SUPPLEMENTARY INFORMATION

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Supplementary Discussion

Sample Overlap

Three of the previously reported families (12325, 12680, and 12647) are the only samples known to overlap with other studies (Sanders et al. 2012).

Rate of *De Novo* CNVs

We expected the *de novo* CNV rate for this cohort would be less than for other ASD cohorts as 77% (94/122) had previously been screened negative for large, disruptive *de novo* events. Nonetheless, our observed rate of *de novo* CNVs (6/122, ~5%) is in line with other recent estimates for ASD[1,2] owing possibly to the increased resolution of detecting gene disruptions with exome sequencing.

Effect of Multiple Genetic Lesions on Intellectual Functioning

We performed a multivariate analysis to examine effect of number of "extreme" *de novo* coding mutations (0, 1 or 2 or more) and the presence of either *de novo* or rare inherited copy number variation (122/189 probands) on nonverbal IQ (NVIQ) and verbal IQ (VIQ) (**Supplementary Fig. 5**). Extreme mutations (n = 62) were defined as *de novo* protein truncating, intersections with known OMIM and ASD candidate genes, and CNVs predicted to be gene breaking and pathogenic. In the sample of 122 individuals for whom CNV analysis had been completed, we observed a significant decrease in NVIQ with increased numbers of events ($F(2,116) = 5.45$, $p<.01$, partial $\eta^2 = 0.09$), but not in VIQ ($F(2,116) = 1.13$, p = ns, partial $\eta^2 = 0.02$). This result in NVIQ was strengthened, but not exclusively driven, by the presence of CNVs ($F(2,116) = 0.97$, p = ns, partial $\eta^2 = 0.02$); there was no main effect of strictly having a CNV on cognitive ability ($F(2,116) = 0.71$, p = ns, partial $\eta^2 = 0.006$). Post hoc analyses indicated individuals with

one and two or more events scored significantly lower in NVIQ than individuals with no events (mean difference = 18.0 points, $p < 0.05$, Cohen's d = 0.63; 38.5 points, $p < 0.01$, d = 1.69; respectively). The significant difference in NVIQ between individuals with no *de novo* coding mutations and those individuals with two or more mutations was also observed with the complete sample of 189 individuals ($F(2,186) = 6.129$, $p<.01$, partial $\eta^2 = 0.06$) (**Fig. 1c**).

IPA Analysis

Within our 49 PPI network members, IPA detected the most significant functional enrichment in Gene Expression (B-H p-value 9.45E-03-8.57E-02), Behavior (B-H p-value 9.45E-03-8.57E-02), Organismal Development (B-H p-value 9.45E-03-7.74E-02), Embryonic Development (B-H p-value 9.45E-03-8.01E-02), and Nervous System Development and Function (B-H p-value 9.45E-03-8.91E-02) (**Supplementary Table 13**).

We then performed an additional IPA analysis on the 126 genes identified in 209 samples. The top interconnected network consists of 22 genes (15 of which are PPI members), of which *CTNNB1* is a central node (**Supplementary Fig. 11**). To further investigate the potential role of *CTNNB1* interactors in autism, we selected all direct upstream interacting genes from beta-Catenin in IPA and noted that 8/358 (p = 0.0030) were present in our mutation list. Furthermore, we note that *CTNNB1* is directly linked to multiple highly interconnected genes in the PPI network (*MYBBP1A*, *PBRM1*, *RUVBL1*, *TBL1XR1*, and *CHD8*), suggesting that additional mutated genes involved in *CTNNB1* function are represented in autism. This enrichment for *CTNNB1* interactors further supports the hypothesis that the *WNT*/beta-catenin pathway may play a role in the etiology of autism[3].

Phenotyping Summaries for Selected Families

Family 13844. Proband is second of three children with an older sister (13844.s1) and younger brother (13844.s2).

Patient ID: 13844.fa

Summary: Father is an adult non-Hispanic white male. Age at conception of proband is 40. Normative range of social responsiveness, but elevated score for rigidity on broader autism phenotype. Some signs of alcoholism (use, attempting to cut down, annoyed by criticism about drinking, feeling bad about drinking, eye opening experience). No medication use endorsed for current or past. Some college education. Annual household income = $101–130K. Father has head circumference of 58.5 cm (z = 1.57) and normative BMI. No comorbid diagnoses endorsed.

Patient ID: 13844.mo

Summary: Mother is an adult non-Hispanic white female. Age at conception of proband is 35. Normative range of social responsiveness. No evidence of broader autism phenotype. Antibiotics taken during second trimester of pregnancy with proband. Currently taking thyroid medication and antidepressant (not taken during pregnancy). Endorsement of current tobacco use and past marijuana use. Some college education. Annual household income = $101–130K. Mother has head circumference of 54 cm (z = -.41) and normative BMI. No comorbid diagnoses endorsed.

Patient ID: 13844.s1

Summary: Sibling is a non-Hispanic white 10-year-old female. Normative adaptive scores and social responsiveness from parent and teacher noted. Behavioral elevations for somatic problems and complaints. Mother was prescribed an unspecified hormone treatment to aid with growth in past (not currently taking). No other endorsement of medication use. Head circumference of 54 cm (z = 0.96) and normative BMI. No comorbid diagnoses endorsed. Cognitive decline following Ebstein-Barr virus reported by parents.

Patient ID: 13844.s2

Summary: Sibling is a non-Hispanic white 5-year-old male. Adaptive scores not available. Normative social responsiveness from parent and teacher. No behavioral elevations across any domain. No endorsement of medication use. Head circumference of 52 cm (z = 0.15) and BMI suggestive of being underweight. No comorbid diagnoses endorsed.

Patient ID: 13844.p1

Event: *de novo CHD8* truncating, *de novo CUBN* truncating, 2X inherited CNV

Summary: Patient is a 99-month-old non-Hispanic white male diagnosed with autism. Extremely low VIQ (20), NVIQ (34), and adaptive (59) scores. Clinical range deficits in social responsiveness (120). Possible loss of language skills during development and elevated social withdrawal behaviors with no comorbid diagnoses. Large head (z = 2.62) and normal BMI. Food allergies (gluten and casein). Gastrointestinal constipation diagnosis with bloating and abdominal pain. Roseola diagnosed at 2.5 years and Epstein bar virus contracted at 8 years. Respiratory problems diagnosed at 11 months and kidney problems diagnosed at 9 months. No diagnosis of cardiac or metabolic syndromes noted. No report of congenital anomalies. Family history of Down syndrome (maternal cousin). NICU admission shortly after birth with oxygen treatment. Meconium aspiration at birth. Family history among several members for migraines. Currently on GFCF diet. Took asthma medication in the past but not currently.

Family 12752. Proband is an only child.

Patient ID: 12752.fa

Summary: Patient is an adult non-Hispanic white male. Age at conception of proband is 38. Normative range social responsiveness. Elevated score for aloofness and pragmatic social skills.

Diagnosis of diabetes. Current tobacco and alcohol use endorsed. Current and past use of antihypertensive meds and medication for high cholesterol. Past use of sedatives and pain killers. Some college education. Annual household income = $36–50K. Father has a head circumference of 59.5 cm (z = 1.56). BMI information unavailable.

Patient ID: 12752.ma

Summary: Patient is an adult non-Hispanic white female. Age at conception of proband is 36. Normative range of social responsiveness. No presence of broader autism phenotype. No endorsement of medications currently or during pregnancy with proband. Current tobacco and alcohol use endorsed. Some college education. Annual household income = $36–50K. Mother has head circumference of 54 cm (z = -.41). BMI information unavailable. Mother has been diagnosed with heart disease.

Patient ID: 12752.p1

Event: *de novo CHD8* truncating, *de novo ETFB* truncating, *de novo IQGAP2* truncating

Summary: Patient is a 55-month-old non-Hispanic white female diagnosed with autism. Normative range VIQ (90) and NVIQ (93) with low adaptive behavior skills (59). Clinical range deficits in social responsiveness (90). Clinical elevations in attention problems, internalizing problems, and affective problems with no comorbid diagnoses. Large head (z = 2.40) and BMI indications of being underweight. No loss or regression of language skills. Diagnosis of chronic constipation, ongoing from 3.5 months with intermittent episodes of abnormal stool. Coordination problems noted since 3.5 months. No cardiac or metabolic syndromes noted. No report of congenital anomalies. Hyperbilirubinema diagnosis with phototherapy shortly after birth, no complications after treatment.

Patient ID: 11660.p1

Event: *de novo NTNG1* missense, inherited CNV

Summary: Patient is a 60-month-old non-Hispanic white female diagnosed with autism. Low range VIQ (63) and NVIQ (60) with low adaptive skills (65). Clinical range deficits in social responsiveness (90). No language loss or regression noted. Clinical elevations in withdrawn behaviors, attention difficulties, and affective problems with no comorbid diagnoses. Large head ($z = 2.5$) with BMI indications of being underweight. Improvement in repetitive behaviors during fever symptoms noted by parents. No cardiac, metabolic, or autoimmune syndromes noted. Dysmorphology assessment indicating nondysmorphic features. No noted congenital anomalies.

Patient ID: 12532.p1

Event: *de novo NTNG1* missense, *de novo NAA40* missense

Summary: Patient is a 141-month-old non-Hispanic white male diagnosed with autism. Very high VIQ (135) and normative range NVIQ (110) with low adaptive behavior composite scores (71). Clinical range elevations in social responsiveness (74) with word loss regression occurring early in development. Borderline and clinical range problems with attention, internalizing, and affective problem behaviors with no comorbid diagnoses. Normal head circumference with BMI suggesting underweight. Penicillin allergy noted beginning at 5 years of age. Diagnosis of chronic otitis media at approximately age 6. No cardiac, metabolic, or autoimmune syndromes noted. No report of congenital anomalies.

Patient ID: 13733.p1

Event: *de novo CHD7* missense, inherited CNV

Summary: Patient is a 160-month-old non-Hispanic white female diagnosed with autism. Normative VIQ scores (90) with very low NVIQ scores (68) and adaptive scores (69). No regression or loss of language. Borderline range anxiety scores and with no comorbid mental health diagnoses. Normal head circumference and BMI. Vision problems with correction. No hearing deficits. Diagnosis of Tourette's Syndrome at six years. Myringotomy procedure for recurrent problems with otitis media. Diagnosis of respiratory problems but no diagnosis of cardiac or metabolic syndromes. No report of congenital anomalies.

Patient ID: 11390.p1

Event: *de novo PTEN* missense

Summary: Patient is a 99-month-old non-Hispanic white female diagnosed with autism. Very low VIQ (57) and low NVIQ (77) with low average adaptive behavior skill scores (79). Clinical range elevations in social responsiveness (90). Language regression and word loss noted in early development as well as occurrence of nonfebrile seizures. Borderline and clinical range problems with social withdrawal, attention, and affective problematic behaviors with no comorbid diagnoses. Large head ($z = 2.84$) with normal range BMI scores. Chronic unusual stools noted from 6 months of age. Chronic otitis media diagnoses at 2.5 years of age with noted improvements in repetitive behaviors during periods of fever. No cardiac, metabolic, or autoimmune syndromes noted. Dysmorphology assessment indicating nondysmorphic features. No report of congenital anomalies. Sleep difficulties noted for falling asleep with night time incontinence. Normal menstrual cycle and pubertal changes taking place. Mood stabilizer medication used in the past but not current. Special education services in school 100% of time

since age 3 and continuing to current. Occupational therapy services 1 hour per week year round beginning at age 3 continuing to current.

Patient ID: 12346.p1

Event: *de novo MBD5* truncating, *de novo MYBBP1A* missense, *de novo PBRM1* missense

Summary: Patient is a 833-month-old non-Hispanic white male diagnosed with autism. Normative VIQ (106) with low NVIQ (77) and adaptive behavior skills (64). Clinical range elevations in social responsiveness (90). No language loss or regression noted in early development. Clinical elevations in withdrawn behaviors and no comorbid diagnoses. Normative head circumference and BMI. Chronic constipation diagnosed by PCP at 3 years of age. Coordination problems diagnosed by PCP at 16 months. Suspected cerebral palsy (unsure) noted at 1 year of age by orthopedist. Grand mal seizure occurrences beginning at 1 month and occurring approximately once per month in frequency. Chicken pox contraction at four years. Chronic Otitis Media and intermittent strep throat occurrences. No report of congenital anomalies.

Patient ID: 13890.p1

Event: *de novo DYRK1A* truncating

Summary: Patient is a 164-month-old non-Hispanic white female diagnosed with autism. Very low VIQ (26) and NVIQ (42) and adaptive behavior skills (41). Clinical range elevations in social responsiveness (82). No language loss or regression noted in development. No clinical elevations in behavior ratings from parents or teacher and no comorbid diagnoses. Small head (z = -1.64) and BMI suggestive of being overweight. Vision difficulties with correction. Pollen allergies. Intermittent constipation (undiagnosed). Chronic otitis media diagnosed by PCP at age

5. Surgery on release tendons and ligaments in right foot. Dysmorphology assessment indicates nonspecific dysmorphic features with microcephaly but no evidence of known syndrome. Abnormal hair growth, ear structure, nose size, face size, philtrum, mouth, lips, fingers, fingernails, and feet noted upon exam.

