SUPPLEMENTAL INFORMATION

Supplemental Figures

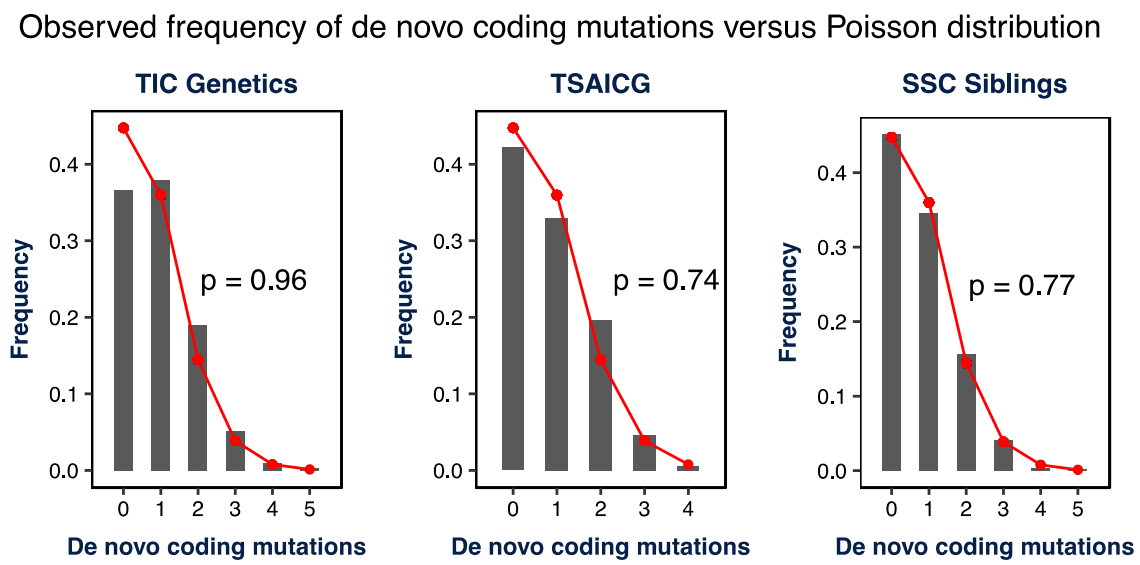

Figure S1 – The distributions of *de novo* coding variants per individual in the TIC Genetics, TSAICG, and SSC siblings cohorts follow an expected Poisson distribution (related to Figures 2-4). To determine whether the observed distribution of the number of *de novo* coding variants per individual follows an expected Poisson distribution we plotted the frequency of the counts of *de novo* coding variants per individual (grey histogram) versus a Poisson distribution with lambda equal to the mean of the counts (red curve). All three cohorts, TIC Genetics (A), TSAICG (B), and the SSC Siblings (C), appear to follow an expected Poisson distribution. To confirm this, we conducted a Chi Square goodness-of-fit test between the observed and expected distributions. In all three cohorts, the distribution of observed *de novo* coding variants per individual is not significantly different from the expected Poisson distribution (TIC Genetics, p = 0.96; TSAICG, p = 0.74; SSC Siblings, p = 0.77), suggesting the observed distributions are well modeled by the Poisson distribution. The distributions of *de novo* variants in ASD (e.g. Neale et al., 2012; Sanders et al., 2012), schizophrenia (e.g. Fromer et al., 2014; Xu et al., 2012), and congenital heart disease (Homsy et al., 2015) are also consistent with the expectation under the Poisson model.

