[For Table S1, please see the separate Excel file.]

Low-Confidence Analyses

Methods. Participants with at least one dnLoF or dnCNV that was not in or including a high-confidence ASD gene or locus were placed into a Low Confidence group. In order to determine whether the pattern of results, when the Low Confidence group was compared to the None group (i.e., no dnLoF or dnCNG in any gene or locus), was similar to the results presented in the main analyses (High Confidence versus None), we performed identical matching procedures. A randomized "nearest neighbor" approach was used to match members of the None group to the members of the Low Confidence group at a 1:1 ratio. Matching procedures were performed separately for males and females, using ranges of 10 nonverbal IQ points and 8 months of age. None matches were found for 284 of the 292 members of the Low Confidence group. Case-control differences were evaluated using a mixed model with a random effect of the case-control pair (to reflect the correlated nature of the data) and a fixed effect of group for continuous variables, or a conditional logistic regression for categorical variables. Raw and false detection rate-corrected p-values are presented.

Results. After correction, several significant differences between the Low Confidence and None groups emerged (Table S1, Figure S1). Individuals in the Low Confidence group had higher verbal IQ, better scores on the Peabody Picture Vocabulary Test, and had lower autism severity scores. Children in the Low Confidence group were reported by their parents to use phrases at a later age and to walk later. Finally the diagnostic certainty ratings were significantly lower for

the Low Confidence group than for the None group. Overall, the differences between the Low Confidence and None groups were similar in pattern but smaller in magnitude than the differences between the High Confidence and None groups.

Figure S1. Phenotypic Profiles of the Low Confidence and Low Confidence-Matched Autism Controls. Variables were Z-normalized using the mean and standard deviation in the full SSC sample (reference). Mean z-scores in each group are plotted. Gray markers indicate a significant difference between cases and controls (see Table 1) and a dagger (†) next to the measure name indicates that a higher value is more severe/more atypical.