Patient ID: 12933.p1

Event: *de novo SETBP1* truncating, *de novo MYO7B* missense, *de novo OR10Z1* missense

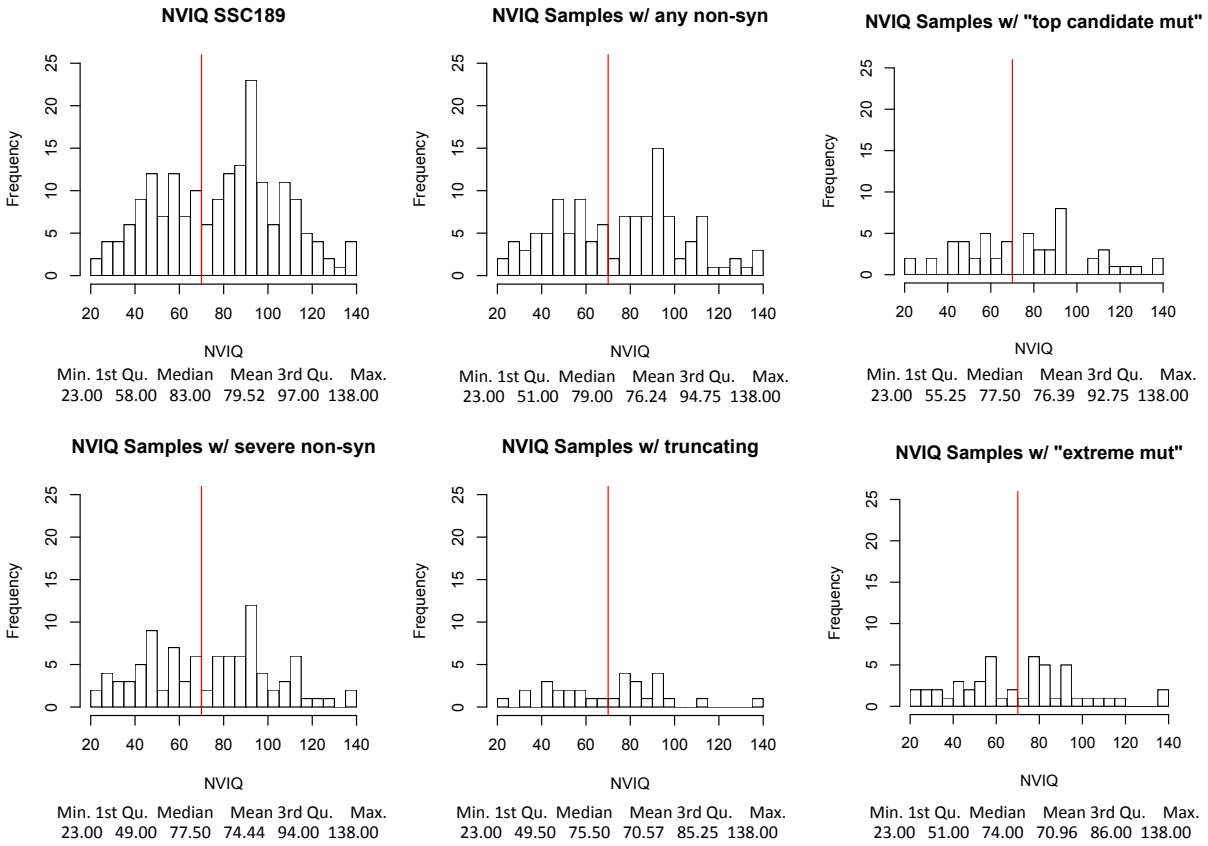
Summary: Patient is a 120-month-old non-Hispanic white male diagnosed with autism. Very low VIQ (44) and NVIQ (41) and low adaptive behavior skills (68). Clinical range elevations in social responsiveness (85). No language loss or regression noted in development. Borderline and clinical elevations in anxious/depressed, attention deficit, aggression, internalizing, affective problems, oppositional problems, and externalizing behavior with no comorbid diagnoses. Normative head circumference and BMI suggestive of being underweight. Vision difficulties with correction. Food allergies diagnosed by PCP at 4 months. Intermittent problems with vomiting diagnosed at 5 years old. Chronic acid reflux diagnosed at 7 years of age. Excessive clumsiness and coordination problems suspected beginning at age 5. Surgery at 1.1 years for undescended testicle. Adenoids removed at 7 years. Dysmorphology assessment indicates nonspecific dysmorphic features without microcephaly. Abnormal ear structure, nose size, face size, teeth, hands, fingers, thumbs, and fingernails noted upon exam.

Patient ID: 11834.p1

Event: inherited 16p12 duplication

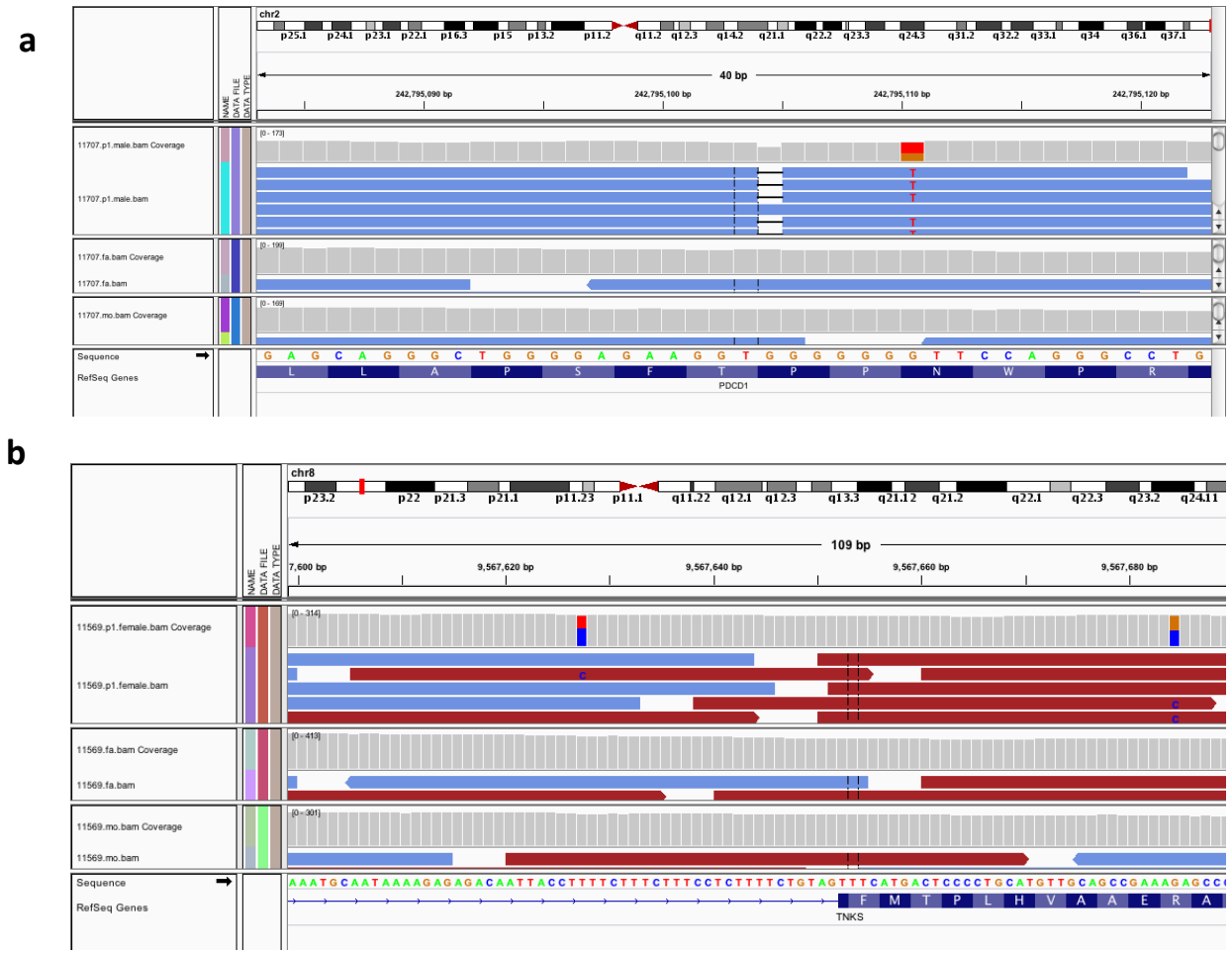
Summary: Patient is a 126-month-old non-Hispanic white male diagnosed with autism. Very low VIQ (43) and normative NVIQ (93) with very low adaptive behavior skills (57). Elevations in

social responsiveness (75) with no word loss or regression in early development. Borderline elevations in anxiety problems with no comorbid diagnoses. Large head (z = 2.29) and normative BMI scores. Diagnosed with Tourette/tics at age 7. Diagnosed with roseola at age 1. No report of congenital anomalies.



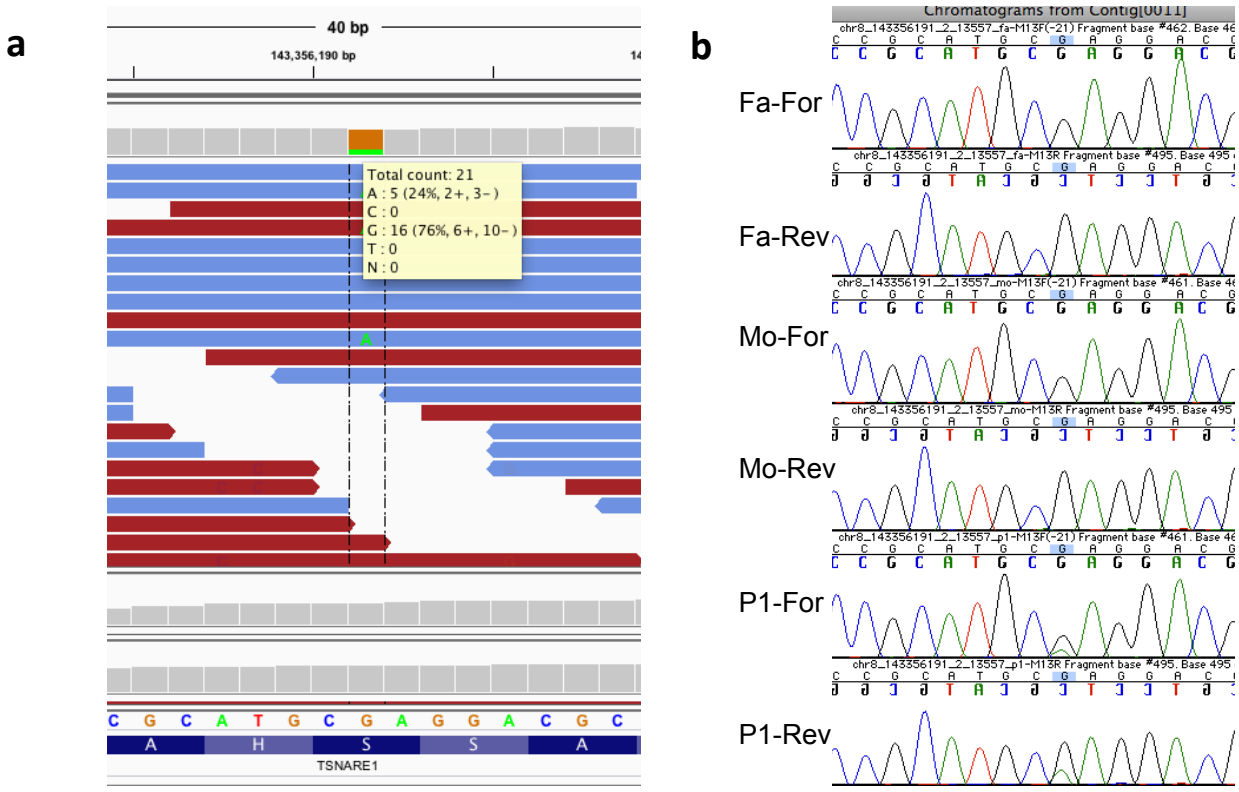
Supplementary Figure 1. Distribution of nonverbal intelligence quotient (NVIQ) of the SSC189 sample based on different mutation groupings.

Histograms in each panel show the distribution of samples based on those having one or more event fitting each mutational category. Initial distribution was approximately bimodal. Summary statistics for each distribution are listed below. Red line indicates NVIQ of 70, the general threshold of intellectual disability.



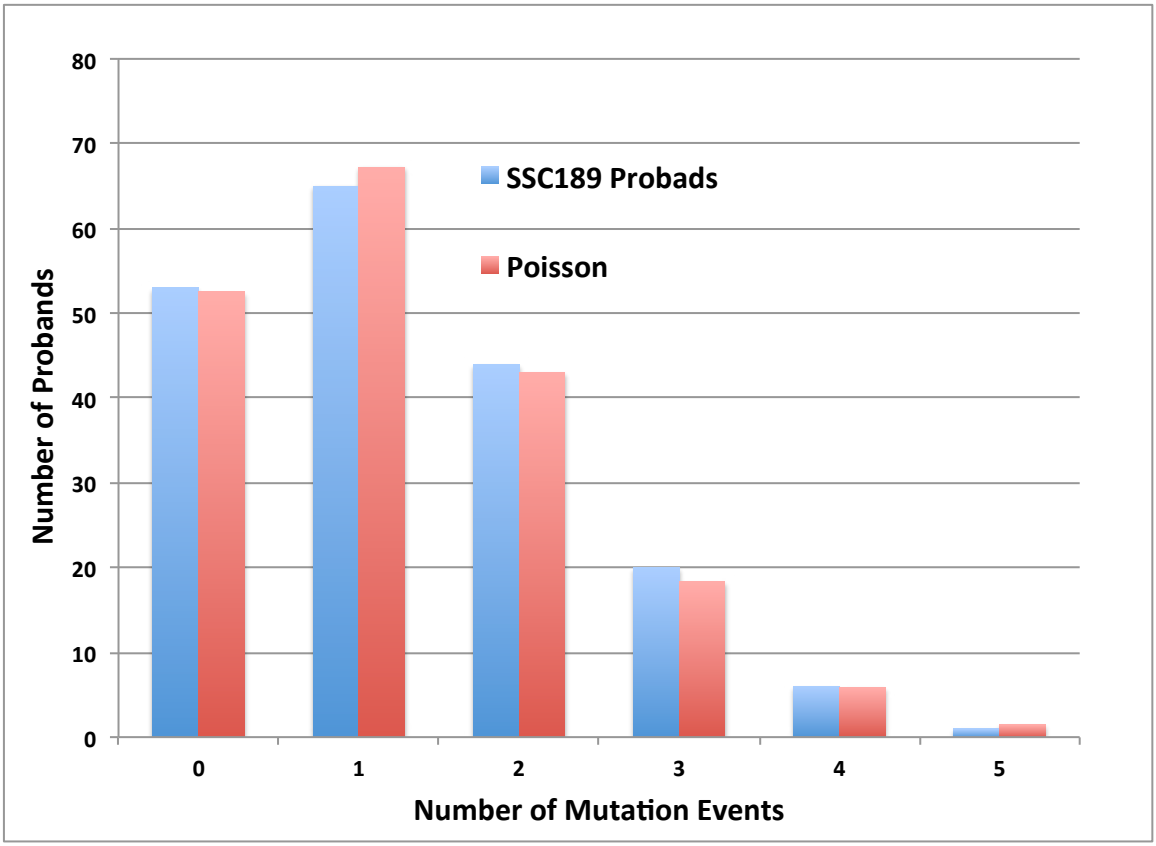
Supplementary Figure 2. Brower views showing complex *de novo* mutation events.

a, Proband reads show deletion of a G base and G/T substitution (Top), neither event is present in the father (middle) or mother (bottom) tracks. **b**, Proband reads show an exonic G/C substitution and intronic T/C substitution (Top), neither event is present in the father (middle) or mother (bottom) tracks.



