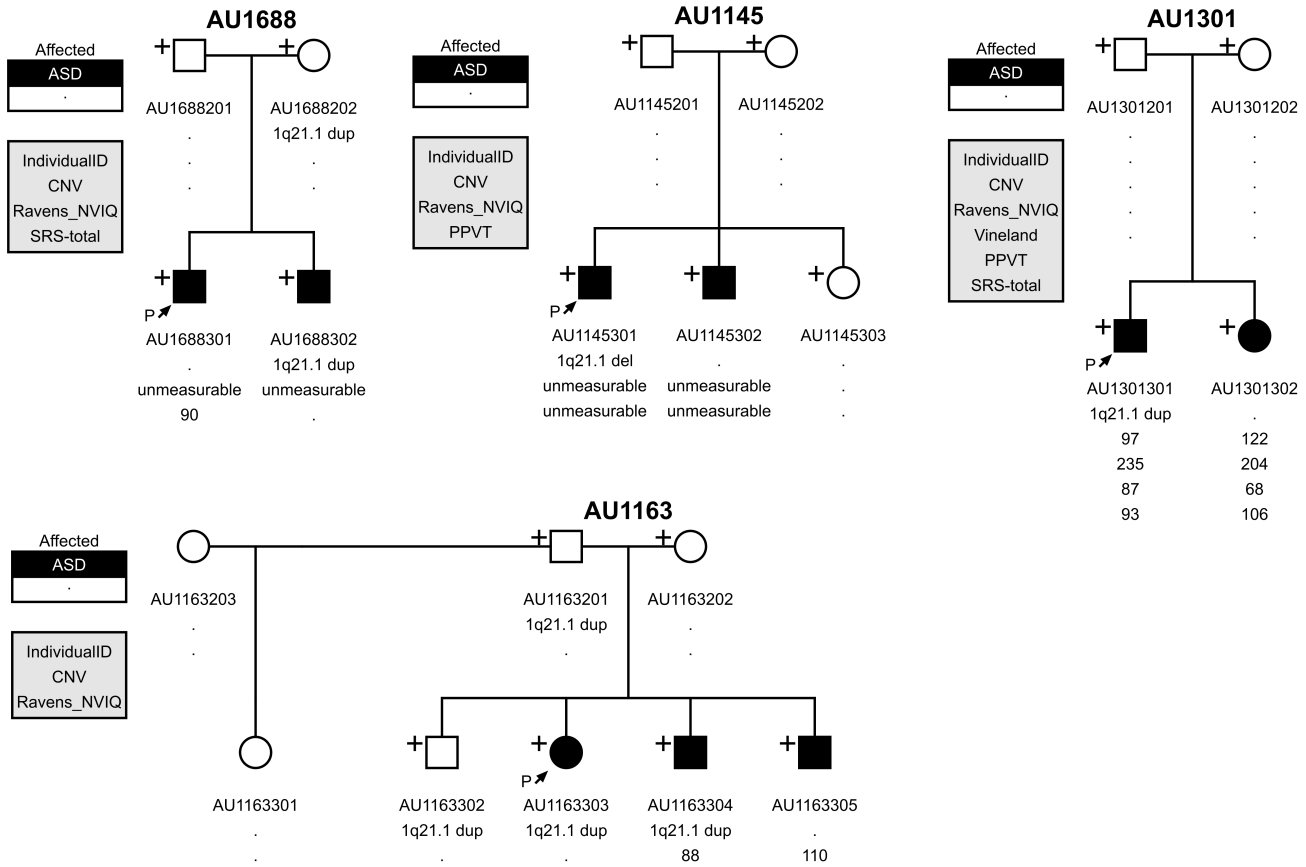
confounded with array and batch. The figure includes only data from parents to minimize potential noise from the affection status.

Figure S2. AGRE CNVs in the *WWOX* locus



There are no CNVs in siblings that overlap the *WWOX* in the AGRE. All CNVs with known mode of inheritance (both parents available) are inherited. Deletions are shown in dark red for affected children and in pink for parents. Duplications are shown in dark blue for affected children and light blue for parents. Centromere on chr16 is depicted as a grey circle on a red background. Genes in

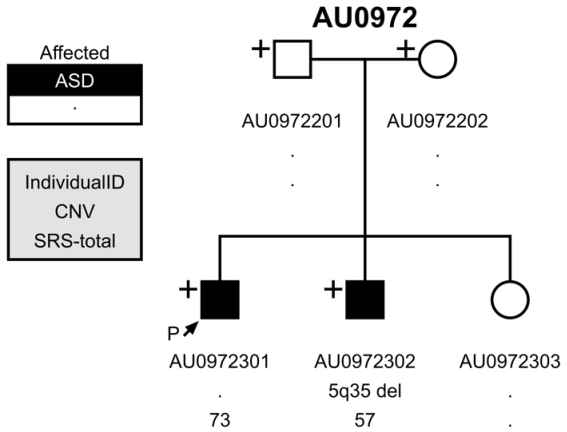
Figure S3. AGRE families with non-segregation of autism and 1q21.1 CNVs.