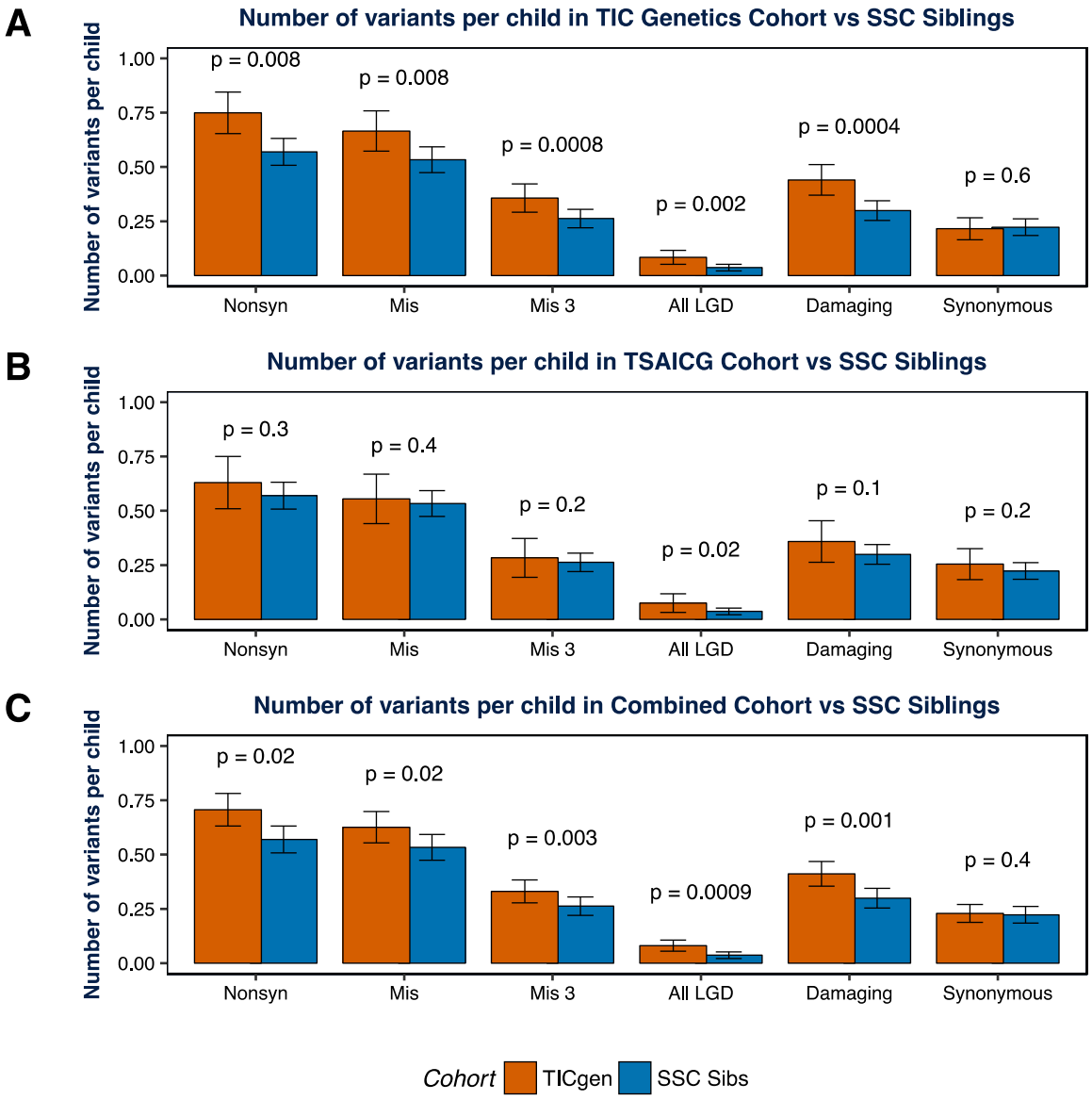

Figure S2 – Binomial exact test also associated *de novo* likely gene disrupting (LGD) variants, *de novo* damaging (LGD + Mis3), and Mis3 variants with TD risk (related to Figures 2-4). As the binomial exact test is more commonly used to assess burden differences, we repeated the analyses in Figures 2-3 with a one-sided binomial exact test. Here the total number of *de novo* variants in the TD probands were compared with the total number in the Simons Simplex Collection (SSC) controls, with the number of trials equal to the total number of proband and control *de novo* variants and the probability of success determined by the proportion of children that were TD probands. The TIC Genetics cohort was compared in (a), TSAICG in (b), and the "Combined" TD cohort in (c). *De novo* LGD variants occurred more often in probands than expected by chance in both independent cohorts, and in the Combined cohort (TIC Genetics, p = 0.002; TSAICG, p = 0.02; Combined, p = 0.0009). *De novo* damaging variants (LGD + Mis3) were significant overrepresented only in the TIC Genetics (p = 0.0004) and Combined (p = 0.001) cohorts, although they showed a modest trend towards significance in the TSAICG cohort (p = 0.12). *De novo* Mis3 variants were similarly enriched in both TIC

Genetics ($p = 0.0008$) and the Combined cohort ($p = 0.003$), while showing a weak trend only in the TSAICG cohort ($p = 0.2$). All p-values are lower than those estimated with the Rate Ratio test in related Figures 2-3.