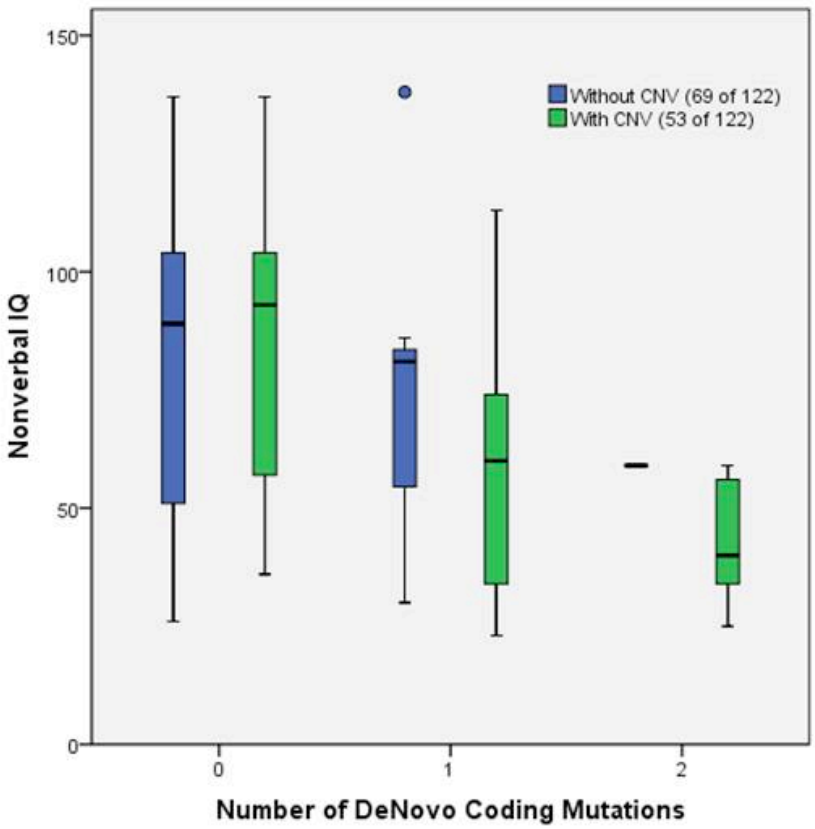
Supplementary Figure 3. Confirmed event showing weak allele signature.

a, Proband reads show G/A substitution at 24% frequency (Top), event is present in the father (middle) or mother (bottom) tracks. **b**, Sanger traces in both forward (For) and reverse (Rev) confirm event and show reduced signal suggesting somatic mosaicism.



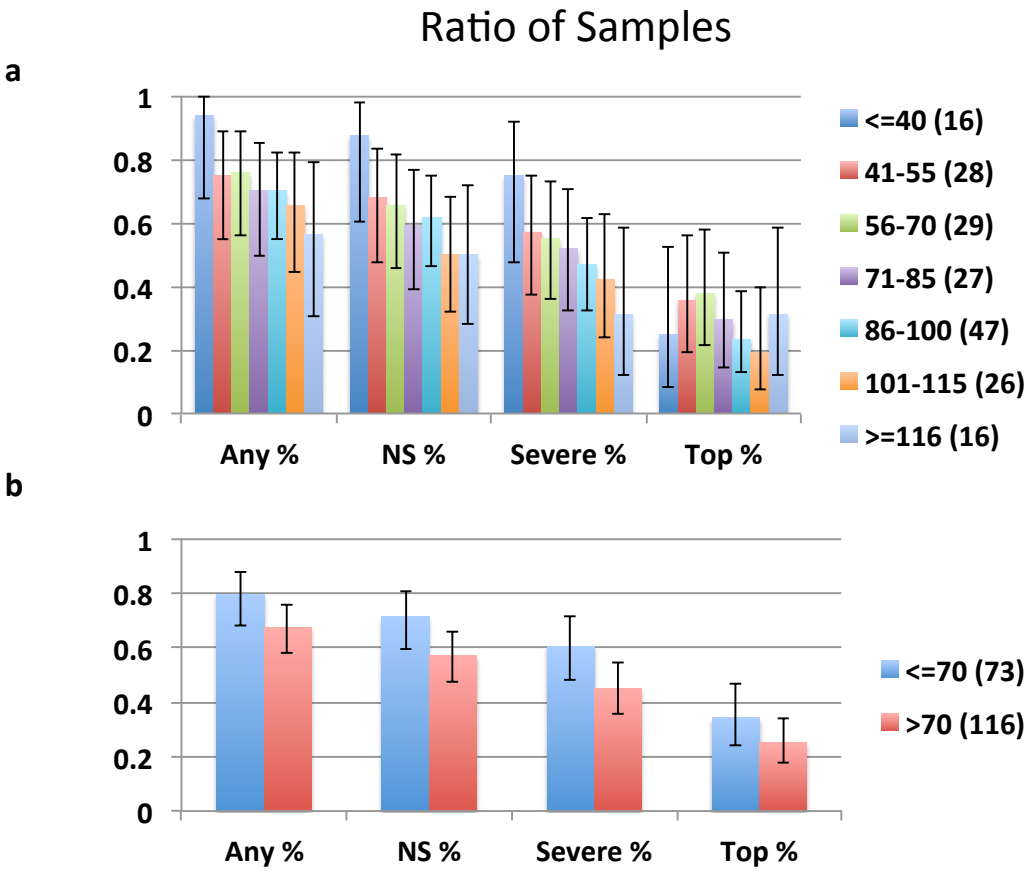
Supplementary Figure 4. Observed number of mutation events fits the expected Poisson distribution.

We calculated the expected counts of mutations per person from the Poisson distribution based on the observed trio mutation rate of 1.28. The observed number of counts per probands matches closely to this distribution.



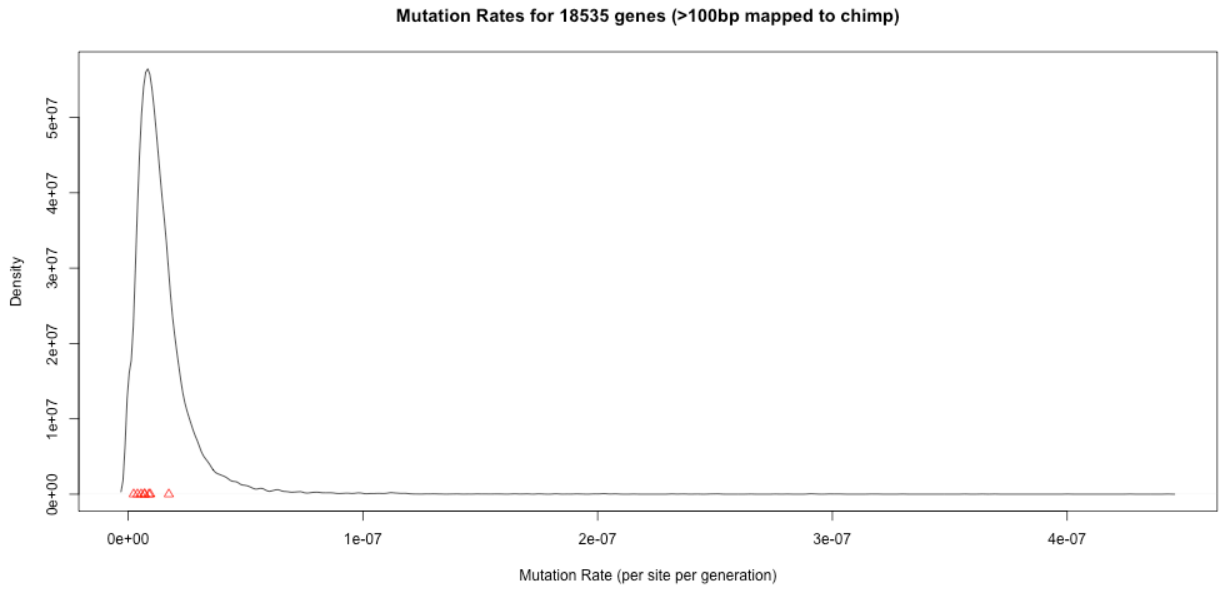
Supplementary Figure 5. Multivariate analysis to examine effect of number of "extreme" *de novo* coding mutations and the presence of a CNV.

Extreme mutations (n = 62) were defined as *de novo* protein-truncating intersections with known OMIM and ASD candidate genes and CNVs predicted to be gene breaking and pathogenic. Boxplots show the samples with and without a CNV, either *de novo* or rare inherited (**Supplementary Discussion**). We observed a significant decrease in NVIQ with increased numbers of events ($F(2,116) = 5.45$, $p<.01$, partial $\eta^2 = 0.09$), but not in VIQ ($F(2,116) = 1.13$, p = ns, partial $\eta^2 = 0.02$). This result in NVIQ was strengthened, but not exclusively driven, by the presence of CNVs ($F(2,116) = 0.97$, p = ns, partial $\eta^2 = 0.02$); there was no main effect of strictly having a CNV on cognitive ability ($F(2,116) = 0.71$, p = ns, partial $\eta^2 = 0.006$).



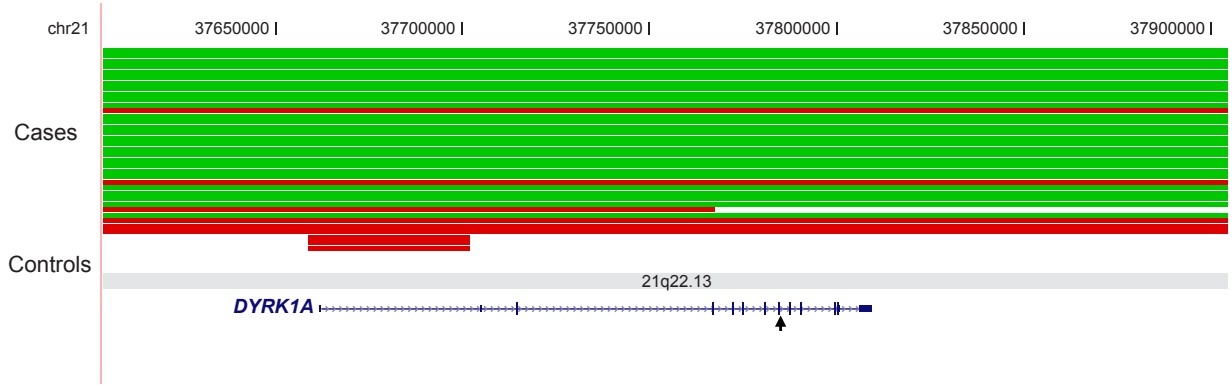
Supplementary Figure 6. Ratio of samples with various mutation types binned by NVIQ.

The proportion of individuals within various NVIQ bins with 1+ event across "disruptive" classification schemes: any event, any nonsynonymous event, any severe nonsynonymous event, and our "top candidate" list (**Table 1**). **a** Grouped by IQ standard deviations. We observed a nonsignificant trend by Fisher's exact test (lower IQ → higher probability of 1+ *de novo* event) for any event ($p = 0.096$), any nonsynonymous event ($p = 0.064$), and any severe nonsynonymous event ($p = 0.052$), but conflicting results for top candidates ($p = 0.19$). **b** Grouped by high (>70) and low (<=70) to increase power. Strongest p-value 0.032, severe nonsynonymous, again suggesting a nonsignificant trend. Error bars are 95% confidence intervals.



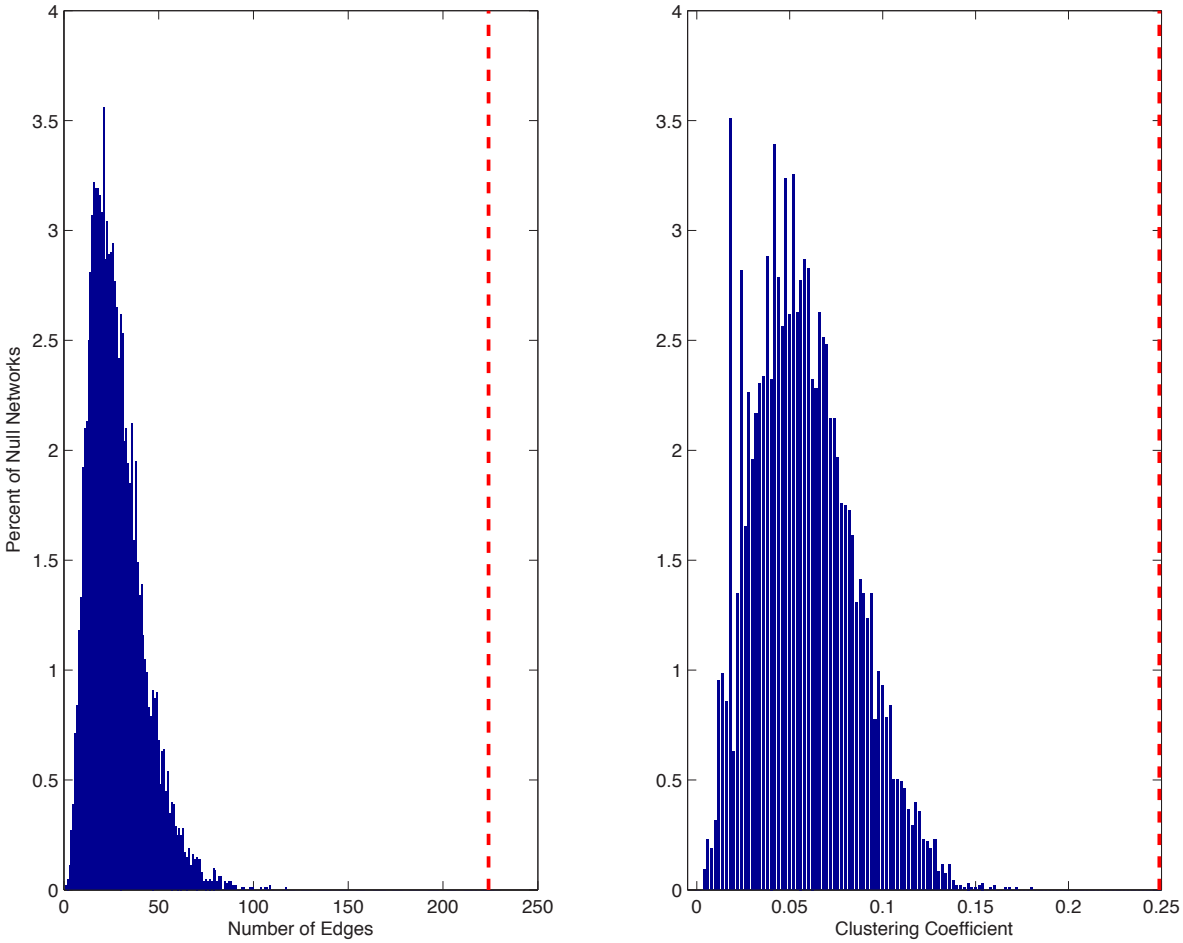
Supplementary Figure 7. Distribution of locus specific mutation rates bases on human-chimp comparisons.