We discovered 30 families with a pathogenic CNV and available genetic information on two or more affected children. Twenty-two of the families had non-segregation of autism and the pathogenic CNV: at least one another affected child didn't carry the pathogenic CNV. This figure depicts families with the 1q21.1 deletions and duplications in some, but not all affected individuals. The pedigrees include information about the CNV (locus and deletion/duplication status) and additional information on Ravens non-verbal IQ, Social Responsiveness Scale, Stanford-Binet Intelligence Scale, Vineland adaptive behavior scale and Peabody Picture Vocabulary test, depending on availability.

We used a simple Bayesian likelihood calculation to estimate, how likely is the observed pattern of inheritance of pathogenic CNVs in data under the current best estimate of inheritance model, a single dominant factor (Gaugler et al. 2014). In our simple test, the alternative model covers all other possible models. For simplicity, we assumed full penetrance for each ASD-associated CNV, although the penetrance estimates ranged from 0.3 to 1 (on average 0.7) in the AGRE data and the recently published Simons Simplex Collection data (Sanders et al. 2015). We used three different sets of priors: family likely true with 0.9, 0.7 and 0.5 probability under the autosomal dominant model. We calculated the likelihood for each family under these assumptions and for each family we replaced the priors with the posterior probabilities from the last step. Changing the priors didn't change the final result in any meaningful way.
+ indicates individuals with available genetic information

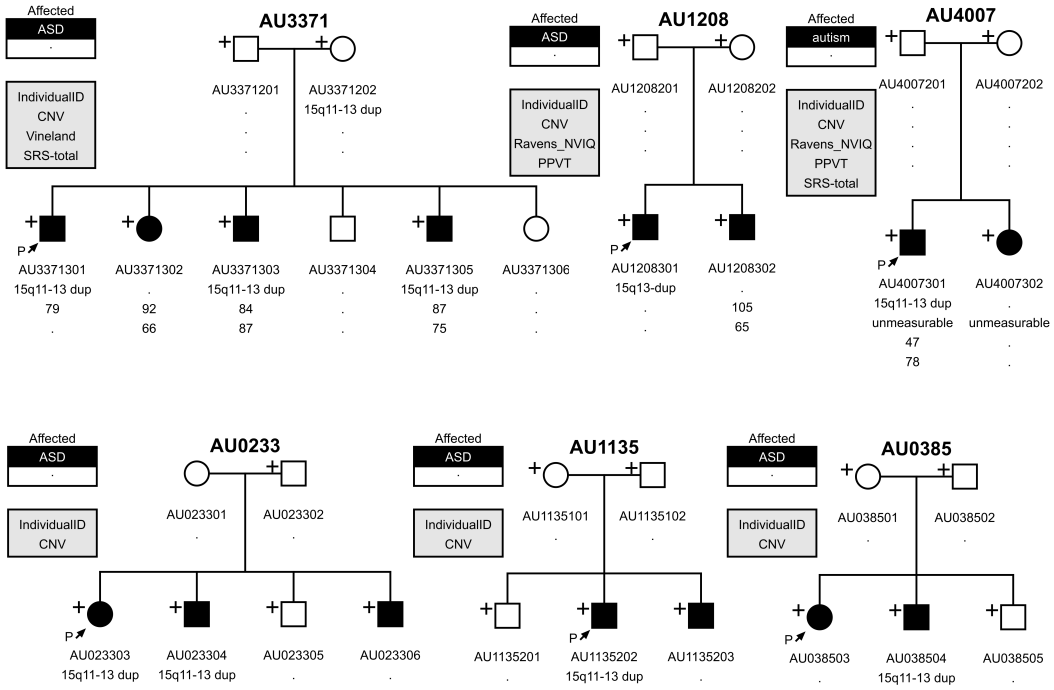
Figure S4. An AGRE family with non-segregation of autism and the 5q35 deletion.



This figure depicts a family with the 5q35 deletion in one, but not the other affected individual. The pedigree includes information about the CNV and additional information on Social Responsiveness Scale for each family member, when available.

+ indicates individuals with available genetic information

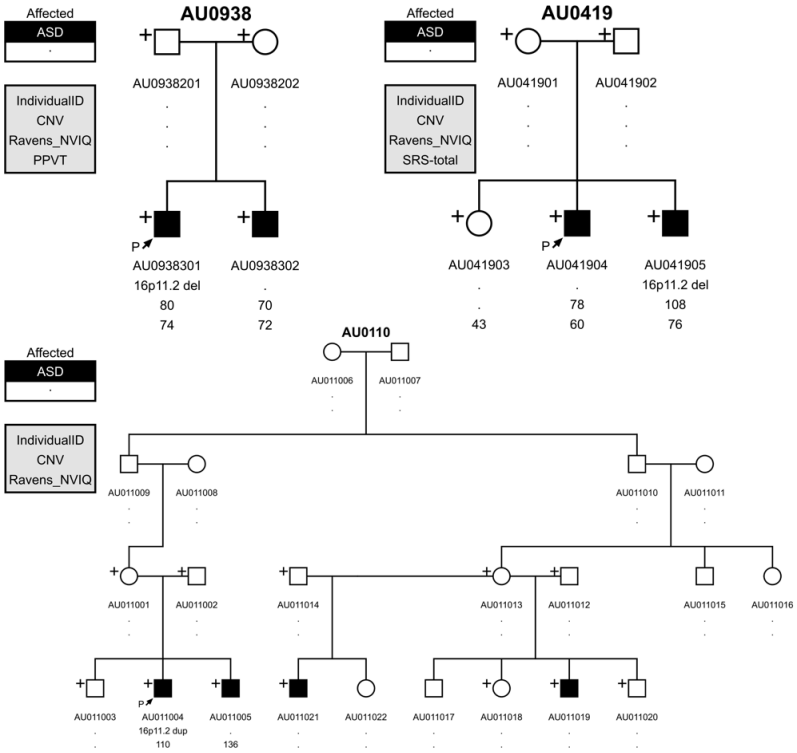
Figure S5. AGRE families with non-segregation of autism and CNVs in the 15q11-13 locus.