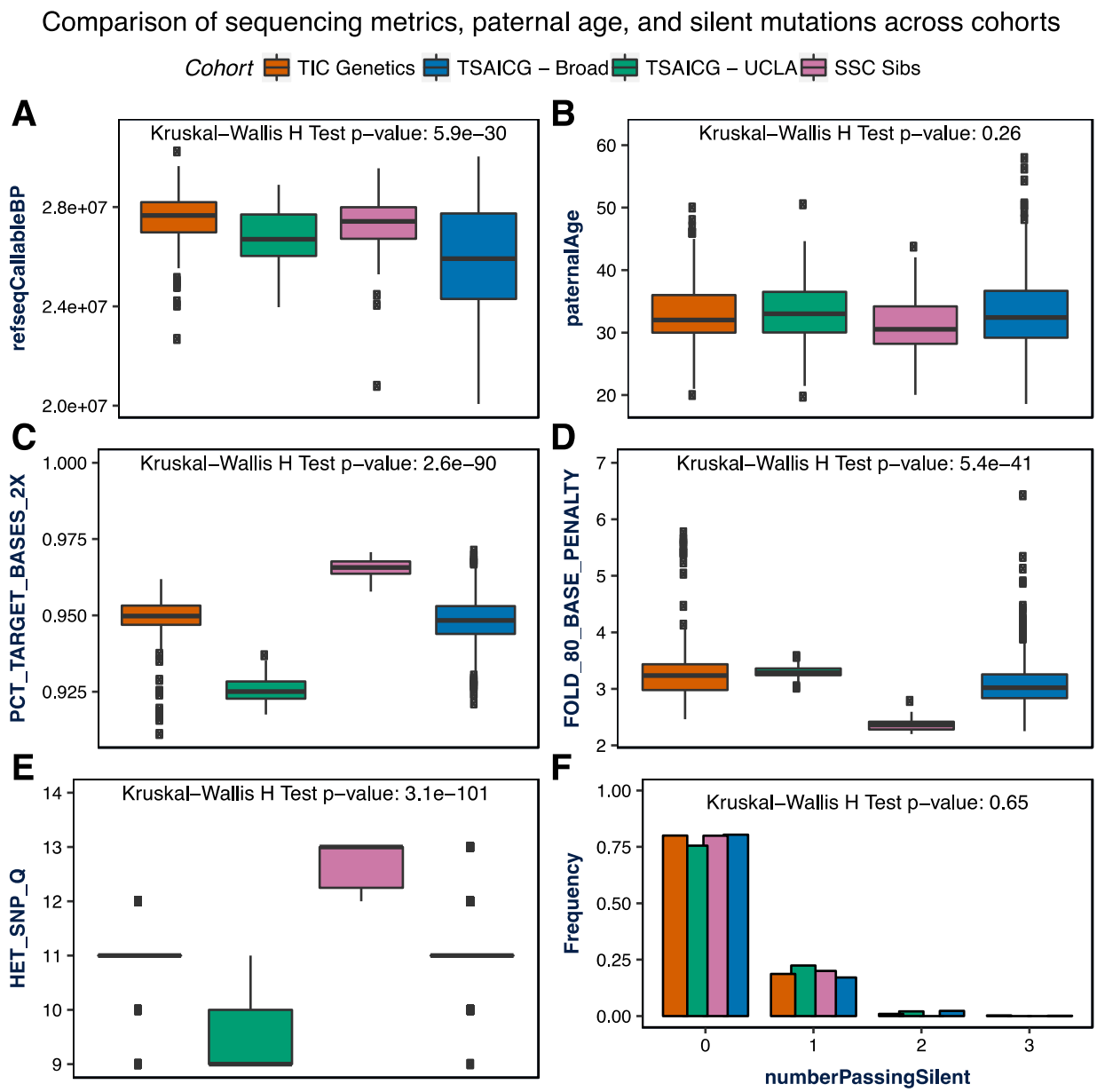

Figure S3 – The callable exome and sequencing coverage differ by cohort (related to Table 1, Figures 2-4). In the Poisson regression in main text Figure 4, we controlled for factors potentially influencing *de novo* variant rate and detection. We utilized the number of callable coding base pairs (A) as an offset. In iterative univariate multiple regression analyses, we observed that paternal age (B), sequencing coverage (percent of exome at 2X coverage; C), sequencing coverage uniformity (fold 80 base penalty; D), heterozygous SNP quality (E), and the number of synonymous variants (F) provided the best model for predicting the number of *de novo* coding variants (when assessing the value of the number of *de* novo synonymous mutations as a covariate we used the number of *de novo* nonsynonymous mutations as the response variable, given that *de novo* coding mutations contain synonymous mutations; STAR Methods). We have plotted these covariates here, by cohort (and subsets of TSAICG sequenced at the Broad Institute and UCLA), to illustrate differences by cohort. These differences are quite profound for most covariates. (A) Within each family, we determined the portion of the coding exome covered at ≥ 20X in all family members (with minimum base quality

≥ 10 and minimum map quality ≥ 20; see STAR Methods). This coverage threshold matches our threshold for *de novo* calling and the base and map quality thresholds correspond to the minimum considered by GATK during variant calling. Therefore, we refer to this target as the "callable coding exome" in each family. In the main text, we measured coding *de novo* mutation rates per base pair based on the size of this target and these values were used as an offset in the Poisson regression. In (A) the callable coding exome per family, for families passing quality control only, is plotted per cohort (or TSAICG subset) and the four groups are compared using a Kruskal-Wallis H Test. The distributions of callable exome are not the same in each group ($p = 5.9 \times 10^{-30}$). (B) We also assessed paternal age between cohorts (18 of the total 1086 families (484 TD trios + 602 SSC control trios) did not have paternal age data), which was not significantly different ($p = 0.26$). However, paternal age was highly correlated with *de novo* mutation