Red triangles represent *CHD8*: 3.95E-09, *NTNG1*: 2.34E-09, *LAMC3*: 1.73E-08, *SCN1A*: 8.83E-09, *GRIN2B*: 6.94E-09, *FOXP2*: 7.01E-09, *FOXP1*: 5.51E-09, and *GRIN2A*: 9.38E-09.



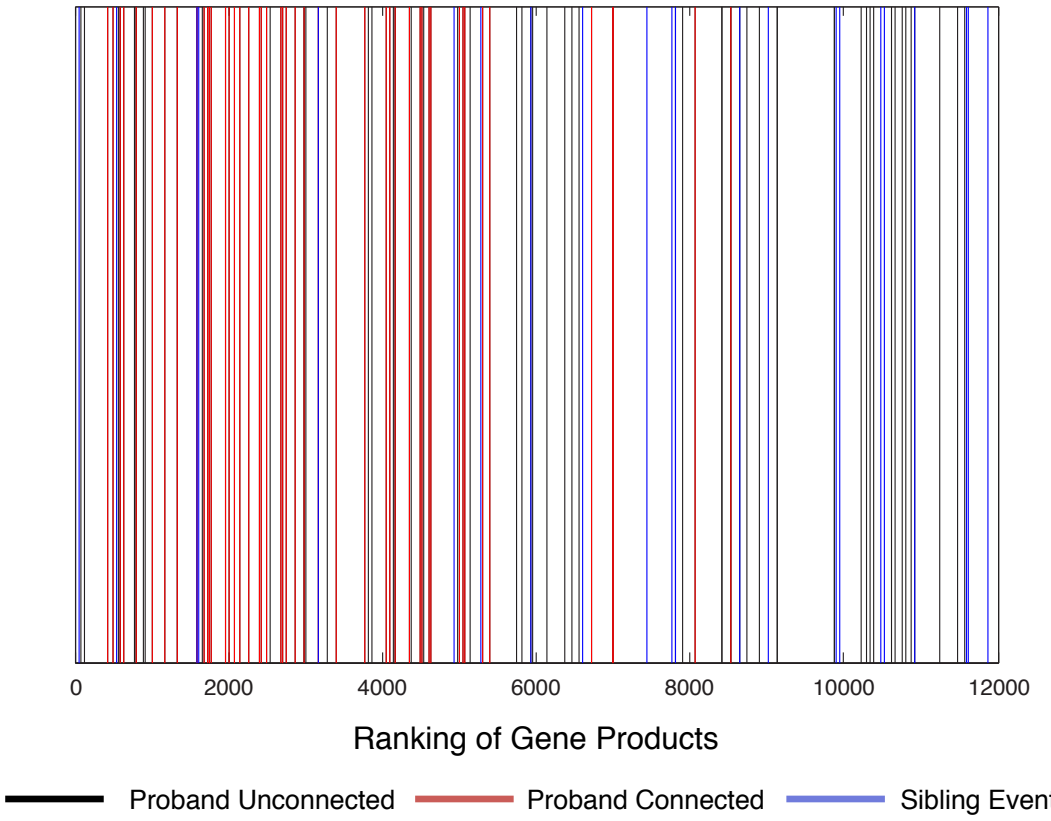
Supplementary Figure 8. *DYRK1A* falls in a Down Syndrome critical region disrupted by CNVs.

Each red (deletion) and green (duplication) line represents an identified CNV in cases (solid lines) versus controls (dashed lines), with arrowheads showing point mutations.



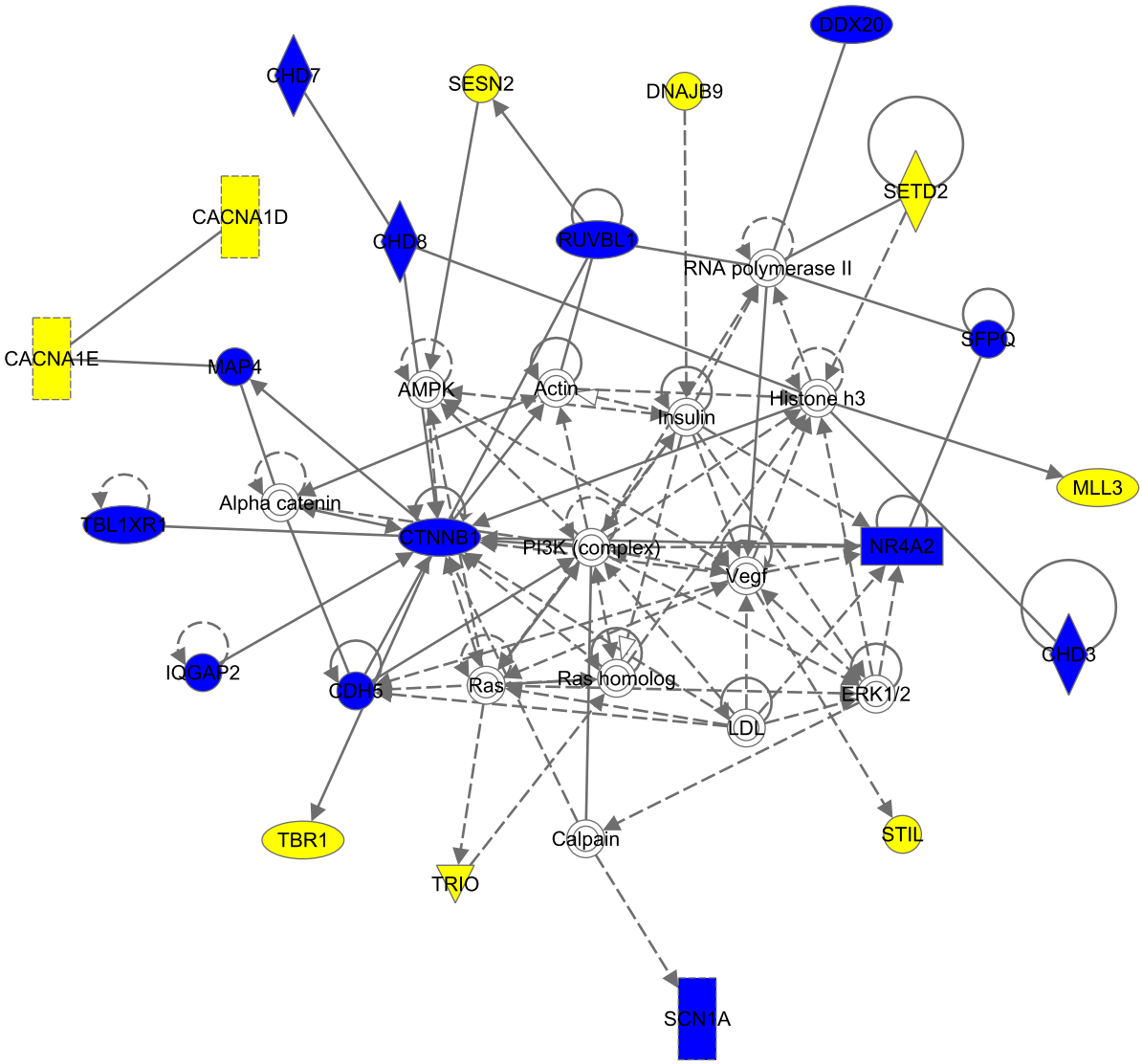
Supplementary Figure 9. Histograms of Network statistics for 10,000 simulated null networks.

Left: Number of edges in the network. Right: Clustering coefficient of the network. Red dotted line indicates the corresponding value in the experimentally determined network.



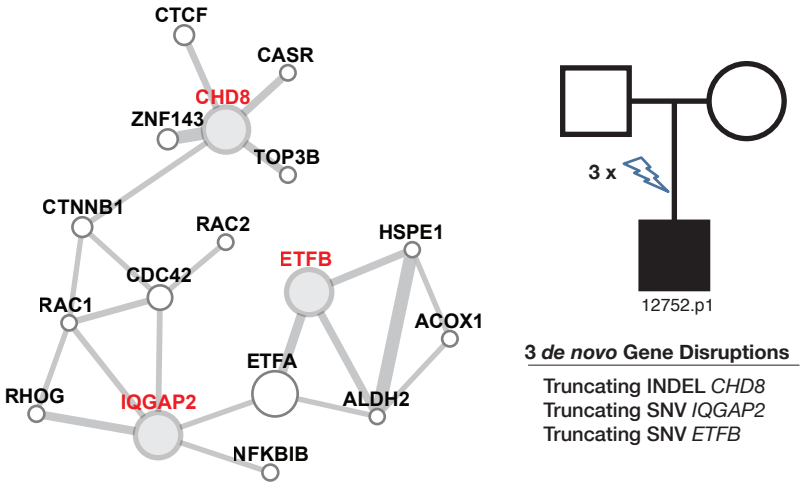
Supplementary Figure 10. Protein-protein interaction network based prioritization of 126 gene products with severe mutations.

X-axis represents the ranking of gene products from GeneMANIA PPI database using ASD associated gene products from Betancaur et al. as a seed. The red lines represents the gene products (49) that are in the largest connected component of the PPI network generated using the proband severe disruptive *de novo* events, gray lines represents the gene products not in the connected component, and the blue lines represent the gene products with severe *de novo* mutations in the unaffected siblings. The gene products of the connected component ranks significantly higher compared to all other gene products (Mann-Whitney U one-sided, $p < 1.6E-08$) whereas the unconnected gene products do not (Mann-Whitney U, one-sided $p < 0.28$). Similarly, the siblings events compared to all other gene products do not show significant rankings (Mann-Whitney U, one-sided $p < 0.26$).



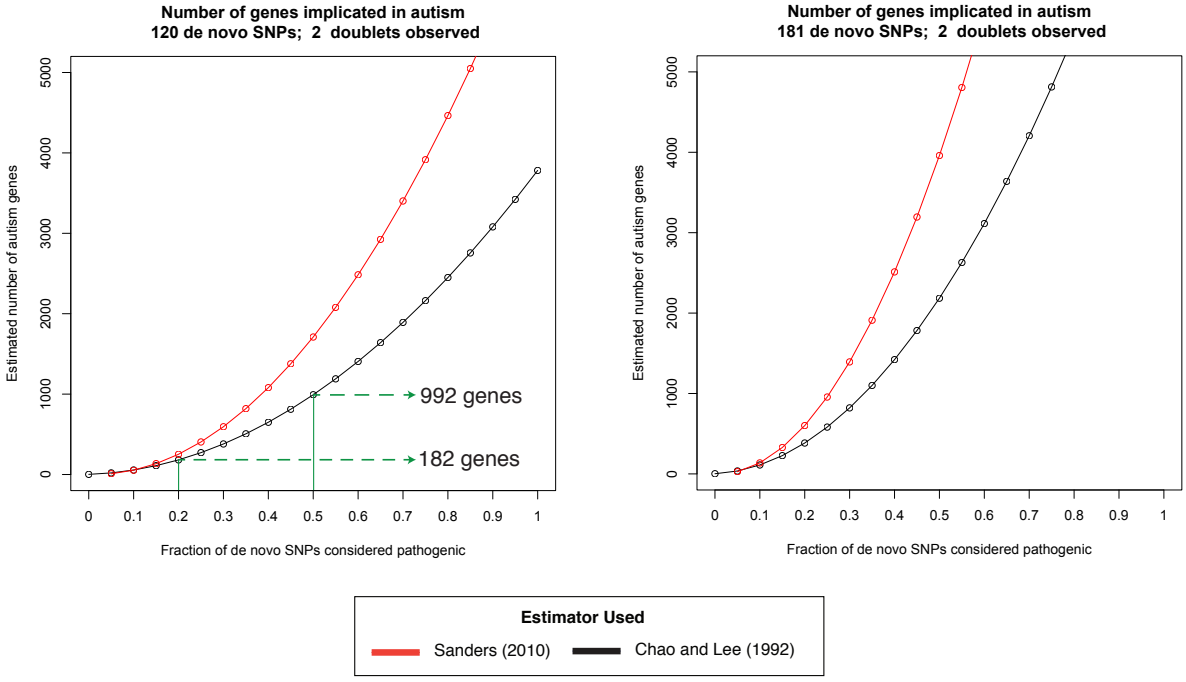
Supplementary Figure 11. Top interaction network from IPA analysis of 126 genes with severe mutations.

Displayed is the highest scoring network from IPA analysis. Solid lines represent direct interactions while dashed lines indicated indirect connections. Genes not found in the PPI connected component are marked in yellow, while those in the PPI connected component are marked in blue.



Supplementary Figure 12. *De novo* mutations in 12752.p1.

GeneMANIA[4] view of three *de novo* truncating mutations (red labels) which encode proteins that are part of a beta-catenin linked network. The proband is macrocephalic (z = 2.4) with normal cognitive ability (VIQ = 90, NVIQ = 93) but has adaptive behavior deficits (Vineland Standard Score = 59) with significant social impairments. (**Supplementary Discussion**).



Supplementary Figure 13. Estimating the number of genes contributing to sporadic autism pathogenicity via recurrent *de novo* mutation.