This figure depicts families with duplications in the 15q11-13 locus in some, but not all affected individuals. The pedigrees include information about the duplication carrier status and additional information on Ravens non-verbal IQ, Social Responsiveness Scale, Vineland adaptive behavior scale and Peabody Picture Vocabulary test, depending on availability.

+ indicates individuals with available genetic information

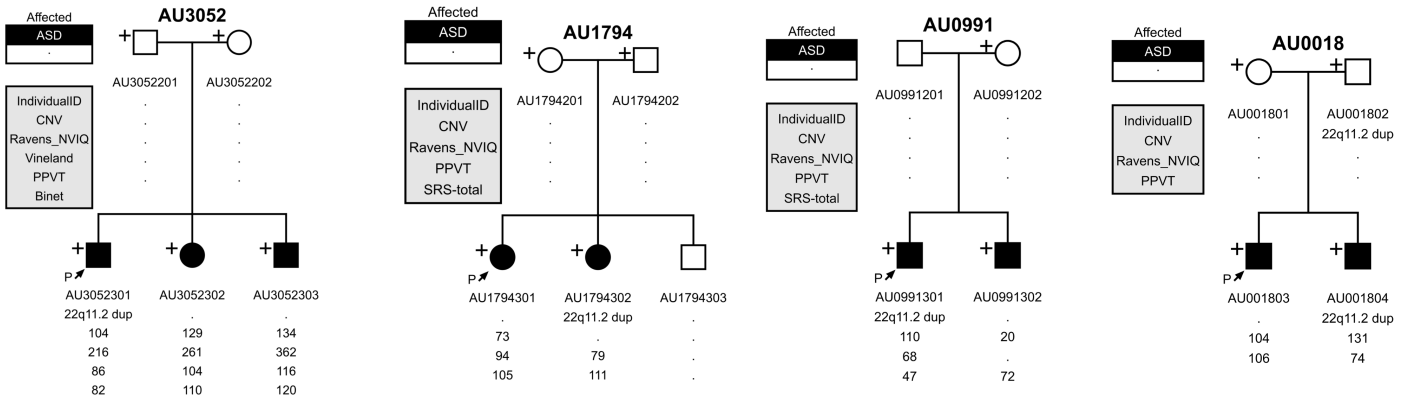
Figure S6. AGRE families with non-segregation of autism and CNVs in the 16p11.2 locus.



This figure depicts families with CNVs in the 16p11.2 locus in some, but not all affected individuals. The pedigrees include information about the CNV (locus and deletion/duplication status) and additional information on Ravens non-verbal IQ, Social Responsiveness Scale, and Peabody Picture Vocabulary test, depending on availability.

+ indicates individuals with available genetic information

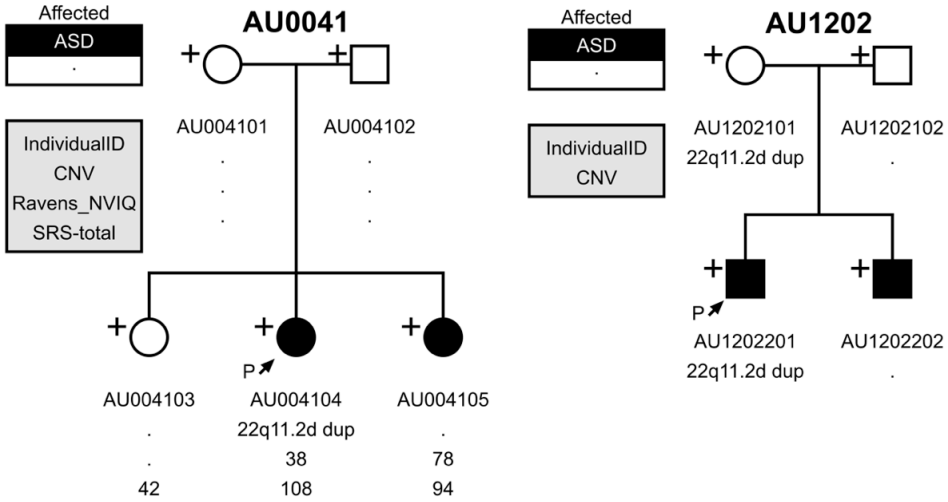
Figure S7. AGRE families with non-segregation of autism and duplications in the classic 22q11.2 locus.



This figure depicts families with duplications in the classic 22q11.2 locus in some, but not all affected individuals. The pedigrees include information about the duplication carrier status and additional information on Ravens non-verbal IQ, Social Responsiveness Scale, Stanford-Binet Intelligence Scale, Vineland adaptive behavior scale and Peabody Picture Vocabulary test, depending on availability.