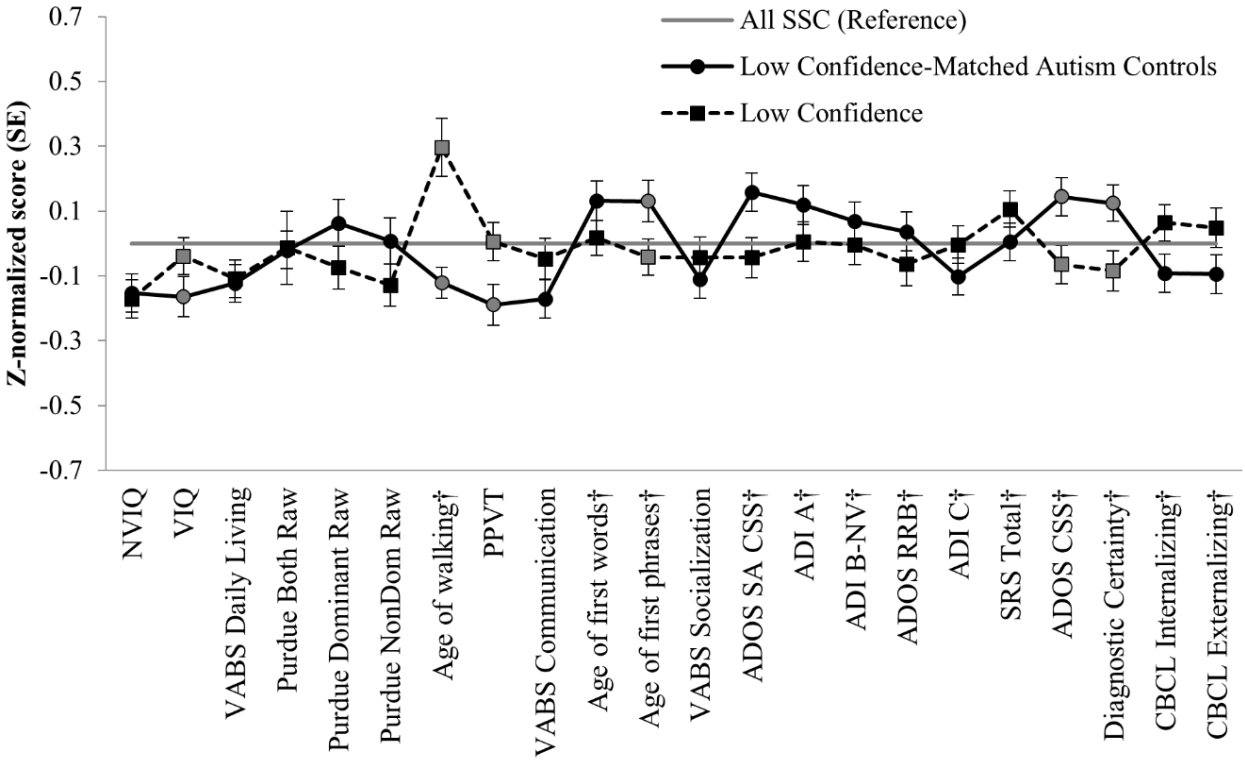

Table S2. Phenotypic Comparison of Low Confidence and Low-Matched Autism Controls

	Low Confidence-Matched Autism Sample (N=284)		Low Confidence (N=284)		Comparison		
					Test Stat	*p*	FDR *p*
	Mean	***SD***	***Mean***	***SD***			
Age (months)	113.31	43.73	113.27	44.12	0.16	0.87	0.93
NVIQ	80.85	26.08	80.39	26.49	1.28	0.20	0.30
VIQ	73.36	32.65	77.29	30.39	-2.56	0.011	0.047
NVIQ-VIQ Difference	7.49	18.28	3.11	16.84	2.97	0.003	0.03
Age of first words†	28.48	20.56	26.18	18.29	1.46	0.15	0.24
Age of first phrases†	46.58	27.68	42.12	24.28	2.6	0.010	0.047
Age of walking†	13.10	3.26	14.77	6.06	-4.1	<.0001	0.003
VABS Communication	74.63	14.47	76.45	15.30	-2.26	0.02	0.08
VABS Daily Living	74.75	13.61	74.94	13.51	-0.23	0.82	0.91
VABS Socialization	69.58	12.47	70.42	13.38	-1.01	0.31	0.36
VABS Composite	71.47	11.95	72.20	12.25	-1.08	0.28	0.36
PPVT	79.35	30.80	85.09	29.16	-3.77	0.000	0.003
Purdue Both Raw	6.45	3.49	6.48	6.96	-0.09	0.93	0.96
Purdue Dominant Raw	9.27	3.69	8.79	3.51	1.95	0.05	0.12
Purdue NonDom Raw	8.27	3.78	7.78	3.52	2.12	0.03	0.10
CBCL Internalizing†	59.51	9.47	61.00	8.99	-1.98	0.05	0.12
CBCL Externalizing†	55.56	10.63	57.06	10.87	-1.71	0.09	0.18
SRS Total†	79.66	10.04	80.70	9.65	-1.32	0.19	0.30
ADI A†	21.08	5.76	20.43	5.87	1.56	0.12	0.21
ADI B-NV†	9.48	3.47	9.22	3.59	1.04	0.30	0.36
ADI C†	6.30	2.42	6.54	2.43	-1.21	0.23	0.32
ADOS CSS†	7.70	1.66	7.35	1.65	2.72	0.007	0.043
ADOS SA CSS†	7.49	1.70	7.14	1.79	2.48	0.01	0.05
ADOS RRB†	7.89	1.81	7.70	2.06	1.16	0.25	0.34
Diagnostic Certainty†	13.40	2.28	12.90	2.54	2.71	0.007	0.043
	%		***%***				
ADOS Mod (3/4)	55		60		2.75	0.10	0.18
High Confidence Autism Diagnosis	78		70		4.39	0.04	0.10
Family History Major Psych. Problems	47		51		1.09	0.30	0.36
Seizure	5		5		0	1.00	1.00
Language Deficit	34		27		3.03	0.08	0.18

†Higher values are more severe/atypical.

(Continued)

Note: NVIQ and VIQ = nonverbal and verbal IQ; ADI-R=Autism Diagnostic Interview, Revised; VABS=Vineland Adaptive Behavior Scales, Second Edition; PPVT=Peabody Vocabulary Test; CBCL=Child Behavior Checklist; SRS=Social Responsiveness Scale; ADOS=Autism Diagnostic Observation Schedule; CSS=Calibrated Severity Score; RRB=Restricted and Repetitive Behavior; FDR=false detection rate. In order to maintain the integrity of our matching procedure, if only one member of a pair was missing data on a given measure, the partner's data was also set to missing. The test statistic depends on the type of dependent variable; continuous variables (described with means) have an associated *t*-statistic, while categorical variables (described with proportions) have an associated χ^2 statistic.