Left: Estimate based on 120 *de novo* mutations especially likely to be pathogenic (including both observed doubletons) based on GERP and Grantham score. Right: Estimate based on all *de novo* nonsynonymous events. Two different estimators for the "unseen species problem" were used.

Supplementary Table 1. Summary of sequenced families, including sex, parental age, NVIQ, CNV pre-screening, trio bases screened, and point mutations.

See attached Excel document

Supplementary Table 2. Summary of Exome Sequencing Results from 209 ASD Families

SNV	Type	Total	Average	Silent	Missense	Nonsense or Read-Through	Splice	Ti/Tv	% CpG Ti
SSC189 Pro	all	3,513,050	18,588	1,859,735	1,631,320	16,449	5,546	3.27	20.9
	rare	32,028	169	10,682	20,515	581	250	2.87	31.1
	DN	225	1.19	61	145	16	3	2.69	36.0
SSC189 Sib (31)[&]	*DN*	29	0.94	9	19	1	0	3.14	41.4
Pilot Pro (20)	*DN*	17	0.85	7	9	0	1	7.50	41.1
Pilot Sib (19)	*DN*	21	1.11	7	12	2	0	1.63	38.1

Indels	Type	Total	Average	3n Indels	Truncating Indels	Splice
SSC189 Pro	all	42,929	227	18,817	23,270	842
	rare	806	4.26	222	561	23
	DN	17	0.09	2	15	0
SSC189 Sib (31)	*DN*	0	0	0	0	0
Pilot Pro (20)	*DN*	1	0.05	0	1	0
Pilot Sib (19)	*DN*	0	0	0	0	0

Estimated Mutation Rates	All Events	Screened Bases*	All Rate[♭]	Sub Rate[♭♯]
SSC189 Pro	242	11,144,644,963	2.17 (1.90-2.46)	1.94 (1.68-2.21)
SSC189 Sib (31)	29	1,838,730,129	1.57 (1.05-2.26)	1.52 (1.01-2.20)
Pilot Pro (20)	18	937,498,416	1.92 (1.14-3.04)	1.81 (1.05-2.90)
Pilot Sib (19)	21	891,825,463	2.35 (1.45-3.59)	2.24 (1.36-3.46)

[&]Number of children. *Count of all bases screened in child (minimum 8X), i.e. concordant in each member of the trio. [♭]Mutations/base/generation x10^-8 with 95% Confidence intervals. [♯]Substitutions only, excludes indels and possible somatic mosaics. Pro = proband, Sib = unaffected sibling, *DN = de novo*, SSC = Simons Simplex Collection

Supplementary Table 3. All 242 *de novo* point mutations found in 189 trios.

See attached Excel document

Supplementary Table 4. Comparison of mutation rates between O'Roak et al. and Sanders et al.

Site/Type	# of Trios	Bases Screened	Total De novo	Substitutions	Indels	Mosaic events	Combined Rate and 95% CI ($x10^{-8}$)	Strict Substitution Rate and 95% CI ($x10^{-8}$)
UW-189 Probands	189	11,144,644,963	242	216	17	9	2.17 (1.90-2.46)	1.94 (1.68-2.21)
UW-31 Matched Probands	31	1,830,218,983	42	39	1	2	2.29 (1.65-3.10)	2.13 (1.51-2.91)
UW-31 Matched Siblings	31	1,838,730,129	29	28	0	1	1.57 (1.05-2.26)	1.52 (1.01-2.20)
UW-Pilot Probands	20	937,498,416	18	17	1	0	1.92 (1.14-3.04)	1.81 (1.05-2.90)
UW-Pilot Matched Probands	19	890,665,738	18	17	1	0	2.02 (1.20-3.19)	1.91 (1.11-3.05)
UW-Pilot Matched Sibs	19	891,825,463	21	20	0	1	2.35 (1.45-3.59)	2.24 (1.36-3.46)
UW-All Probands	**209**	**12,082,143,379**	**260**	**233**	**18**	**9**	**2.15 (1.90-2.43)**	**1.93 (1.69-2.19)**
Yale-Quartet Probands	200	9,718,659,190	156	153	3	0	1.61 (1.34-1.87)	1.57 (1.31-1.84)
Yale-Quartet Siblings	200	9,718,659,190	124	124	0	0	1.28 (1.05-1.50)	1.28 (1.05-1.50)
Yale-Trio Probands	24	1,082,156,674	15	15	0	0	1.39 (0.67-2.10)	1.39 (0.67-2.10)
Yale-All Probands	**225**	**10,800,815,864**	**171**	**168**	**3**	**0**	**1.58 (1.33-1.83)**	**1.56 (1.31-1.80)**

UW: Variant calling threshold was a minimum of 8x in each member of a trio. Bases screened were calculated based on trio concordant positions at 8x (n) and converting to diploid bases (2n), adjusting for sex chromosomes. Probands and siblings were calculated separately as trio units. Observed mutation rate was calculated by dividing the total number of events by total number of bases. The exact 95% Poisson confidence intervals were generated from the observed counts and then dividend by the total number of bases to get the rate confidence intervals.

Yale: The variant calling threshold was a minimum of 20x unique reads in each member of the quartet and a minimum of 8x unique non-reference reads in the child. Bases screened were estimated by assessing the number of nucleotides in each family with a minimum of 20x unique reads in each member of the quartet and converting to diploid bases (2n). Observed mutation rates were calculated by dividing the total events per sample by the number of nucleotides analyzed per sample and averaging across individuals. The 95% confidence intervals were calculated from the variance of this measure.

Supplementary Table 5. *De novo* events identified in 50 unaffected siblings and 20 pilot probands.

See attached Excel document

Supplementary Table 6. 70 rare inherited and 6 *de novo* CNVs identified in 122 trios.

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
chr20	6706891	8271234	11013.p1	Gain	Inherited	Mother	BMP2 (Gene Broken), HAO1, TMX4, PLCB1 (Gene Broken)
chr2	197997071	198254315	11023.p1	Gain	Inherited	Mother	SF3B1 (Gene Broken), COQ10B, HSPD1, HSPE1, MOBKL3, RFTN2
chr2	208742960	208763173	11023.p1	Loss	Inherited	Mother	C2orf80 (Gene Broken)
chr2	33593707	36437270	11064.p1	Gain	Inherited	Mother	RASGRP3 (Gene Broken), FAM98A, MYADML, CRIM1 (Gene Broken)
chr13	49022622	49083205	11083.p1	Gain	Inherited	Father	RCBTB1 (Gene Broken)
chr4	47538	117452	11093.p1	Gain	Inherited	Mother	ZNF595 (Gene Broken), ZNF718 (Gene Larger Than CNV)
chr8	13295432	15139503	11141.p1	Gain	Inherited	Mother	DLC1 (Gene Broken), C8orf48, SGCZ (Gene Broken), MIR383
chr19	48612452	48651954	11141.p1	Loss	Inherited	Mother	TEX101 (Gene Broken)
chr16	79736150	79748195	11184.p1	Loss	Inherited	Father	PKD1L2 (Gene Larger Than CNV)
chr4	108066404	109130669	11190.p1	Gain	Inherited	Father	DKK2 (Gene Broken), PAPSS1, SGMS2, CYP2U1, HADH (Gene Broken)
chr4	5781934	5823956	11224.p1	Gain	Inherited	Father	EVC (Gene Larger Than CNV)
chr7	33097353	33153804	11346.p1	Gain	Inherited	Mother	RP9, BBS9 (Gene Broken)
chr5	157006525	157051157	11375.p1	Loss	Inherited	Father	SOX30 (Gene Broken), C5orf52
chr7	11117201	12440046	11398.p1	Gain	Inherited	Father	PHF14 (Gene Broken), THSD7A, TMEM106B, VWDE

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
chr12	43879949	43967314	11452.p1	Loss	Inherited	Mother	PLEKHA9 (Gene Broken), ANO6 (Gene Broken)
chr6	88374109	88424279	11459.p1	Loss	Inherited	Father	ORC3L (Gene Larger Than CNV)
chr1	173697478	174026214	11469.p1	Gain	Inherited	Father	TNR (Gene Broken)
chr5	112931249	113726857	11469.p1	Gain	Inherited	Father	YTHDC2 (Gene Broken), KCNN2 (Gene Broken)
chr6	26077937	26393662	11480.p1	Gain	Inherited	Father	TRIM38 (Gene Broken), HIST1H1A, HIST1H3A, HIST1H4A, HIST1H4B, HIST1H3B, HIST1H2AB, HIST1H2BB, HIST1H3C, HIST1H1C, HFE, HIST1H4C, HIST1H1T, HIST1H2BC, HIST1H2AC, HIST1H1E, HIST1H2BD, HIST1H2BE, HIST1H4D, HIST1H3D, HIST1H2AD, HIST1H2BF, HIST1H4E, HIST1H2BG, HIST1H2AE, HIST1H3E, HIST1H1D, HIST1H4F, HIST1H4G, HIST1H3F, HIST1H2BH, HIST1H3G, HIST1H2BI, HIST1H4H (Gene Broken)
chr8	15992606	16066256	11556.p1	Loss	Inherited	Father	MSR1 (Gene Broken)
chr3	147531173	147649939	11653.p1	Gain	Inherited	Father	PLSCR2 (Gene Broken)
chr2	110167952	110510396	11660.p1	Loss	Inherited	Mother	MIR4267, MALL, NPHP1, NCRNA00116
chr7	16805611	17800441	11696.p1	Gain	Inherited	Father	AGR2 (Gene Broken), AGR3, AHR, SNX13 (Gene Broken)

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
chr3	37265222	37416340	11696.p1	Loss	*de novo*	NA	GOLGA4, C3orf35 (Gene Broken)
chr1	205383785	205599637	11707.p1	Gain	Inherited	Father	C4BPA (Gene Broken), CD55 (Gene Broken)
chr9	28181261	28338013	11707.p1	Loss	Inherited	Mother	LINGO2 (Gene Larger Than CNV)
chr17	3946651	4368839	11707.p1	Gain	Inherited	Father	ZZEF1 (Gene Broken), CYB5D2, ANKFY1, UBE2G1, SPNS3, SPNS2 (Gene Broken)
chr2	160248507	160313660	11711.p1	Gain	Inherited	Mother	MARCH7 (Gene Broken)
chr10	67942427	68177427	11711.p1	Loss	Inherited	Father	CTNNA3 (Gene Larger Than CNV)
chr4	135140571	135406410	11715.p1	Loss	Inherited	Mother	PABPC4L
chr7	48259354	48398102	11722.p1	Loss	Inherited	Mother	ABCA13 (Gene Larger Than CNV)
chr8	30067949	30170383	11722.p1	Gain	Inherited	Father	LEPROTL1, MBOAT4, DCTN6
chr19	62680865	62710992	11753.p1	Gain	Inherited	Father	ZNF419, ZNF773 (Gene Broken)
chr16	21675903	22357384	11834.p1	Gain	Inherited	Father	OTOA (Gene Broken), RRN3P1, LOC100190986, UQCRC2, PDZD9, C16orf52, VWA3A, EEF2K, POLR3E, CDR2, RRN3P3, LOC641298 (Gene Broken)
chr7	153588034	154254473	11843.p1	Loss	Inherited	Mother	DPP6 (Gene Larger Than CNV)
chr12	7882951	8015652	11843.p1	Loss	Inherited	Father	SLC2A14 (Gene Broken), SLC2A3
chr2	86145907	86418710	11895.p1	Gain	Inherited	Father	POLR1A (Gene Broken), PTCD3, SNORD94, IMMT, MRPL35, REEP1 (Gene Broken)
chr15	28712984	30303265	11928.p1	Gain	*de novo*	NA	ARHGAP11B (Gene Broken), FAN1,

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
							MTMR10, TRPM1, MIR211, KLF13, LOC283711, OTUD7A, CHRNA7
chr6	162692702	162951722	11947.p1	Gain	Inherited	Father	PARK2 (Gene Larger Than CNV)
chr22	39048803	39223310	11947.p1	Gain	Inherited	Father	TNRC6B (Gene Broken), ADSL, SGSM3, MKL1 (Gene Broken)
chr11	14831730	14864039	11964.p1	Gain	Inherited	Father	PDE3B (Gene Broken), CYP2R1 (Gene Broken)
chr16	82990535	83030397	11964.p1	Loss	Inherited	Mother	ATP2C2 (Gene Larger Than CNV)
chr10	133426828	134361413	12118.p1	Gain	Inherited	Father	PPP2R2D, BNIP3, JAKMIP3, DPYSL4, STK32C, LRRC27, PWWP2B, C10orf91, INPP5A (Gene Broken)
chr5	112941833	112974949	12130.p1	Gain	Inherited	Mother	YTHDC2 (Gene Broken)
chr8	15992606	16066256	12130.p1	Loss	Inherited	Mother	MSR1 (Gene Broken)
chr6	107599923	107887182	12212.p1	Loss	Inherited	Father	PDSS2 (Gene Larger Than CNV)
chr11	31133684	31384778	12430.p1	Loss	Inherited	Mother	DCDC1, DNAJC24 (Gene Broken)
chr12	110659017	110799706	12581.p1	Gain	Inherited	Mother	ACAD10 (Gene Broken), ALDH2, C12orf47, MAPKAPK5 (Gene Broken)
chr9	139800210	140131086	12581.p1	Loss	*de novo*	NA	EHMT1 (Gene Broken), MIR602, CACNA1B
chr1	183364423	183402407	12667.p1	Gain	Inherited	Mother	C1orf25 (Gene Broken), C1orf26 (Gene Broken)
chr18	37874638	37962267	12667.p1	Gain	Inherited	Mother	PIK3C3 (Gene Broken)
chr11	50035201	50669978	12810.p1	Gain	Inherited	Father	LOC441601, LOC646813
chr22	30835976	31086819	12810.p1	Gain	Inherited	Father	SLC5A1 (Gene