rate, and was one of the top predictors in the Poisson regression. (C) We determined the percent of the target region (callable coding exome) at 2X coverage within in each family passing quality control. The four groups have significantly different distributions of percent target at 2X coverage ($p = 2.6 \times 10^{-90}$), with the TSAICG UCLA samples having the highest percent coverage, followed by the TIC Genetics samples. (D) Similarly, the distributions of fold 80 base penalty are significantly different across the four groups ($p = 5.4 \times 10^{-41}$). This metric is the fold over the current coverage necessary to raise 80% of bases in "non-zero-coverage" targets to the mean coverage level in those targets (Picard Metrics Definitions; https://broadinstitute.github.io/picard/picard-metric-definitions.html), and therefore, reflects uniformity of coverage. Interestingly, the TSAICG UCLA subset has the lowest fold 80 base penalty, even though it has the lowest median target coverage (not shown), reflecting the relatively uniform coverage of this cohort. (E) The heterozygous SNP quality (Phred Scaled Q Score of the theoretical HET SNP sensitivity; Picard Metrics Definitions) is substantially different between the cohorts ($p = 3.1 \times 10^{-101}$), suggesting that the cohorts have varying ability to detect heterozygous variants. The TSAICG UCLA cohort has the highest heterozygous SNP quality. Finally, the proportions of 0, 1, 2, or 3 synonymous *de novo* variants per individual are not different between the four cohorts (F). This fits well with the results in Figure S1, which suggest that the number of *de novo* variants per individual in each of these cohorts follows a Poisson distribution. However, the number of *de novo* synonymous variants was still a good predictor of *de novo* nonsynonymous mutations). It is important to note that the SSC control trios have a small callable exome (A), and do not have the "best" percent of target bases at 2X (C), fold 80 base penalty (D), or heterozygous SNP quality (E). This highlights the need to control for these sequencing metrics, as was done in the Poisson regression (see main text Figure 4). Paternal age and sequencing coverage (percent of exome at 2X coverage) were the strongest predictors of *de novo* coding variants (and nonsynonymous *de novo* coding variants).