+ indicates individuals with available genetic information

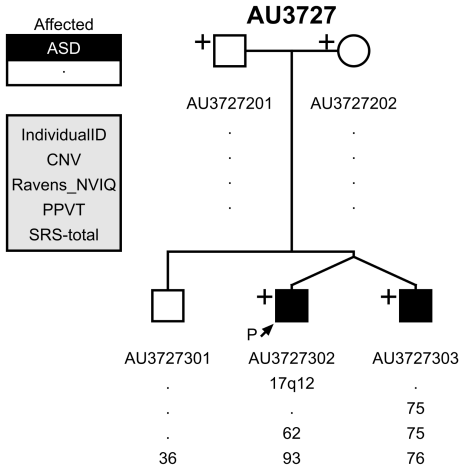
Figure S8. AGRE families with non-segregation of autism and duplications in the distal 22q11.2 locus.



This figure depicts families with duplications in the distal 22q11.2 locus in some, but not all affected individuals. The pedigrees include information about the CNV (locus and deletion/duplication) and additional information on Ravens non-verbal IQ and Social Responsiveness Scale.

+ indicates individuals with available genetic information

Figure S9. An AGRE family with non-segregation of autism and a duplication in the 17q12 locus.



This figure depicts a family with a *de novo* duplication in the 17q12 locus in one, but not both affected individuals. The pedigree includes the duplication carrier status and additional information on Ravens non-verbal IQ, Peabody Picture Vocabulary test and Social Responsiveness Scale.

+ indicates individuals with available genetic information

Table S1. Sample QC overview by genotyping set.

Set	Total samples	Total families	Removed [a]	Samples remaining	Families remaining	Included in previous CNV studies
550k.v3,v.1[a]	4013	941[b]	995 (23%)	2974	895[b]	Yes[c]
Omni-1 A	963	250[b]	95 (7%)	871	248[b]	No
Omni-1 B	191	82	21 (4%)	170	69	No
Omni-1 C	111	34[b]	14 (10%)	97	33[b]	No
Omni-2.5	1019	285[b]	61 (5%)	958	281[b]	No
Total	**6197**	**1592**	**1186**	**5100**	**1526**	

The sample set before and after QC.

[a] Number of samples removed for bad quality arrays, sex chromosome discrepancies or extremely high copy number

[b] Sample sets have overlapping families due to re-genotyping after a sample failure or missing biomaterials at the first genotyping time.

[c] These samples have been a part of previous studies by Girirajan et al. 2013, Matsunami et al. 2013, Miller et al. 2009, Bucan et al. 2009 and Glessner et al. 2009, and 74 families have also been included in the AGP CNV publications by Pinto et al. 2010 and 2014 (Bucan et al., 2009, Girirajan et al., 2013, Glessner et al., 2009, Matsunami et al., 2013, Miller et al., 2009, Moreno-De-Luca et al., 2013, Morrow et al., 2008, Pinto et al., 2014, Pinto et al., 2010).

Table S2. Batch Effect within different CNV categories

Category	p-value, all data	p-value, multiplex families
Total number of		
CNVs	1.052×10^{-6}	0.0004059
Rare CNVs	8.267×10^{-5}	0.004966
Rare deletions	0.01826	0.11
Rare duplications	0.05353	0.2029
Rare ≥500kb CNVs	0.5419	0.617
Rare *de novo*	0.3036	0.7596
Rare ≥500kb *de novo*	0.4851	0.923
Genes in CNVs	0.1615	0.07789
Genes in rare CNVs	0.006832	0.03195
Genes in rare deletions	0.03202	0.02658
Genes in rare duplications	0.01406	0.0639
Genes in rare ≥ 500kb CNVs	0.6092	0.7165
Genes in rare *de novo* CNVs	0.3163	0.6385
Genes in rare ≥500kb *de novo* CNVs	0.489	0.9247
Percentage of samples with		
Rare CNV	0.0002625	0.01438
Rare ≥500kb CNVs	0.5481	0.6259
Rare *de novo*	0.3019	0.7612
Rare ≥500kb *de novo*	0.4845	0.9232
Rare gene containing CNV	0.006047	0.01182
Rare gene containing *de novo*	0.3162	0.6391
Rare large gene containing CNV	0.6507	0.7579

The Kruskal-Wallis non-parametric test was used to assess the existence of batch or set effect in the AGRE data set. We used one affected per family and one unaffected sibling, if available.