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
							Broken), C22orf42, RFPL2, SLC5A4, RFPL3 (Gene Broken), RFPL3S (Gene Broken)
chr3	28443079	28490738	13008.p1	Loss	Inherited	Father	ZCWPW2 (Gene Larger Than CNV)
chr12	180014	645460	13008.p1	Gain	Inherited	Mother	SLC6A12 (Gene Broken), SLC6A13, KDM5A, CCDC77, B4GALNT3, NINJ2
chr3	143305311	143566711	13335.p1	Gain	Inherited	Father	TFDP2 (Gene Broken), GK5, XRN1 (Gene Broken)
chr17	613719	644926	13335.p1	Loss	Inherited	Father	GLOD4 (Gene Broken), RNMTL1
chr16	29502984	30107398	13335.p1	Gain	*de novo*	NA	SLC7A5P1, SPN, QPRT, C16orf54, MAZ, PRRT2, C16orf53, MVP, CDIPT, LOC440356, SEZ6L2, ASPHD1, KCTD13, TMEM219, TAOK2, HIRIP3, INO80E, DOC2A, C16orf92, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, GDPD3, MAPK3, LOC100271831, CORO1A (Gene Broken)
chr17	69851956	70220158	13409.p1	Gain	Inherited	Father	KIF19 (Gene Broken), BTBD17, GPR142, GPRC5C, CD300A, CD300LB, CD300C, CD300LD, C17orf77, CD300E, RAB37 (Gene

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
							Broken), CD300LF (Gene Broken)
chr6	57019780	57062509	13415.p1	Loss	Inherited	Father	KIAA1586 (Gene Broken)
chr15	55430140	55596476	13415.p1	Gain	Inherited	Mother	CGNL1 (Gene Broken)
chr10	67981151	68085796	13494.p1	Loss	Inherited	Mother	CTNNA3 (Gene Larger Than CNV)
chr18	75004789	75209184	13494.p1	Loss	Inherited	Father	ATP9B (Gene Larger Than CNV)
chr14	67088466	67343145	13530.p1	Gain	Inherited	Father	PLEKHH1 (Gene Broken), PIGH, ARG2, VTI1B, RDH11, RDH12, ZFYVE26 (Gene Broken)
chr4	91076267	91171447	13533.p1	Loss	Inherited	Father	MMRN1 (Gene Broken)
chr14	73586157	73611473	13533.p1	Loss	Inherited	Father	C14orf45 (Gene Broken), ALDH6A1 (Gene Broken)
chr10	67724488	67879503	13557.p1	Loss	Inherited	Mother	CTNNA3 (Gene Larger Than CNV)
chr11	56599848	59990367	13726.p1	Loss	*de novo*	NA	LRRC55, APLNR, TNKS1BP1, SSRP1, P2RX3, PRG3, PRG2, SLC43A3, RTN4RL2, SLC43A1, TIMM10, SMTNL1, UBE2L6, SERPING1, MIR130A, YPEL4, CLP1, ZDHHC5, MED19, TMX2, C11orf31, BTBD18, CTNND1, OR9Q1, OR6Q1, OR9I1, OR9Q2, OR1S2, OR1S1, OR10Q1, OR10W1, OR5B17, OR5B3, OR5B2,

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
							OR5B12, OR5B21, LPXN, ZFP91, ZFP91-CNTF, CNTF, GLYAT, GLYATL2, LOC283194, GLYATL1, FAM111B, FAM111A, DTX4, MPEG1, OR5AN1, OR5A2, OR5A1, OR4D6, OR4D10, OR4D11, OR4D9, OSBP, MIR3162, PATL1, OR10V1, STX3, MRPL16, GIF, TCN1, PLAC1L, MS4A3, MS4A2, MS4A6A, MS4A4A, MS4A6E, MS4A7, MS4A14, MS4A5, MS4A1 (Gene Broken)
chr17	10287416	10297580	13733.p1	Loss	Inherited	Mother	MYH4 (Gene Larger Than CNV)
chr8	102800655	103493638	13741.p1	Gain	Inherited	Father	NCALD (Gene Broken), RRM2B, UBR5 (Gene Broken)
chr12	19361460	19461747	13793.p1	Gain	Inherited	Mother	PLEKHA5 (Gene Broken)
chr15	55423402	55596476	13812.p1	Gain	Inherited	Father	CGNL1 (Gene Broken)
chr19	62524033	62624661	13815.p1	Loss	Inherited	Mother	ZNF543 (Gene Broken), ZNF304, TRAPPC2P1, ZNF547, ZNF548, ZNF17 (Gene Broken)
chr16	74808505	75067064	13815.p1	Loss	*de novo*	NA	TERF2IP (Gene Broken), CNTNAP4 (Gene Broken)

Chr (hg18)	Start	End	Family ID	CNV	Type	Inheritance	Genes
chr10	3113861	3204971	13844.p1	Loss	Inherited	Mother	PFKP (Gene Broken), PITRM1 (Gene Broken)
chr21	34648298	34909180	13844.p1	Gain	Inherited	Mother	KCNE2, FAM165B, KCNE1, RCAN1 (Gene Broken)

Supplementary Table 7. Expanded top *de novo* ASD risk contributing mutations*

Proband	NVIQ	Candidate Gene	AA change	GERP	Gran-tham	Location (hg19)	Chrom	Position	Ref	Alt
12225.p1	89	*ABCA2*	p.VAL1845MET	3.4	21	9q34	9	139906388	C	T
11653.p1	44	*ADCY5*	p.ARG603CYS	3.74	180	3q13.2-q21	3	123046605	G	A
12130.p1	55	*ADNP*	frameshift indel			20q13.13	20	49510027	*	-TT
11224.p1	112	*AP3B2*	p.ARG435HIS	4.81	29	15q	15	83346497	C	T
13447.p1	51	*ARID1B*	frameshift indel			6q25.3	6	157527664	*	-TGTT
13415.p1	48	*BRSK2*	3n indel			11p15.5	11	1466811	*	-AGA
14292.p1	49	*BRWD1*	frameshift indel			21q22.2	21	40568453	*	-T
11872.p1	65	*CACNA1D*	p.ALA769GLY	4.91	60	3p14.3	3	53764493	C	G
11773.p1	50	*CACNA1E*	p.GLY1209SER	4.96	56	1q25-q31	1	181708295	G	A
13606.p1	60	*CDC42BPB*	p.ARG764TERM	3.19		14q32.32	14	103434646	G	A
12086.p1	108	*CDH5*	p.ARG545TRP	4.9	101	16q22.1	16	66434715	C	T
12630.p1	115	*CHD3*	p.ARG1818TRP	2.97	101	17p13	17	7812028	C	T
13733.p1	68	*CHD7*	p.GLY996SER	5.48	56	8q12.2	8	61735090	G	A
13844.p1	34	*CHD8*	p.GLN959TERM	4.98		14q11.2	14	21871178	G	A
12752.p1	93	*CHD8*	frameshift indel			14q11.2	14	21861376	*	-CT
13415.p1	48	*CNOT4*	p.ASP48ASN	5.52	23	7q22-qter	7	135122938	C	T
12703.p1	58	*CTNNB1*	p.THR551MET	5.43	81	3p21	3	41275757	C	T
11452.p1	80	*CUL3*	p.GLU246TERM	5.51		2q36.2	2	225376218	C	A
11571.p1	94	*CUL5*	p.VAL355ILE	NA	29	11q22.3	11	107944174	G	A
13890.p1	42	*DYRK1A*	splice site	5.63		21q22.13	21	38865466	G	A
12741.p1	87	*EHD2*	p.ARG167CYS	2.55	180	19q13.3	19	48221860	C	T
11629.p1	67	*FBXO10*	p.GLU54LYS	4.25	56	9p13.1	9	37541606	C	T
13629.p1	63	*GPS1*	p.ARG492GLN	3.66	43	17q25.3	17	80014816	G	A
13757.p1	91	*GRINL1A*	3n indel			15q22.1	15	58001002	*	-AGA
11184.p1	94	*HDGFRP2*	p.GLU83LYS	4.77	56	19p13.3	19	4475539	G	A
11610.p1	138	*HDLBP*	p.ALA639SER	5.81	99	2q37.3	2	242186202	C	A
11872.p1	65	*KATNAL2*	splice site	5.48		18q21.1	18	44603833	G	C

12346.p1	77	*MBD5*	frameshift indel			2q23.2	2	149225965	*	-TC
11947.p1	33	*MDM2*	p.GLU433LYS/ p.TRP160TERM	3.59	56	12q13-q14	12	69233432	G	A
11148.p1	82	*MLL3*	p.TYR4691TERM	-6.76		7q36	7	151842339	G	T
12157.p1	91	*NLGN1*	p.HIS795TYR	5.55	83	3q26.32	3	173999004	C	T
11193.p1	138	*NOTCH3*	p.GLY1134ARG	3.63	125	19p13.2-p13.1	19	15290235	C	G
11172.p1	60	*NR4A2*	p.TYR275HIS	4.53	83	2q22-q23	2	157185876	A	G
11660.p1	60	*NTNG1*	p.THR135ILE	5.36	89	1p13.2-p13.1	1	107867061	C	T
12532.p1	110	*NTNG1*	p.TYR23CYS	3.97	194	1p13.2-p13.1	1	107691283	A	G
11093.p1	91	*OPRL1*	p.ARG157CYS	3.42	180	20q13.33	20	62729390	C	T
13793.p1	56	*PCDHB4*	p.ASP555HIS	3.76	81	5q31	5	140503243	G	C
11707.p1	23	*PDCD1*	frameshift indel			2q37.3	2	242795103	*	-G & K
12304.p1	83	*PSEN1*	p.THR421ILE	5.61	89	14q24.3	14	73685855	C	T
11390.p1	77	*PTEN*	p.THR167ASN	5.39	65	10q23	10	89711882	C	A
13629.p1	63	*PTPRK*	p.ARG784HIS	5.52	29	6q22.2-q22.3	6	128326372	C	T
13333.p1	69	*RGMA*	p.VAL379ILE	3.41	29	15q26.1	15	93588446	C	T
13222.p1	86	*RPS6KA3*	p.SER369TERM	4.32		Xp22.2-p22.1	X	20193403	G	C
11257.p1	128	*RUVBL1*	p.LEU365GLN	4.62	113	3q21	3	127806574	A	T
11843.p1	113	*SESN2*	p.ALA46THR	4.88	58	1p35.2	1	28595739	G	A
12933.p1	41	*SETBP1*	frameshift indel			18q21.1	18	42532021	*	+GG, -C
12565.p1	79	*SETD2*	frameshift indel			3p21.31	3	47098932	*	-T
12335.p1	47	*TBL1XR1*	p.LEU282PRO	5.43	98	3q26.33	3	176765107	A	G
11480.p1	41	*TBR1*	frameshift indel			2q24.2	2	162273322	*	-C
11569.p1	67	*TNKS*	p.ARG568THR	4.94	71	8p23.1	8	9567684	G	C
12621.p1	120	*TSC2*	p.ARG1580TRP	2.06	101	16p13.3	16	2136269	C	T
11291.p1	83	*TSPAN17*	p.SER75TERM	1.09		5q35.3	5	176078840	C	A
11006.p1	125	*UBE3C*	p.SER845PHE	5.39	155	7q36.3	7	157041114	C	T
12161.p1	95	*UBR3*	frameshift indel			2q31.1	2	170732427	*	-AAA, +C

12521.p1	78	*USP15*	frameshift indel			12q14	12	62775296	*	-TGAG
11526.p1	92	*ZBTB41*	p.TYR886HIS	5.28	83	1q31.3	1	197128563	A	G
13335.p1	25	*ZNF420*	p.LEU76PRO	2.54	98	19q13.12	19	37618120	T	C

CNV

Proband		**Candidate Gene**	**Type**	**Location**	**Chrom**	**Start**	**Stop**
11928.p1	66	*CHRNA7*	DUPLICATION	15q13.3	15	30925692	32515973
13815.p1	56	*CNTNAP4*	DELETION	16q23.1	16	75690104	76523780
13726.p1	59	*CTNND1*	DELETION	11q12.1	11	56843272	60233791
12581.p1	34	*EHMT1*	DELETION	9	9	140680073	141023914
13335.p1	25	*TBX6*	DUPLICATION	16p11.2	16	29595483	30199897

*Top candidate *de novo* mutations based on severity and/or supporting evidence from the literature.

Supplementary Table 8. Mutation rates and probability of recurrence for genes with >1 mutation.

Gene	*GRIN2B*	*LAMC3*	*SCN1A*	*NTNG1*	*CHD8*
chimp diffs	15	40	26	2	15
length mapped to chimp	4503	4815	6134	1782	7904
total length of sequence	4503	4840	6134	1782	7904
mut rate per site (diffs / mapped seq)	3.33E-03	8.31E-03	4.24E-03	1.12E-03	1.90E-03
Mutation rate/base/generation	6.94E-09	1.73E-08	8.83E-09	2.34E-09	3.95E-09
People_Screened	1703	1703	1703	189	189
Size of Coding and Splice	4499	4836	6130	1778	7900
# of bases screened	15323594	16471416	20878780	672084	2986200
Avg# DN events	1.06E-01	2.85E-01	1.84E-01	1.57E-03	1.18E-02
#of *De Novo*	3	2	2	2	2
P(X+)	1.85E-04	3.37E-02	1.50E-02	1.23E-06	6.92E-05

***De Novo* Events**	**Proband**	**Type**	**Chrom**	**Pos (hg19)**	**Genotype**
MIP					
GRIN2B	12681	splice	12	13722953	Y
GRIN2B	12547	nonsense	12	13764762	Y
GRIN2B	11691	frameshift indel	12	14019043	+G/*
LAMC3	11666	missense	9	133914290	R
LAMC3	11704	missense	9	133952690	R
SCN1A	12499	missense	2	166848071	R
SCN1A	12340	missense	2	166848006	Y
Exome					
NTNG1	11660	missense	1	107867061	Y
NTNG1	12532	missense	1	107691283	R
CHD8	12752	frameshift indel	14	21861376	-CT
CHD8	13844	nonsense	14	21871178	R

Supplementary Table 9. Selected inherited hemizygous and compound heterozygous sites.