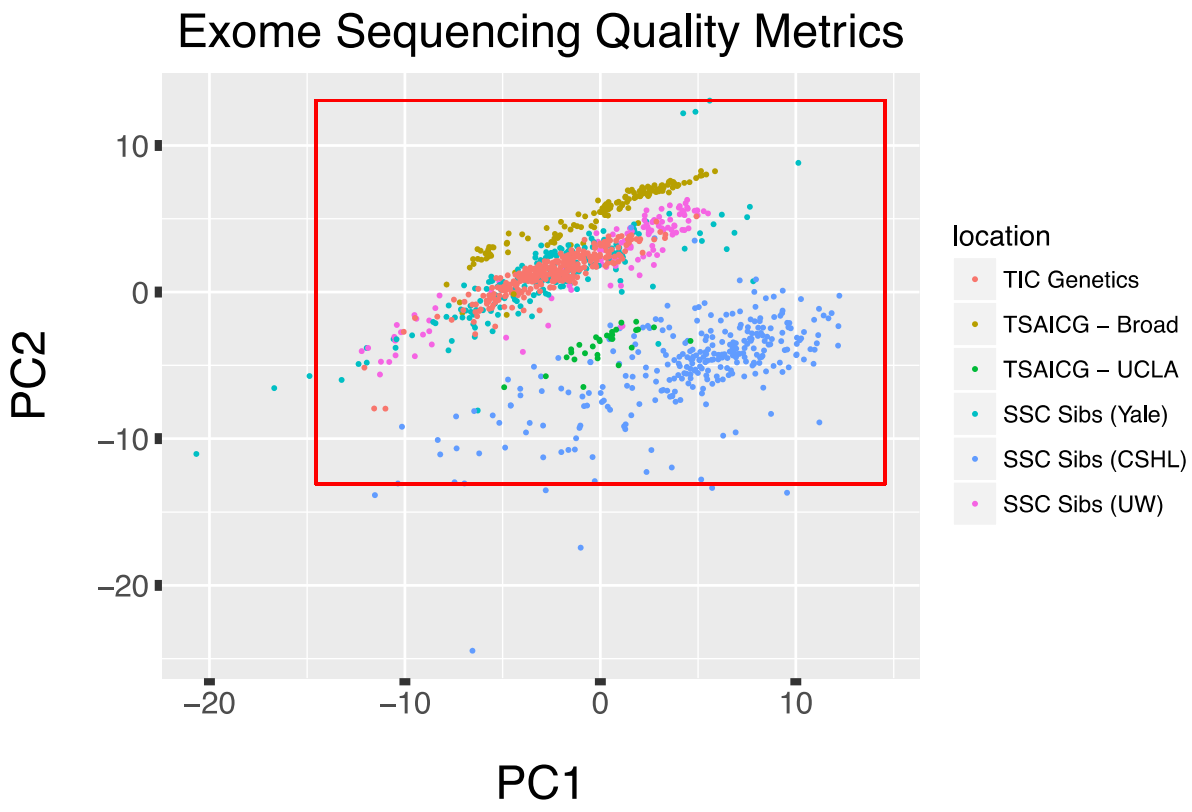

Figure S4 – Principal components analysis reveals clear batch effects by cohort and by sequencing location (related to Figures 3-4). We processed the 324 TIC Genetics trios, the 187 TSAICG trios, and the 602 SSC control trios jointly according to GATK best practices. However, these trios were sequenced at different times using different capture platforms, sequencing machines, and genomic core facilities (see Figure 1, Table 1). TSAICG was sequenced at two locations: the Broad Institute and UCLA; and the SSC control trios were sequenced at three different locations: Yale, Cold Spring Harbor Laboratory, and University of Washington (Iossifov et al., 2014). Therefore, we performed principal components analysis (PCA) to check for potential batch effects. We collected generated capture, sequencing, alignment, and variant level quality metrics using the Picard tools "CollectHsMetrics", "CollectAlignmentSummaryMetrics", and "CollectVariantCallingMetrics" (https://broadinstitute.github.io/picard/). The GATK walker DepthOfCoverage generated coverage metrics for the exome intervals. We also estimated the number of callable base pairs within each trio as the number of base pairs at ≥ 20X coverage in all family members ("total callable", or "callable exome" when referring to RefSeq hg19 coding regions only). These metrics, as well as paternal and maternal age, where available, informed the PCA (see Supplemental Table S1 for a complete listing of these metrics). The PCA revealed clear batch effects based on sequencing facility, particularly with respect to the TSAICG Broad and UCLA subsets, and also within the SSC control trios. We focused on the first 4 principal components (PCs), which explain 61.6% of the variance in the quality metrics. Samples greater than three standard deviations (SD) from the mean (delimited by the red boundaries) in any of the first four principal components were considered outliers and the entire family containing that sample was removed from the analysis (n = 23 of 1219 families or 1.89% of all families; see Supplemental Table S1 for a listing of these families). Overall, 311 TIC Genetics trios (311/325, 95.7%), 173 TSAICG trios (173/186, 93.0%), and 602 SSC trios (602/625, 96.3%) passed quality control.