Table S5. Overview of results by CNV and array type

	All samples:						Multiplex families					
	Aff		Unaff		OR (95% CI)	P	Aff		Unaff		OR	P
Large >500kb, rare CNVs		%		%				%		%		
% with ≥1	147/1123	13.1	36/406	8.9	1.7 (1.3-2.1)	0.01	114/878	13.0	23/279	8.4	1.6 (1.2-1.9)	0.022
% with genic	133/1123	11.8	33/406	8.1	1.6 (1.2-2.0)	0.03	104/878	11.8	20/279	7.2	1.5 (1.1-1.9)	0.031
% with *de novo*	25/1033	2.4	3/286	1.0	2.4 (0.7-12.2)	ns	21/896	2.3	1/200	0.5	4.7 (0.8-198)	ns
% with inherited	102/852	7.1	21/295	7.1	1.4 (1.0-1.8)	ns	84/695	12.1	12/216	7.9	1.5 (1.0-1.9)	ns
mean number of, ±*SD*	0.14±0.37		0.10±0.34		1.5 (1.1 -1.8)	0.03	0.14±0.37		0.09±0.33		1.5 (1.1-1.8)	0.05
All rare, *de novo* CNVs		%		%				%		%		
% with ≥1	56/1033	5.4	16/286	5.6	1.0 (0.9-1.1)	ns	48/896	5.4	11/200	5.5	1.1 (0.4-1.9)	ns
% with genic	49/1033	4.7	15/286	5.2	0.9 (0.3-1.5)	ns	41/896	4.6	10/200	5.0	1.0 (0.3-1.7)	ns
Total kb, ±SD	59±460		25±185		1.3 (0.9-1.8)	ns	57±429		33±223		1.2 (0.8-1.7)	ns
Number of genes in, ±SD	0.88±7.6		0.22±1.07		1.00 (1.0-1.1)	ns	0.88±7.3		0.29±1.27		1.00 (1.0-1.1)	ns
All rare, *inherited* CNVs		%		%				%		%		
% with ≥1	577/852	67.7	188/295	63.7	1.2 (1.0-1.4)	ns	465/695	66.9	143/216	66.5	1.1 (0.8-1.4)	ns
Mean # CNV, ±SD	0.95±0.85		0.93±0.93		1.0 (0.9-1.2)	ns	0.94±0.85		0.97±0.93		1.0 (0.9-1.2)	ns
Mean # deletions, ±SD	0.45±0.61		0.43±0.63		1.1 (0.9-1.3)	ns	0.45±0.61		0.41±0.63		1.2 (1.0-1.4)	ns
Mean # duplications, ±SD	0.50±0.68		0.50±70		0.9 (0.8-1.1)	ns	0.50±0.74		0.56±0.74		0.9 (0.7-1.1)	ns
% with genic	457/852	53.6	146/295	49.5	1.2 (0.9-1.4)	ns	365/695	52.5	113/216	52.3	1.1 (0.8-1.4)	ns
Total kb, ±SD	296±580		229±371		1.0 (1.0-1.0)	ns	300±619		243±391		1.0 (1.0-1.0)	ns
Number of genes in, ±SD	2.7±9.5		2.1±4.5		1.0 (1.0-1.0)	ns	2.8±10.9		2.3±4.7		1.0 (1.0-1.0)	ns
All rare CNVs		%		%				%		%		
% with ≥1	778/1123	69.3	265/406	65.3	1.1 (0.9-1.4)	ns	606/878	69.0	190/279	68.1	1.2 (1.0-1.5)	ns
% with ≥1 genie	581/1123	50.8	194/406	47.8	1.1 (0.9-1.3)	0.04	449/878	51.1	141/279	50.5	1.2 (1.0-1.5)	ns
% with inherited rare	577/852	67.7	188/295	63.7	1.2 (1.0-1.4)	ns	458/695	66.9	143/216	66.5	1.1 (0.8-1.4)	ns
Mean total #, ±SD	1.00±0.87		0.95±0.95		1.00 (0.9-1.1)	ns	1.00±0.87		0.98±0.93		1.02 (0.8-1.2)	ns
Mean total # deletions, ±SD	0.49±0.64		0.46±0.67		1.00 (0.8-1.2)	ns	0.49±0.65		0.47±0.67		1.0 (0.8-1.2)	ns
Mean total # duplications, ±SD	0.51±0.68		0.49±0.69		1.00 (0.8-1.2)	ns	0.51±0.69		0.52±0.70		0.9 (0.7-1.1)	ns
Mean total # genes, ±SD	3.4±12.3		2.3±4.5		1.0 (1.0-1.0)	ns	3.5±12.6		2.4±4.4		1.00 (1.0-1.0)	ns
Mean total length (kb), ±SD	357±754		269±428		1.3 (1.1-1.6)	0.03	356±740		288±459		1.2 (1.0-1.5)	ns

All results were calculated as each genotyping set as its own strata. Analyses for frequencies were done using general linear model with binomial distribution. The OR and 95% CI for averages were estimated from logistic regression model effect sizes and standard errors. Due to the variable family structures, the number of available samples for different types of analyses varied. The frequencies are reported as family based, one family contributing maximum of one additional value to the affected or unaffected sample column.

Table S9. 2q24.1 deletions in AGRE, DECIPHER and ClinGen.

Set	ID	Deletion	Inheritance	Phenotype
AGRE	AU1778303	1Mb	*de novo*	Non-verbal, extremely low IQ, ASD
AGRE	AU3566301	3.3Mb	*de novo*	Language impairment, low IQ, reported mild ID, seizures, ASD
ClinGen	Nssv1602827	4.6Mb	n/a	Delayed speech, ID, ADD, ASD
DECIPHER	254867	2.2Mb	*de novo*	Delayed language development, macrocephaly, Sotos-like behavior
DECIPHER	290757	170kb	*de novo*	Delayed language development, behavioral/cognitive disorders
DECIPHER	296098	1Mb	n/a	Psychomotor delay, ASD
DECIPHER	293228	4.7Mb	n/a	unknown

All identified individuals with a hemizygous 2q24.1 (*NR4A2*) deletion in AGRE and the DECIPHER and ClinGen databases. n/a = no information available.