Hemizygous rare singletons

Gene	Proband	Type	Chrom	Pos (hg19)	Geno	Type
AFF2	11056	missense	X	147743569	G	xmr
ATP7A	11388	missense	X	77245127	A	xmr
ATRX	11096	missense	X	76938115	G	xmr
ATRX	11504	missense	X	76939319	G	xmr
ATRX	11827	missense	X	76938353	C	xmr
AWAT1	12238	nonsense	X	69455937	A	x_truncating
CASK	11291	missense	X	41469222	C	xmr
CNGA2	13793	nonsense	X	150912962	T	x_truncating
DMD	12157	missense	X	31284928	T	xmr
FMR1	12390	splice	X	147019617	A	xmr
FRMPD4	12036	missense	X	12712524	C	xasd
FTSJ1	11425	missense	X	48340830	C	xmr
GPR119	11172	nonsense	X	129518668	A	x_truncating
IQSEC2	11526	missense	X	53265000	A	xmr
NHS	11989	missense	X	17745600	T	xmr
OCRL	11388	missense	X	128674731	C	xmr
PRKY	13822	splice	Y	7224175	T	y_truncating
PTCHD1	11083	missense	X	23397843	T	xmr
PTCHD1	11638	missense	X	23411984	C	xmr
RPGR	12157	splice	X	38178241	T	x_truncating
RPGR	11218	missense	X	38145259	A	x_truncating
ZNF185	12373	splice	X	152101415	C	x_truncating
NLGN4Y	12373	nonsense	Y	16734300	T	yasd_truncating
Compound Het rare singletons						
Gene	**Proband**	**Type**	**Chrom**	**Pos (hg19)**	**Geno**	**Type**
CNTNAP4	11009	missense	16	76482674	M	asd_rc
CNTNAP4	11009	missense	16	76482817	R	asd_rc
VPS13B	11659	missense	8	100568761	R	asd_rc
VPS13B	11659	missense	8	100729575	M	asd_rc
MYH7B	11390	frameshift indel	20	33574698	-TCTG	rc
MYH7B	11390	missense	20	33574761	Y	rc
ITGAM	11863	missense	16	31308874	R	rc
ITGAM	11863	splice	16	31340548	R	rc
MATN2	11947	frameshift indel	8	99045849	-C	rc
MATN2	11947	missense	8	99045883	S	rc
QRFPR	12667	nonsense	4	122254158	Y	rc
QRFPR	12667	missense	4	122301478	Y	rc
SCN5A	13169	missense	3	38622556	Y	rc
SCN5A	13169	nonsense	3	38648178	Y	rc_truncating_ms

xmr = X-linked mental retardation loci, asd = ASD candidate loci, rc = possible recessive loci

Supplementary Table 10. List of the 21 severe *de novo* mutations that map to regions of recurrent CNV associated with Developmental Delay and ASD.

Gene	Type of mutation	Genomic disorder	Proband	Gains all cases	Gains CT	Gains ASD	Sig ASD gains*	Sig all gains#	Loss all cases	Loss CT	Loss ASD	Sig ASD loss*	Sig all loss#
MBD5	fs	2q23.1 del	12346	0	0	0	~	~	11	1	2	5.48E-02	4.52E-02
HDLBP	ms	2q37 del	11610	1	0	0	~	6.54E-01	24	3	1	4.58E-01	5.77E-03
PDCD1	ms	2q37 del	11707	3	0	0	~	2.80E-01	25	1	1	2.64E-01	2.38E-04
UIMC1	ms	5q35.2 del	12285	0	0	0	~	~	9	0	0	~	2.20E-02
PSMG4	ms	6p25.3 del	11064	2	0	0	~	4.28E-01	8	0	0	~	3.36E-02
GPR146	ms	7p22.1 del/dup	11518	13	1	2	5.48E-02	2.21E-02	8	3	0	~	4.38E-01
TSNARE1	ms	8q24.3 del	13557	3	0	2	2.02E-02	2.80E-01	14	10	2	5.25E-01	~
PTGES	ms	9q34 del	13822	2	0	0	~	4.28E-01	10	0	2	2.02E-02	1.44E-02
PAEP	ms	9q34 del	11109	4	2	0	~	6.56E-01	56	0	3	2.86E-03	4.68E-11
ABCA2	ms	9q34 del	12225	5	0	0	~	1.20E-01	67	4	4	1.76E-02	6.82E-09
PNPLA7	ms	9q34 del	12249	14	0	1	1.42E-01	2.60E-03	64	3	4	9.92E-03	3.39E-09
SLC6A13	ms	12p13.3 del/dup	11388	14	1	0	~	1.54E-02	6	2	1	3.69E-01	4.38E-01
TSC2	ms	16p13.3 del/dup	12621	16	0	3	2.86E-03	1.10E-03	48	4	1	5.35E-01	6.42E-06
KIAA0182	ms	16p13.3 del/dup	11711	5	0	0	~	1.20E-01	14	0	1	1.42E-01	2.63E-03
SYNRG	ms	17q12 del/dup	11599	18	3	0	~	3.61E-02	15	2	1	3.69E-01	3.54E-02
DNAH17	ms	17q25 del	11587	3	2	0	~	~	42	1	4	1.80E-03	2.80E-07
GPS1	ms	17q25 del	13629	1	1	0	~	~	45	4	4	1.76E-02	1.82E-05
DUS1L	ms	17q25 del	13274	1	1	0	~	~	45	3	4	9.92E-03	4.10E-06
POLRMT	ns	19p13.3 del/dup	13333	28	1	3	1.02E-02	7.00E-05	14	1	1	2.64E-01	1.54E-02
HDGFRP2	ms	19p13.3 del/dup	11184	31	1	3	1.02E-02	2.00E-05	7	0	1	1.42E-01	5.13E-02
SBF1	ms	22q13 del/dup	13793	9	0	0	~	2.20E-02	53	0	3	2.86E-03	1.68E-10

ms = missense, ns = nonsense, fs = frameshifting indel, All Signature Cases (n = 15,767), ASD (n = 1,379), Controls (n = 8,329) *Fisher exact p-values ASD cases versus controls, #all cases versus controls[5].

Supplementary Table 11. Other mutations intersecting previous CNV loci and animal models for ASD.

Gene	Type	Region	Proband	Notes
ADNP	fs	20q13.13	12130	Animal Model
MYH10	ms	17p13	13742	Animal Model
CACNA1D	ms	3p14.3	11872	Animal Model
CACNA1E	ms	1q25-q31	11773	Animal Model
AP3B2	ms	15q	11224	CNV Region
ARID1B	fs	6q25.3	13447	CNV Region
BRSK2	del_aa	11p15.5	13415	CNV Region
DYRK1A	sp	21q22.13	13890	CNV Region
NLGN1	ms	3q26.32	12157	CNV Region
SETBP1	fs	18q21.1	12933	CNV Region
TNKS	ms	8p23.1	11569	CNV Region
TSPAN17	ns	5q35.3	11291	CNV Region

ms = missense, ns = nonsense, fs = frameshifting indel, del_aa = deletion of conserved amino acid

Supplementary Table 12. List of the 126 genes/proteins with severe mutations used for the PPI, along w/ summary stats.

Protein	Degree	Clustering Coefficient	Connected component?
ADCY5	2	1	Yes
ADNP	15	0.949	Yes
ARID1B	2	1	Yes
BRSK2	2	1	Yes
BRWD1	1	0	Yes
CDC42BPB	15	0.94285714	Yes
CDH5	1	0	Yes
CHD3	13	1	Yes
CHD7	13	1	Yes
CHD8	18	0.68	Yes
CNOT1	16	0.858	Yes
CNOT3	12	0.894	Yes
CTNNB1	10	0.333	Yes
CUL3	16	0.292	Yes
DDX20	9	0.694	Yes
DEPDC7	15	0.943	Yes
DYRK1A	2	0	Yes
EIF4G1	6	0.867	Yes
FBXW9	1	0	Yes
H2AFV	7	1	Yes
HDGFRP2	4	0.833	Yes
HDLBP	16	0.842	Yes
HNRNPF	30	0.37	Yes
INCENP	2	0	Yes
IQGAP2	8	0.857	Yes
KATNAL2	4	1	Yes
KRT80	6	1	Yes
MAP4	6	1	Yes
MKI67	6	0.667	Yes
MYBBP1A	29	0.34	Yes
MYH10	6	0.467	Yes
NACA	6	1	Yes
NOTCH3	1	0	Yes
NR4A2	1	0	Yes
PBRM1	18	0.647	Yes
PDIA6	13	0.628	Yes
POLRMT	2	1	Yes
PSEN1	2	0	Yes
RPS6KA3	1	0	Yes
RUVBL1	24	0.489	Yes
SCN1A	5	0.7	Yes
SFPQ	29	0.374	Yes
SRBD1	1	0	Yes
SYNE1	2	1	Yes
TBL1XR1	16	0.858	Yes
TSR2	8	0.929	Yes
UBE3C	5	1	Yes
UBR3	2	1	Yes
YTHDC2	19	0.661	Yes
AMY2B	0	0	No
APAF1	0	0	No
ASAH2	0	0	No
ASAH2C	0	0	No
BMP1	0	0	No
CACNA1D	0	0	No
CACNA1E	0	0	No
COL25A1	0	0	No
CUBN	0	0	No
DDR2	0	0	No
DNAH17	0	0	No
DNAH5	0	0	No
DNAJB9	0	0	No
DUS1L	0	0	No
EFCAB8	0	0	No
EHD2	0	0	No
ETFB	0	0	No
FAM45A	0	0	No
FBXO10	0	0	No
FOXP1	0	0	No
GPR146	0	0	No
GRIN2B	0	0	No
KIAA0100	0	0	No
KIAA0182	0	0	No
KRBA1	0	0	No
L1TD1	0	0	No
LAMC3	0	0	No

Protein	Degree	Clustering Coefficient	Connected component?
MBD5	0	0	No
MCAM	0	0	No
MDM2	0	0	No
MEGF11	0	0	No
MLL3	0	0	No
MUC16	0	0	No
MYO7B	0	0	No
NAA40	0	0	No
NLGN1	0	0	No
NTNG1	0	0	No
OPRL1	0	0	No
OR10Z1	0	0	No
PCDHB4	0	0	No
PCNX	0	0	No
PDCD1	0	0	No
PHF19	0	0	No
PION	0	0	No
PITPNM3	0	0	No
PLEKHA8	0	0	No
PNPLA7	0	0	No
POLQ	0	0	No
PTEN	0	0	No
PTGR1	0	0	No
RBMS3	0	0	No
RGS22	0	0	No
RNF160	0	0	No

Protein	Degree	Clustering Coefficient	Connected component?
SESN2	0	0	No
SETBP1	0	0	No
SETD2	0	0	No
SGSM3	0	0	No
SLC30A5	0	0	No
SLC7A7	0	0	No
SP7	0	0	No
ST3GAL3	0	0	No
STIL	0	0	No
STK36	0	0	No
SYNRG	0	0	No
TBR1	0	0	No
TLK2	0	0	No
TNKS	0	0	No
TRIO	0	0	No
TRPM5	0	0	No
TSC2	0	0	No
TSNARE1	0	0	No
TSPAN17	0	0	No
USP15	0	0	No
VPS39	0	0	No
ZBTB41	0	0	No
ZNF420	0	0	No
ZNF644	0	0	No

Supplementary Table 13. Top IPA function for the PPI connected component.

Category	Function	Function Annotation	B-H p-value	Molecules	#
Gene Expression	transcription	transcription	9.45E-03	ARID1B, BRWD1, CHD3, CHD8, CTNNB1, DDX20, DYRK1A, MYBBP1A, NOTCH3, NR4A2, POLRMT, PSEN1, RUVBL1, SFPQ, TBL1XR1	15
Gene Expression	transcription	transcription of DNA endogenous promoter	3.06E-02	BRWD1, CHD3, CHD8, CTNNB1, DDX20, NR4A2, RUVBL1, TBL1XR1	8
Gene Expression	transcription	transcription of AP1/CRE element	3.42E-02	CTNNB1	1
Gene Expression	transcription	transcription of simian virus 40	3.42E-02	CHD3	1
Gene Expression	transcription	transcription of LEF1 binding site	4.32E-02	CTNNB1	1
Gene Expression	transcription	transcription of DNA	4.57E-02	ARID1B, CTNNB1, MYBBP1A, NOTCH3, NR4A2, TBL1XR1	6
Gene Expression	transcription	transcription of Ets1 binding site	4.90E-02	CTNNB1	1
Gene Expression	transcription	transcription of mitochondrial DNA	5.42E-02	POLRMT	1
Gene Expression	transcription	transcription of T-cell factor recognition sequence	6.82E-02	CTNNB1	1
Gene Expression	transcription	transcription of TCF binding site	6.82E-02	CTNNB1	1
Gene Expression	transcription	transcription of Ets element	7.06E-02	CTNNB1	1
Gene Expression	transcription	transcription of TATA box	8.01E-02	CTNNB1	1
Gene Expression	activation	activation of promoter fragment	3.06E-02	CTNNB1, RPS6KA3	2
Gene Expression	activation	activation of LEF1 binding site	3.06E-02	CTNNB1, PSEN1	2
Gene Expression	activation	activation of Tbe3 response element	4.10E-02	CTNNB1	1
Gene Expression	activation	activation of Tcf-4 response element	4.10E-02	CTNNB1	1

Gene Expression	activation	activation of T-cell factor responsive element	5.42E-02	CTNNB1	1
Gene Expression	activation	activation of Smad3-Smad4 binding element	8.25E-02	CTNNB1	1
Gene Expression	activation	activation of T-cell factor recognition sequence	8.25E-02	CTNNB1	1
Gene Expression	transactivation	transactivation of LEF1 binding site	4.10E-02	CTNNB1	1
Gene Expression	transactivation	transactivation of TCF binding site	4.10E-02	CTNNB1	1
Gene Expression	transactivation	transactivation of Tcf4 binding site	4.10E-02	CTNNB1	1
Gene Expression	transactivation	transactivation of RBP-J/CBF binding site	4.57E-02	NOTCH3	1
Gene Expression	transactivation	transactivation of androgen receptor binding site	4.57E-02	CTNNB1	1
Gene Expression	transactivation	transactivation of thyroid hormone response element	5.42E-02	TBL1XR1	1
Gene Expression	transactivation	transactivation	7.00E-02	CTNNB1, DDX20, NOTCH3, NR4A2, TBL1XR1	5
Gene Expression	transactivation	transactivation of DNA endogenous promoter	8.57E-02	NOTCH3	1
Gene Expression	binding	binding of progesterone response element	4.57E-02	SFPQ	1
Gene Expression	binding	binding of gene	5.42E-02	PSEN1	1
Gene Expression	binding	binding of TPA response element	6.21E-02	PSEN1	1
Gene Expression	expression	expression of Nfat binding site	4.57E-02	DYRK1A	1
Gene Expression	expression	expression of synthetic promoter	6.82E-02	CTNNB1, DYRK1A, NOTCH3, PSEN1	4
Gene Expression	repression	repression of p53 consensus binding site	4.57E-02	CUL3	1
Gene Expression	translation	translation of reporter mRNA	7.74E-02	EIF4G1	1
Behavior	freezing behavior	freezing behavior of mice	9.45E-03	DYRK1A, PSEN1	2
Behavior	locomotion	locomotion	3.06E-02	ADCY5, CHD7, NR4A2, PSEN1, SCN1A	5