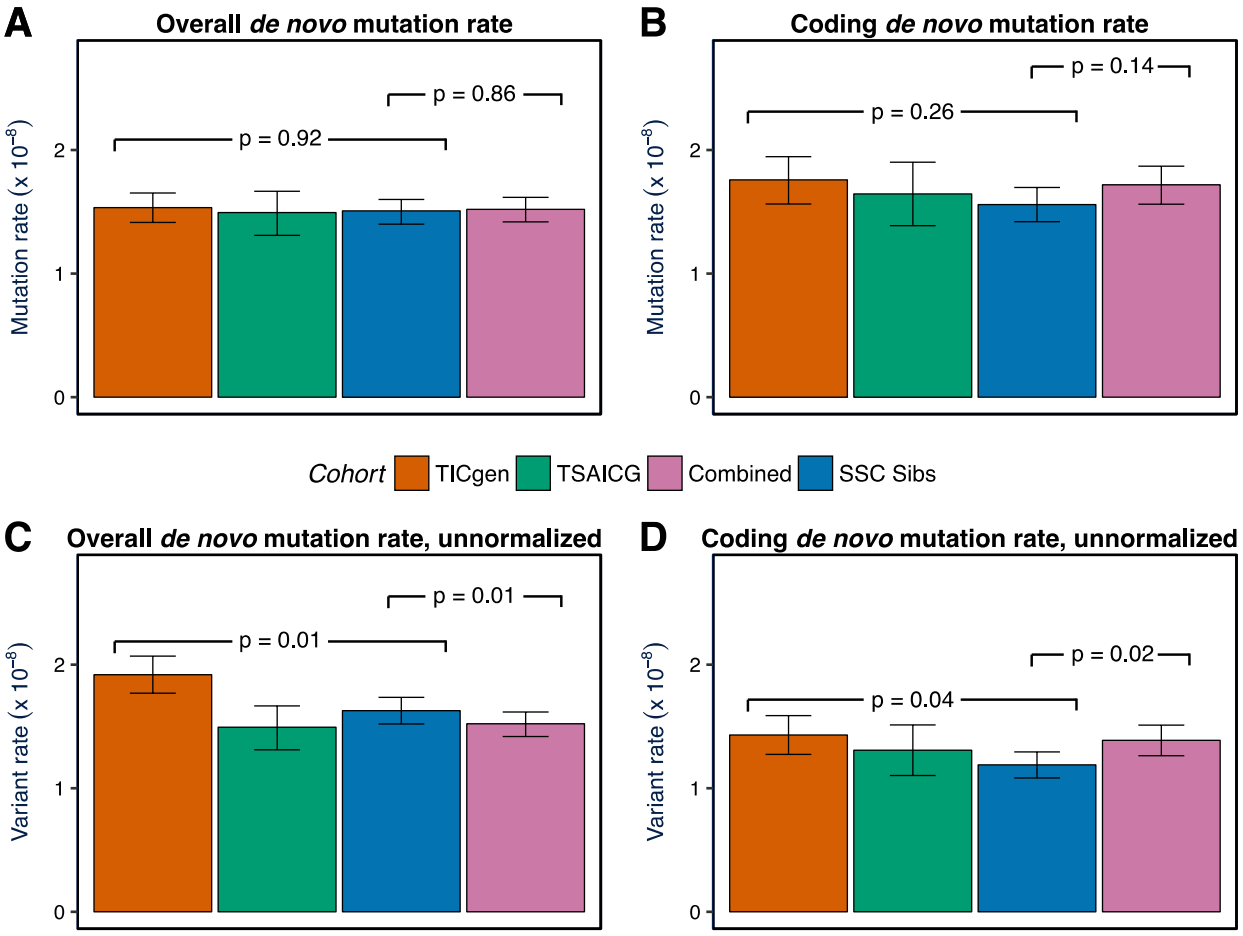

Figure S5 – Normalized *de novo* mutation rates do not differ across the TD cohorts and the SSC control trios (related to Table 2, Figures 3-4). Before assessing burden in the TSAICG (Figure 3), we compared the overall rate of *de novo* mutations (A). Overall rate was calculated as the total number of *de novo* variants, both coding and non-coding, divided by the sum of total callable bp in each cohort, where total callable was defined as all the bases with ≥ 20X coverage within the exome capture array intervals plus the 100 bp of interval padding added during GATK processing. We observed no significant difference in overall *de novo* mutation rate across the TIC Genetics (red), TSAICG (green), and SSC trios (blue; p = 0.92, Chi-squared test of Analysis of Deviance table from Poisson regression model with number of *de novo* variants versus callable bp and cohort). Indeed, we observe a maximum difference of less than 4 x 10^{-10} *de novo* mutations per bp between any of these cohorts. The combined TIC Genetics and TSAICG cohort (purple) is also not different from the SSC (rate ratio 1.01, p = 0.86, Chi-squared test). This suggests there are no substantial biases in *de novo* detection across the three cohorts, even though three different exome library capture kits were utilized (Table 1, Table S1). For B, the rate was calculated based on the size of the possible callable (coding) exome, defined as all the bases with ≥ 20X coverage within the intersection of all RefSeq hg19 coding exons with the respective exome capture array intervals (plus 100 bp of interval padding added by GATK during processing). Within coding regions however, coding variants may be modestly elevated in TD probands with a trend towards a significant difference (p = 0.36, Chi-squared test; rate ratio 1.1, p=0.14, for combined cohort versus SSC, Chi-squared test). This is likely due to the fact that coding variants are more enriched for TD risk (Figures 2-3). We next plotted the 'unnormalized' mutation rates per bp, based on either the

number of bp contained within the respective exome capture array intervals plus 100 bp of interval padding (for overall mutation rate, panel C); or the number of bp contained within Refseq hg19 coding intervals (for coding mutation rate; panel D). The Nimblegen EZ Exome V2 intervals covered 44,001,748 bp (TIC Genetics and SSC Siblings), the Nimblegen EZ Exome V3 intervals covered 63,564,965 bp (TSAICG – UCLA cohort), and the Agilent SureSelect v1.1 covered 32,760,120 bp. The size of the Refseq hg19 coding intervals is 33828798. Unlike the normalized rates, the unnormalized rates are significantly different across the cohorts ($p = 0.01$ for overall mutation rate and $p = 0.04$ for coding mutation rate). The combined cohort is also different than the SSC Siblings ($p = 0.01$ for overall mutation rate, and $p = 0.02$ for coding mutation rate). Together, this suggests that controlling for the number of callable bp is a good method for correcting for different capture arrays, sequencing technology, and coverage distribution.