Table S11. *WWOX* CNV and Individual Characteristics

IID	CNV	Mbp	Status	Inheritance	Phenotype
AU4112303	Dup	77.6-78.1	Affected	Unknown	SRS 85, Raven's NVIQ 97, can carry a conversation, tells friends from non-friends, no seizures
AU4010301	Dup	78.0-78.5	Affected	Unknown	SRS 71, Raven's NVIQ 85, no conversation, few words, no seizures
AU3381303	Dup	80.0-78.6	Affected	Paternal	SRS 98, Vineland 72, language delay, no seizures
AU1141201	Dup	78.9-79.4	Affected	Unknown	SRS NA, no additional information, no seizures
AU2488303	Dup	78.0-78.5	Affected	Paternal	Vineland 60, Raven's NVIQ 114, Stanford-Binet FSIQ 84, self-care, social interaction, good at school, no seizures
AU2607301	Del	78.3-78.6	Affected	Maternal	SRS 83, Ravens NVIQ 75, Stanford-Binet FSIQ 77, Vineland 81, no seizures
AU2607302					SRS 86, Ravens NVIQ 85, Stanford-Binet FSIQ 90, Vineland 77, no seizures
AU1993301	Del	78.3-78.4	Affected	Maternal	SRS NA, Raven's NVIQ 94, Stanford-Binet FSIQ 102, Asperger's/high-functioning, speech delay, no seizures
AU1993302					SRS 96, Raven's NVIQ 90, Vineland 62, speech delay, OCD, mild intellectual disability, no seizures
AU2073303	Del	78.9-79.1	Affected	Maternal	SRS NA, Stanford-Binet FSIQ 120, Vineland 80, Asperger's/high functioning, ADHD, delayed echolalia, no seizures
14415.p1	Dup	77.7-78.4	Affected	Maternal	SRS 76, PPVT 139, Vineland 79, no seizures
14415.s1			Unaffected		SRS 52, IQ estimate NA, no seizures
13375.p1	Dup	75.6-78.8	Affected	Paternal	SRS 90, PPVT 85, Vineland 79, febrile seizures
14517.p1	Del	77.7-78.4	Affected	Maternal	SRS 90, PPVT 97, Vineland 64, infantile spasms
13199.p1	Del	78.8-78.9	Affected	Maternal	SRS 90, PPVT 107, Vineland 72, no seizures, mother has migraines

All samples with 100kb CNVs in *WWOX* in AGRE are listed here with all the available phenotype information. Most individuals are in in normal IQ range, and values that indicate moderate to less severe phenotype. IID= Individual identifier, CNV= copy number variation type, Del = deletion, Dup = duplication, Status = affection status (affected/unaffected), Inheritance = inheritance pattern, parent of origin for the CNV, Phenotype = phenotype description: SRS = Social Responsiveness Scale normalized T value (parent evaluation), Raven's NVIQ = Raven's non-verbal intelligence quotient measurement, PPVT = Peabody Picture Vocabulary Test standardized score, FSIQ = full scale intelligence quotient measure, Vineland = Vineland adaptive behavior score.

Supplementary References

BUCAN, M., ABRAHAMS, B. S., WANG, K., GLESSNER, J. T., HERMAN, E. I., SONNENBLICK, L. I., ALVAREZ RETUERTO, A. I., IMIELINSKI, M., HADLEY, D., BRADFIELD, J. P., KIM, C., GIDAYA, N. B., LINDQUIST, I., HUTMAN, T., SIGMAN, M., KUSTANOVICH, V., LAJONCHERE, C. M., SINGLETON, A., KIM, J., WASSINK, T. H., MCMAHON, W. M., OWLEY, T., SWEENEY, J. A., COON, H., NURNBERGER, J. I., LI, M., CANTOR, R. M., MINSHEW, N. J., SUTCLIFFE, J. S., COOK, E. H., DAWSON, G., BUXBAUM, J. D., GRANT, S. F., SCHELLENBERG, G. D., GESCHWIND, D. H. & HAKONARSON, H. 2009. Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. *PLoS Genet,* 5**,** e1000536.

COLELLA, S., YAU, C., TAYLOR, J. M., MIRZA, G., BUTLER, H., CLOUSTON, P., BASSETT, A. S., SELLER, A., HOLMES, C. C. & RAGOUSSIS, J. 2007. QuantiSNP: an Objective Bayes Hidden-Markov Model to detect and accurately map copy number variation using SNP genotyping data. *Nucleic Acids Res,* 35**,** 2013-25.

GIRIRAJAN, S., DENNIS, M. Y., BAKER, C., MALIG, M., COE, B. P., CAMPBELL, C. D., MARK, K., VU, T. H., ALKAN, C., CHENG, Z., BIESECKER, L. G., BERNIER, R. & EICHLER, E. E. 2013. Refinement and discovery of new hotspots of copy-number variation associated with autism spectrum disorder. *Am J Hum Genet,* 92**,** 221-37.