Behavior	behavior	behavior	3.42E-02	ADCY5, DYRK1A, NR4A2, PSEN1, SCN1A, UBR3	6
Behavior	behavior	behavior of mice	7.11E-02	DYRK1A, PSEN1, SCN1A	3
Behavior	walking	walking	3.42E-02	CHD7, SCN1A	2
Behavior	psychological process	psychological process of mice	4.35E-02	ADCY5, DYRK1A, PSEN1, SCN1A	4
Behavior	learning	learning by mice	4.57E-02	ADCY5, PSEN1	2
Behavior	cognition	cognition	4.58E-02	ADCY5, CHD7, PSEN1	3
Behavior	motor learning	motor learning by mice	4.90E-02	ADCY5	1
Behavior	long-term memory	long-term memory of mice	6.82E-02	PSEN1	1
Behavior	startle response	startle response of mice	7.06E-02	DYRK1A	1
Behavior	mating behavior	mating behavior of mice	8.25E-02	SCN1A	1
Organismal Development	development	development of organism	9.45E-03	ADNP, CDH5, CHD7, CHD8, CTNNB1, CUL3, DYRK1A, MYH10, PSEN1, RUVBL1, UBR3	11
Organismal Development	development	development of animal	9.45E-03	CDH5, CHD7, CHD8, CTNNB1, CUL3, DYRK1A, MYH10, PSEN1, UBR3	9
Organismal Development	development	development of embryo	9.45E-03	CHD7, CHD8, CTNNB1, CUL3, MYH10, PSEN1, UBR3	7
Organismal Development	development	development of mice	3.06E-02	CDH5, CTNNB1, DYRK1A, MYH10, PSEN1	5
Organismal Development	development	development of capillary plexus	4.10E-02	CDH5	1
Organismal Development	development	development of blood vessel	4.55E-02	CDH5, CHD7, CTNNB1, MYH10, PSEN1	5
Organismal Development	development	development of head	6.21E-02	CTNNB1	1
Organismal Development	development	delay in development of mice	6.82E-02	DYRK1A	1
Organismal Development	developmental process	developmental process of animal	9.45E-03	ADNP, CDH5, CHD7, CHD8, CTNNB1, CUL3, DYRK1A, MYH10, PSEN1, UBR3	10
Organismal Development	developmental process	developmental process of mice	3.06E-02	ADNP, CDH5, CTNNB1, DYRK1A, MYH10, PSEN1	6
Organismal Development	formation	formation of body axis	3.06E-02	CHD8, CTNNB1	2
Organismal Development	formation	formation of dorsal-ventral axis	3.42E-02	CTNNB1	1
Organismal Development	morphology	morphology of aortic root	3.06E-02	MYH10	1

Organismal Development	neovascularization	neovascularization of corpus luteum	3.06E-02	CDH5	1
Organismal Development	patterning	patterning of umbilical vessels	3.06E-02	CTNNB1	1
Organismal Development	patterning	patterning of embryo	4.54E-02	CTNNB1, PSEN1	2
Organismal Development	patterning	patterning of vasculature	7.06E-02	CTNNB1	1
Organismal Development	morphogenesis	morphogenesis of limb	3.28E-02	CHD7, CTNNB1, PSEN1	3
Organismal Development	morphogenesis	morphogenesis of hindlimb	3.32E-02	CHD7, CTNNB1	2
Organismal Development	morphogenesis	morphogenesis of arm	4.57E-02	CTNNB1	1
Organismal Development	duplication	duplication of body axis	4.32E-02	CHD8	1
Organismal Development	angiogenesis	angiogenesis of mice	4.90E-02	CDH5, MYH10	2
Organismal Development	segmentation	segmentation of somites	4.90E-02	PSEN1	1
Organismal Development	segmentation	segmentation of embryo	5.77E-02	PSEN1	1
Organismal Development	growth	growth of mice	5.19E-02	ADNP, CTNNB1, DYRK1A	3
Organismal Development	growth	delay in growth of mice	7.74E-02	DYRK1A	1
Embryonic Development	development	development of embryo	9.45E-03	CHD7, CHD8, CTNNB1, CUL3, MYH10, PSEN1, UBR3	7
Embryonic Development	development	development of trophoblast	4.32E-02	PBRM1	1
Embryonic Development	development	development of second branchial arch	6.82E-02	PSEN1	1
Embryonic Development	patterning	patterning of embryonic tissue	3.06E-02	CTNNB1, PSEN1	2
Embryonic Development	patterning	patterning of vitelline vessel	3.06E-02	CTNNB1	1
Embryonic Development	patterning	patterning of embryo	4.54E-02	CTNNB1, PSEN1	2
Embryonic Development	maintenance	maintenance of apical ectodermal ridge	3.06E-02	CTNNB1	1
Embryonic Development	regression	onset of regression of apical ectodermal ridge	3.06E-02	CTNNB1	1
Embryonic Development	size	size of ventricular zone	3.06E-02	CTNNB1	1
Embryonic Development	morphogenesis	morphogenesis of limb	3.28E-02	CHD7, CTNNB1, PSEN1	3
Embryonic Development	morphogenesis	morphogenesis of hindlimb	3.32E-02	CHD7, CTNNB1	2
Embryonic Development	morphogenesis	morphogenesis of arm	4.57E-02	CTNNB1	1
Embryonic Development	morphogenesis	morphogenesis of metanephros	4.57E-02	CTNNB1	1

Embryonic Development	morphogenesis	morphogenesis of foregut	6.82E-02	CTNNB1	1
Embryonic Development	adhesion	adhesion of blastomeres	3.42E-02	CTNNB1	1
Embryonic Development	formation	formation of renal vesicle	3.42E-02	CTNNB1	1
Embryonic Development	formation	formation of apical ectodermal ridge	4.32E-02	CTNNB1	1
Embryonic Development	formation	formation of visceral endoderm	4.57E-02	MYH10	1
Embryonic Development	formation	formation of endoderm	5.77E-02	CTNNB1	1
Embryonic Development	maturation	maturation of embryonic cell lines	3.42E-02	NR4A2	1
Embryonic Development	thickness	thickness of ventricular zone	3.42E-02	PSEN1	1
Embryonic Development	morphology	morphology of outflow tract	4.10E-02	MYH10	1
Embryonic Development	quantity	quantity of somites	4.32E-02	ADNP	1
Embryonic Development	quantity	quantity of mesenchymal cells	4.57E-02	PSEN1	1
Embryonic Development	quantity	quantity of embryonic cell lines	8.01E-02	ADNP	1
Embryonic Development	apoptosis	apoptosis of neural crest cells	4.90E-02	CTNNB1	1
Embryonic Development	segmentation	segmentation of somites	4.90E-02	PSEN1	1
Embryonic Development	segmentation	segmentation of embryo	5.77E-02	PSEN1	1
Embryonic Development	specification	specification of dorsal-ventral axis	6.62E-02	CTNNB1	1
Embryonic Development	developmental process	developmental process of embryonic cell lines	7.25E-02	DYRK1A, NR4A2	2
Nervous System Development and Function	development	development of nervous system	9.45E-03	CHD7, CTNNB1, DYRK1A, MYH10, NOTCH3, NR4A2, PSEN1, RPS6KA3	8
Nervous System Development and Function	development	development of central nervous system	1.65E-02	CHD7, CTNNB1, MYH10, NOTCH3, PSEN1, RPS6KA3	6
Nervous System Development and Function	development	development of forebrain	3.06E-02	CTNNB1, NOTCH3, PSEN1	3
Nervous System Development and Function	development	development of fourth cerebral ventricle	3.06E-02	MYH10	1

Nervous System Development and Function	development	development of third cerebral ventricle	3.06E-02	MYH10	1
Nervous System Development and Function	development	development of brain	3.06E-02	CTNNB1, MYH10, NOTCH3, PSEN1	4
Nervous System Development and Function	development	development of lateral cerebral ventricle	4.32E-02	MYH10	1
Nervous System Development and Function	development	development of dopaminergic neurons	5.42E-02	NR4A2	1
Nervous System Development and Function	size	size of brain	3.06E-02	CTNNB1, DYRK1A	2
Nervous System Development and Function	size	size of superior colliculus	3.06E-02	DYRK1A	1
Nervous System Development and Function	neurological process	neurological process of brain cells	3.06E-02	ADCY5, ADNP, PSEN1	3
Nervous System Development and Function	neurological process	neurological process of neurons	3.42E-02	ADCY5, ADNP, CTNNB1, PSEN1, SCN1A	5
Nervous System Development and Function	neurological process	neurological process of corticostriatal neurons	4.32E-02	ADCY5	1
Nervous System Development and Function	neurological process	neurological process of cerebral cortex cells	4.42E-02	ADNP, PSEN1	2
Nervous System Development and Function	neurological process	neurological process of mice	4.57E-02	ADCY5, DYRK1A, NR4A2, PSEN1	4
Nervous System Development and Function	differentiation	differentiation of neuronal progenitor cells	3.06E-02	NOTCH3, PSEN1	2
Nervous System Development and Function	differentiation	differentiation of neurons	4.32E-02	BRSK2, NOTCH3, NR4A2, PSEN1	4
Nervous System Development and Function	differentiation	differentiation of amacrine cells	4.90E-02	NR4A2	1

Nervous System Development and Function	differentiation	differentiation of neuroepithelial cells	7.74E-02	PSEN1	1
Nervous System Development and Function	differentiation	differentiation of dopaminergic neurons	8.25E-02	NR4A2	1
Nervous System Development and Function	differentiation	differentiation of neuroglia	8.25E-02	CTNNB1, NOTCH3	2
Nervous System Development and Function	cell cycle progression	re-entry into cell cycle progression of neuroepithelial cells	3.06E-02	CTNNB1	1
Nervous System Development and Function	cytostasis	cytostasis of neurites	3.06E-02	MYH10	1
Nervous System Development and Function	recovery	recovery of brain tissue	3.06E-02	ADNP	1
Nervous System Development and Function	surface area	surface area of cerebral cortex	3.06E-02	CTNNB1	1
Nervous System Development and Function	cell-cell contact	cell-cell contact of nervous tissue cell lines	3.42E-02	CDH5	1
Nervous System Development and Function	shrinkage	shrinkage of cerebral cortex	3.42E-02	PSEN1	1
Nervous System Development and Function	maturation	maturation of dopaminergic neurons	4.10E-02	NR4A2	1
Nervous System Development and Function	morphology	morphology of cerebral cortex	4.10E-02	CTNNB1	1
Nervous System Development and Function	neurogenesis	neurogenesis of brain	4.10E-02	PSEN1	1
Nervous System Development and Function	neurogenesis	neurogenesis	8.02E-02	NOTCH3, PSEN1, SYNE1	3
Nervous System Development and Function	retraction	retraction of neurites	4.20E-02	MYH10, PSEN1	2

Nervous System Development and Function	retraction	retraction of dendrites	6.21E-02	PSEN1	1
Nervous System Development and Function	neurotransmission	neurotransmission	4.32E-02	ADNP, CTNNB1, PSEN1, SCN1A	4
Nervous System Development and Function	neuroprotection	neuroprotection of cortical neurons	4.32E-02	ADNP	1
Nervous System Development and Function	tubulation	tubulation of nervous tissue cell lines	4.32E-02	CDH5	1
Nervous System Development and Function	migration	migration of neurons	4.55E-02	MYH10, NR4A2, PSEN1	3
Nervous System Development and Function	quantity	quantity of neurons	4.55E-02	DYRK1A, NR4A2, PSEN1	3
Nervous System Development and Function	quantity	quantity of Cajal-Retzius neurons	4.57E-02	PSEN1	1
Nervous System Development and Function	quantity	quantity of amacrine cells	5.77E-02	NR4A2	1
Nervous System Development and Function	quantity	quantity of neuroepithelial cells	6.21E-02	CTNNB1	1
Nervous System Development and Function	quantity	quantity of dopaminergic neurons	8.57E-02	NR4A2	1
Nervous System Development and Function	learning	learning by mice	4.57E-02	ADCY5, PSEN1	2
Nervous System Development and Function	motor learning	motor learning by mice	4.90E-02	ADCY5	1
Nervous System Development and Function	morphogenesis	morphogenesis of brain	5.77E-02	PSEN1	1
Nervous System Development and Function	morphogenesis	morphogenesis of neurites	8.65E-02	MYH10, SYNE1	2

Nervous System Development and Function	survival	survival of nervous tissue	5.77E-02	ADNP	1
Nervous System Development and Function	synaptic transmission	synaptic transmission of neurons	5.77E-02	ADNP, CTNNB1, PSEN1	3
Nervous System Development and Function	synaptic transmission	synaptic transmission of hippocampal neurons	6.82E-02	PSEN1	1
Nervous System Development and Function	long-term memory	long-term memory of mice	6.82E-02	PSEN1	1
Nervous System Development and Function	long-term potentiation	long-term potentiation of hippocampal neurons	6.82E-02	PSEN1	1
Nervous System Development and Function	proliferation	proliferation of cerebral cortex cells	7.06E-02	DYRK1A	1
Nervous System Development and Function	proliferation	proliferation of neural precursor cells	8.01E-02	DYRK1A	1
Nervous System Development and Function	startle response	startle response of mice	7.06E-02	DYRK1A	1
Nervous System Development and Function	extension	extension of neurites	8.01E-02	ADNP, MYH10	2
Nervous System Development and Function	axonogenesis	axonogenesis of axons	8.57E-02	PSEN1	1
Nervous System Development and Function	long term depression	long term depression of brain cells	8.57E-02	ADCY5	1
Nervous System Development and Function	long term depression	long term depression of neurons	8.91E-02	ADCY5	1

Supplementary References

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