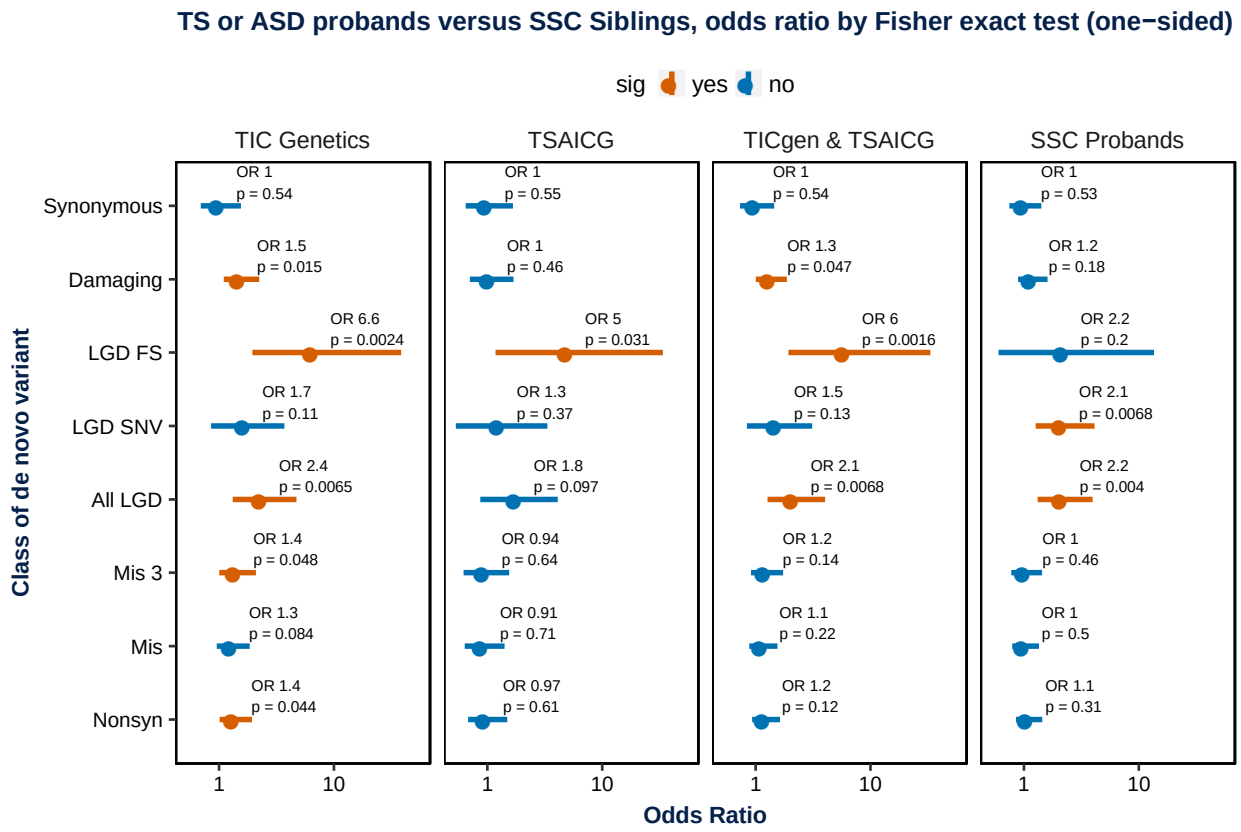

Figure S6: Normalization by the number of *de novo* synonymous variants associates likely gene disrupting (LGD) variants with TD risk (related to Figure 4). As an alternative method to control for batch effects, we repeated the burden analyses in main text Figures 2-4 with a one-sided Fisher exact test. For each class of *de novo* variant, we compared the number of probands with ≥ 1 *de novo* variants to the number of siblings with ≥ 1 *de novo* variants; however, in each case, the second row of the contingency table was equal to the number of probands or the number of siblings with ≥ 1 *de novo* synonymous variants, respectively (in contrast to the number of probands or the number of siblings without a *de novo* variant of that particular class). In other words, we are essentially normalizing by the number of synonymous variants. We reasoned that this method would control for batch effects because capture array and sequencing platform should not influence the expected balance between variant types within coding regions. Likely gene disrupting (LGD) variants are significantly associated with TD risk in both the TIC Genetics cohort (leftmost panel) and the Combined TD cohort (panel second from right), and show a trend towards significance in the TSAICG TD cohort alone (OR 1.8, p = 0.097, panel second from left). Similarly, *de novo* damaging variants are significant in both the TIC Genetics and the Combined TD cohorts, but show little evidence in the TSAICG cohort. We also assessed the SSC probands matched to the SSC siblings (i.e. these are proband and sibling from SSC quartet families) used as controls, as a positive control for these analyses. These samples were processed jointly with the other data, and were sequenced at the same time, on the same platforms as the SSC control siblings. We observe odds ratios consistent with prior results in autism spectrum disorder (e.g. OR = 2.1 for *de novo* LGD SNVs versus OR 2.21 in Willsey et al. (2013), which used an entirely different pipeline), suggesting that our sequence alignment and *de novo* calling pipelines are not introducing artifacts into these analyses.

Supplemental Tables

Table S1 – Detailed sample and cohort level information (related to Table 1).

This table provides detailed sample level information for every sample sequenced in this study. Pedigree information, including sex and phenotype are included, as is quality control status (e.g. pass, or reason for failure). Paternal and maternal age are included where available. The number of *de novo* variants of each class, per individual, are also included in this table, as are all capture, sequencing, alignment, and variant level quality metrics generated by the Picard tools "CollectHsMetrics", "CollectAlignmentSummaryMetrics", and "CollectVariantCallingMetrics"; as well as the GATK walker DepthOfCoverage. Sequencing location is described.

The sex ratio in the TD cohorts is male biased: 244:67 (3.64) male:female ratio for TIC Genetics and 144:29 (4.97) male:female ratio for TSAICG (see also Table 1). In contrast, the SSC sibling control trios have a slightly female biased sex ratio (275:327 or 0.84 male:female ratio). Therefore, we assessed the influence of sex on *de novo* mutation rate to ensure our burden analyses were not confounded by the differences in the sex ratios in the TD and control trios. First, sex was not a significant predictor of nonsynonymous *de novo* variants in either the TIC Genetics (p = 0.36) or the TSAICG (p = 0.31) cohorts when added into the Poisson regression utilized in the main text (see below)

$$nonsynonsymous\ de\ novo\ variants \sim phenotype\ +\ paternalAge\ +\ sex\ +\ percent\ of\ target\ bases\ at\ 2X\ +\ fold\ 80\ base\ penalty\ +\ heterozygous\ SNP\ quality\ +\ offset(\log(callable\ bp))$$

Second, the rate of coding *de novo* variants in male probands versus female probands is not significantly different in the TIC Genetics (rate ratio =0.89, p = 0.4), TSAICG (rate ratio = 0.98, p = 0.9), or combined (rate ratio = 0.91, p = 0.4) TD cohorts; nor is there a difference between male and female SSC siblings (rate ratio = 0.90, p = 0.3). These data suggest that, if anything, there is a slightly higher rate of *de novo* variants in females, and therefore, a male biased TD cohort and a non-male biased control cohort should be more conservative as opposed to permissive.

See attached TS-manuscript_TableS1.xlsx.

Table S2 – Detailed information on all predicted de novo variants, including validation status (related to Table 2, Figures 2-5).