GLESSNER, J. T., WANG, K., CAI, G., KORVATSKA, O., KIM, C. E., WOOD, S., ZHANG, H., ESTES, A., BRUNE, C. W., BRADFIELD, J. P., IMIELINSKI, M., FRACKELTON, E. C., REICHERT, J., CRAWFORD, E. L., MUNSON, J., SLEIMAN, P. M., CHIAVACCI, R., ANNAIAH, K., THOMAS, K., HOU, C., GLABERSON, W., FLORY, J., OTIENO, F., GARRIS, M., SOORYA, L., KLEI, L., PIVEN, J., MEYER, K. J., ANAGNOSTOU, E., SAKURAI, T., GAME, R. M., RUDD, D. S., ZURAWIECKI, D., MCDOUGLE, C. J., DAVIS, L. K., MILLER, J., POSEY, D. J., MICHAELS, S., KOLEVZON, A., SILVERMAN, J. M., BERNIER, R., LEVY, S. E., SCHULTZ, R. T., DAWSON, G., OWLEY, T., MCMAHON, W. M., WASSINK, T. H., SWEENEY, J. A., NURNBERGER, J. I., COON, H., SUTCLIFFE, J. S., MINSHEW, N. J., GRANT, S. F., BUCAN, M., COOK, E. H., BUXBAUM, J. D., DEVLIN, B., SCHELLENBERG, G. D. & HAKONARSON, H. 2009. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature,* 459**,** 569-73.

ILLUMINA. 2010a. *Interpreting Infinium® Assay Data for Whole-Genome Structural Variation* [Online]. Available: http://res.illumina.com/documents/products/technotes/technote_cytoanalysis.pdf [Accessed].

ILLUMINA. 2010b. *Updated Cluster Generation Protocol for X Chromosome SNPs* [Online]. http://www.illumina.com. Available: http://res.illumina.com/documents/products/technotes/technote_x_chromosome_snp_cluster_generation.pdf [Accessed].

MATSUNAMI, N., HADLEY, D., HENSEL, C. H., CHRISTENSEN, G. B., KIM, C., FRACKELTON, E., THOMAS, K., DA SILVA, R. P., STEVENS, J., BAIRD, L., OTTERUD, B., HO, K., VARVIL, T., LEPPERT, T., LAMBERT, C. G., LEPPERT, M. & HAKONARSON, H. 2013. Identification of rare recurrent copy number

variants in high-risk autism families and their prevalence in a large ASD population. *PLoS One,* 8**,** e52239.
MILLER, D. T., SHEN, Y., WEISS, L. A., KORN, J., ANSELM, I., BRIDGEMOHAN, C., COX, G. F., DICKINSON, H., GENTILE, J., HARRIS, D. J., HEGDE, V., HUNDLEY, R., KHWAJA, O., KOTHARE, S., LUEDKE, C., NASIR, R., PODURI, A., PRASAD, K., RAFFALLI, P., REINHARD, A., SMITH, S. E., SOBEIH, M. M., SOUL, J. S., STOLER, J., TAKEOKA, M., TAN, W. H., THAKURIA, J., WOLFF, R., YUSUPOV, R., GUSELLA, J. F., DALY, M. J. & WU, B. L. 2009. Microdeletion/duplication at 15q13.2q13.3 among individuals with features of autism and other neuropsychiatric disorders. *J Med Genet,* 46**,** 242-8.
MORENO-DE-LUCA, D., SANDERS, S. J., WILLSEY, A. J., MULLE, J. G., LOWE, J. K., GESCHWIND, D. H., STATE, M. W., MARTIN, C. L. & LEDBETTER, D. H. 2013. Using large clinical data sets to infer pathogenicity for rare copy number variants in autism cohorts. *Mol Psychiatry,* 18**,** 1090-5.
MORROW, E. M., YOO, S. Y., FLAVELL, S. W., KIM, T. K., LIN, Y., HILL, R. S., MUKADDES, N. M., BALKHY, S., GASCON, G., HASHMI, A., AL-SAAD, S., WARE, J., JOSEPH, R. M., GREENBLATT, R., GLEASON, D., ERTELT, J. A., APSE, K. A., BODELL, A., PARTLOW, J. N., BARRY, B., YAO, H., MARKIANOS, K., FERLAND, R. J., GREENBERG, M. E. & WALSH, C. A. 2008. Identifying autism loci and genes by tracing recent shared ancestry. *Science,* 321**,** 218-23.
PINTO, D., DELABY, E., MERICO, D., BARBOSA, M., MERIKANGAS, A., KLEI, L., THIRUVAHINDRAPURAM, B., XU, X., ZIMAN, R., WANG, Z., VORSTMAN, J. A., THOMPSON, A., REGAN, R., PILORGE, M., PELLECCHIA, G., PAGNAMENTA, A. T., OLIVEIRA, B., MARSHALL, C. R., MAGALHAES, T. R., LOWE, J. K., HOWE, J. L., GRISWOLD, A. J., GILBERT, J., DUKETIS, E., DOMBROSKI, B. A., DE JONGE, M. V., CUCCARO, M., CRAWFORD, E. L., CORREIA, C. T., CONROY, J., CONCEICAO, I. C., CHIOCCHETTI, A. G., CASEY, J. P., CAI, G., CABROL, C., BOLSHAKOVA, N., BACCHELLI, E., ANNEY, R., GALLINGER, S., COTTERCHIO, M., CASEY, G., ZWAIGENBAUM, L., WITTEMEYER, K., WING, K., WALLACE, S., VAN ENGELAND, H., TRYFON, A., THOMSON, S., SOORYA, L., ROGE, B., ROBERTS, W., POUSTKA, F., MOUGA, S., MINSHEW, N., MCINNES, L. A., MCGREW, S. G., LORD, C., LEBOYER, M., LE COUTEUR, A. S., KOLEVZON, A., JIMENEZ GONZALEZ, P., JACOB, S., HOLT, R., GUTER, S., GREEN, J., GREEN, A., GILLBERG, C., FERNANDEZ, B. A., DUQUE, F., DELORME, R., DAWSON, G., CHASTE, P., CAFE, C., BRENNAN, S., BOURGERON, T., BOLTON, P. F., BOLTE, S., BERNIER, R., BAIRD, G., BAILEY, A. J., ANAGNOSTOU, E., ALMEIDA, J., WIJSMAN, E. M., VIELAND, V. J., VICENTE, A. M., SCHELLENBERG, G. D., PERICAK-VANCE, M., PATERSON, A. D., PARR, J. R., OLIVEIRA, G., NURNBERGER, J. I., MONACO, A. P., MAESTRINI, E., KLAUCK, S. M., HAKONARSON, H., HAINES, J. L., GESCHWIND, D. H., FREITAG, C. M., FOLSTEIN, S. E., ENNIS, S., et al. 2014. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *Am J Hum Genet,* 94**,** 677-94.
PINTO, D., PAGNAMENTA, A. T., KLEI, L., ANNEY, R., MERICO, D., REGAN, R., CONROY, J., MAGALHAES, T. R., CORREIA, C., ABRAHAMS, B. S., ALMEIDA, J., BACCHELLI, E., BADER, G. D., BAILEY, A. J., BAIRD, G., BATTAGLIA, A.,