This table provides detailed information on all predicted *de novo* variants, from all cohorts (TIC Genetics, TSAICG, and the Simons Simplex Collection control trios). These variants are annotated with Annovar, based on Refseq hg19 gene definitions. Confirmation status is noted (only *de novo* variants predicted in TD proband were confirmed). For *de novo* nonsynonymous variants only, we assessed overlap with *de novo* variants identified in other developmental disorders: autism (Sanders et al., 2015); schizophrenia (Fromer et al., 2014; Gulsuner et al., 2013); epilepsy (EuroEPINOMICS-RES Consortium et al., 2014); developmental disorders, including intellectual disability (Deciphering Developmental Disorders Study, 2017); and congenital heart disease (Homsy et al., 2015).

See attached TS-manuscript_TableS2.xlsx.

Table S3 – Comparison of mean mutation rate per base pair and overall rate per base pair (related to Figures 2-3).

We plotted the mean rate per base pair, along with 95% CIs in Figures 2-3, and in Figure S5. We also used these values for most downstream analyses, except for the rate ratio tests, which used the total number of *de novo* variants in each class and the total number of callable bp. Table S3 compares the mean and overall rates, which are very similar.

Cohort	**TIC Gen (n = 311)**		**TSAICG (n = 173)**		**Combined (n = 484)**	
Variant Type	**Mean Rate per base pair (95% CI)**	**Overall Rate**	**Mean Rate per base pair (95% CI)**	**Overall Rate**	**Mean Rate per base pair (95% CI)**	**Overall Rate**
All	1.53 (1.41-1.65)	1.53	1.49 (1.31-1.67)	1.49	1.52 (1.42-1.62)	1.52
Coding	**1.75 (1.56-1.95)**	**1.76**	1.64 (1.39-1.9)	1.64	1.72 (1.56-1.87)	1.72
Synonymous	0.39 (0.30-0.49)	0.39	0.47 (0.34-0.61)	0.47	0.42 (0.35-0.50)	0.42
Nonsynonymous	1.36 (1.18-1.53)	1.36	1.17 (0.95-1.39)	1.17	1.29 (1.15-1.43)	1.29
Missense (Mis)	1.21 (1.04-1.37)	1.21	1.03 (0.82-1.24)	1.03	**1.14 (1.01-1.28)**	**1.15**
Missense 3 (Mis3)	0.65 (0.53-0.77)	0.65	0.53 (0.36-0.70)	0.53	0.61 (0.51-0.70)	0.61
Likely Gene Disrupting (LGD)	0.15 (0.092-0.21)	0.15	0.14 (0.059-0.21)	0.14	0.15 (0.099-0.19)	0.15
Damaging (LGD + Mis3)	0.80 (0.67-0.93)	0.80	0.67 (0.49-0.84)	0.67	0.75 (0.65-0.85)	0.75
LGD SNV	**0.092 (0.048-0.14)**	**0.093**	**0.083 (0.026-0.14)**	**0.086**	**0.089 (0.054-0.12)**	**0.091**
LGD FS Indel	0.058 (0.022-0.093)	0.058	**0.053 (0.0068-0.10)**	**0.054**	**0.056 (0.028-0.084)**	**0.057**
In-Frame Indel	0.0058 (-0.0056-0.017)	0.0058	**0.021 (-0.0081-0.050)**	**0.022**	0.011 (-0.0015-0.024)	0.011

Variants were annotated with Annovar according to RefSeq hg19 gene definitions. “Missense 3” are missense variants with a Polyphen2 (HDIV) score ≥0.957 (probably damaging). “Likely Gene Disrupting (LGD)” are nonsense variants, canonical splice site variants, and frameshift indels. We determined *de novo* mutation rates per base pair based on the size of the total callable coding exome (or for all variants, the total callable). The mean rate is the mean of the per individual rate per bp; the 95% confidence interval (CI) was calculated with the *t.test* function in R. We calculated the overall rate by summing the callable exome across all of the families in a particular cohort. The rate per bp was then calculated as the number of *de novo* mutations of a particular class observed divided by the total number of callable bp (see STAR Methods and Figures 2-3 for more details). The mean rate and overall rate are very similar. Rates that differ are highlighted in bold. The rates per individual were used in the Poisson regression (number of mutations was the dependent variable and the number of callable base pair per individual as an offset; see Figure 4 and STAR Methods) and the overall rate was used in the rate ratio tests (total number of mutations per total number of callable base pairs; see STAR Methods and Figures 2-3).

Table S4 – TADA gene association p- and q-values (related to Figure 5).

For every gene defined in Refseq hg19 we utilized TADA (He et al., 2013) to estimate the p- and q-values for association with TD, based on the number of *de novo* LGD and Mis3 variants identified in this study in unrelated probands (see STAR methods for more details). The overall probability of *de novo* mutation is listed in column B, and the probability of *de novo* LGD and Mis3 variants in columns C-D. The observed number of *de novo* LGD and Mis3 variants is summarized in columns E-F, and the p- and q-values resulting from these observations are listed in columns G-H. $q < 0.1$ is considered strong evidence for association, and $q < 0.3$ evidence for probable association (De Rubeis et al., 2014; He et al., 2013; Sanders et al., 2015).

See attached TS-manuscript_TableS4.xlsx.

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TIC Genetics

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