BERNEY, T., BOLSHAKOVA, N., BOLTE, S., BOLTON, P. F., BOURGERON, T., BRENNAN, S., BRIAN, J., BRYSON, S. E., CARSON, A. R., CASALLO, G., CASEY, J., CHUNG, B. H., COCHRANE, L., CORSELLO, C., CRAWFORD, E. L., CROSSETT, A., CYTRYNBAUM, C., DAWSON, G., DE JONGE, M., DELORME, R., DRMIC, I., DUKETIS, E., DUQUE, F., ESTES, A., FARRAR, P., FERNANDEZ, B. A., FOLSTEIN, S. E., FOMBONNE, E., FREITAG, C. M., GILBERT, J., GILLBERG, C., GLESSNER, J. T., GOLDBERG, J., GREEN, A., GREEN, J., GUTER, S. J., HAKONARSON, H., HERON, E. A., HILL, M., HOLT, R., HOWE, J. L., HUGHES, G., HUS, V., IGLIOZZI, R., KIM, C., KLAUCK, S. M., KOLEVZON, A., KORVATSKA, O., KUSTANOVICH, V., LAJONCHERE, C. M., LAMB, J. A., LASKAWIEC, M., LEBOYER, M., LE COUTEUR, A., LEVENTHAL, B. L., LIONEL, A. C., LIU, X. Q., LORD, C., LOTSPEICH, L., LUND, S. C., MAESTRINI, E., MAHONEY, W., MANTOULAN, C., MARSHALL, C. R., MCCONACHIE, H., MCDOUGLE, C. J., MCGRATH, J., MCMAHON, W. M., MERIKANGAS, A., MIGITA, O., MINSHEW, N. J., MIRZA, G. K., MUNSON, J., NELSON, S. F., NOAKES, C., NOOR, A., NYGREN, G., OLIVEIRA, G., PAPANIKOLAOU, K., PARR, J. R., PARRINI, B., PATON, T., PICKLES, A., PILORGE, M., et al. 2010. Functional impact of global rare copy number variation in autism spectrum disorders. *Nature,* 466**,** 368-72.

SANDERS, S. J., ERCAN-SENCICEK, A. G., HUS, V., LUO, R., MURTHA, M. T., MORENO-DE-LUCA, D., CHU, S. H., MOREAU, M. P., GUPTA, A. R., THOMSON, S. A., MASON, C. E., BILGUVAR, K., CELESTINO-SOPER, P. B., CHOI, M., CRAWFORD, E. L., DAVIS, L., WRIGHT, N. R., DHODAPKAR, R. M., DICOLA, M., DILULLO, N. M., FERNANDEZ, T. V., FIELDING-SINGH, V., FISHMAN, D. O., FRAHM, S., GARAGALOYAN, R., GOH, G. S., KAMMELA, S., KLEI, L., LOWE, J. K., LUND, S. C., MCGREW, A. D., MEYER, K. A., MOFFAT, W. J., MURDOCH, J. D., O'ROAK, B. J., OBER, G. T., POTTENGER, R. S., RAUBESON, M. J., SONG, Y., WANG, Q., YASPAN, B. L., YU, T. W., YURKIEWICZ, I. R., BEAUDET, A. L., CANTOR, R. M., CURLAND, M., GRICE, D. E., GUNEL, M., LIFTON, R. P., MANE, S. M., MARTIN, D. M., SHAW, C. A., SHELDON, M., TISCHFIELD, J. A., WALSH, C. A., MORROW, E. M., LEDBETTER, D. H., FOMBONNE, E., LORD, C., MARTIN, C. L., BROOKS, A. I., SUTCLIFFE, J. S., COOK, E. H., JR., GESCHWIND, D., ROEDER, K., DEVLIN, B. & STATE, M. W. 2011. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron,* 70**,** 863-85.

WANG, K., LI, M., HADLEY, D., LIU, R., GLESSNER, J., GRANT, S. F., HAKONARSON, H. & BUCAN, M. 2007. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. *Genome Res,* 17**,** 1665-74.