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Supplemental Data

Rare and *de novo* coding variants in chromodomain genes in Chiari I malformation

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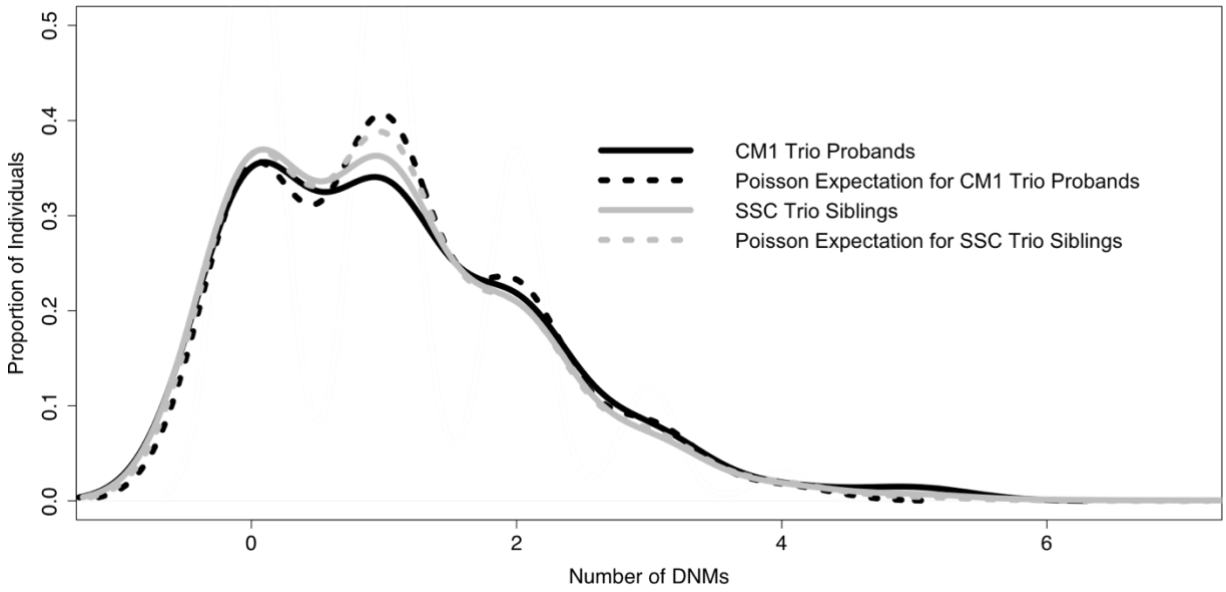
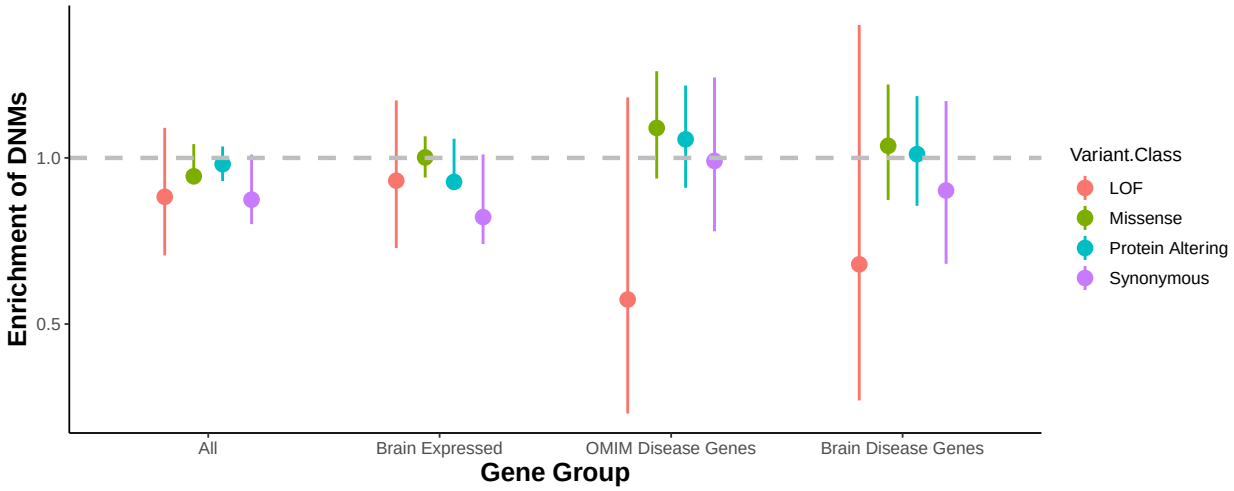
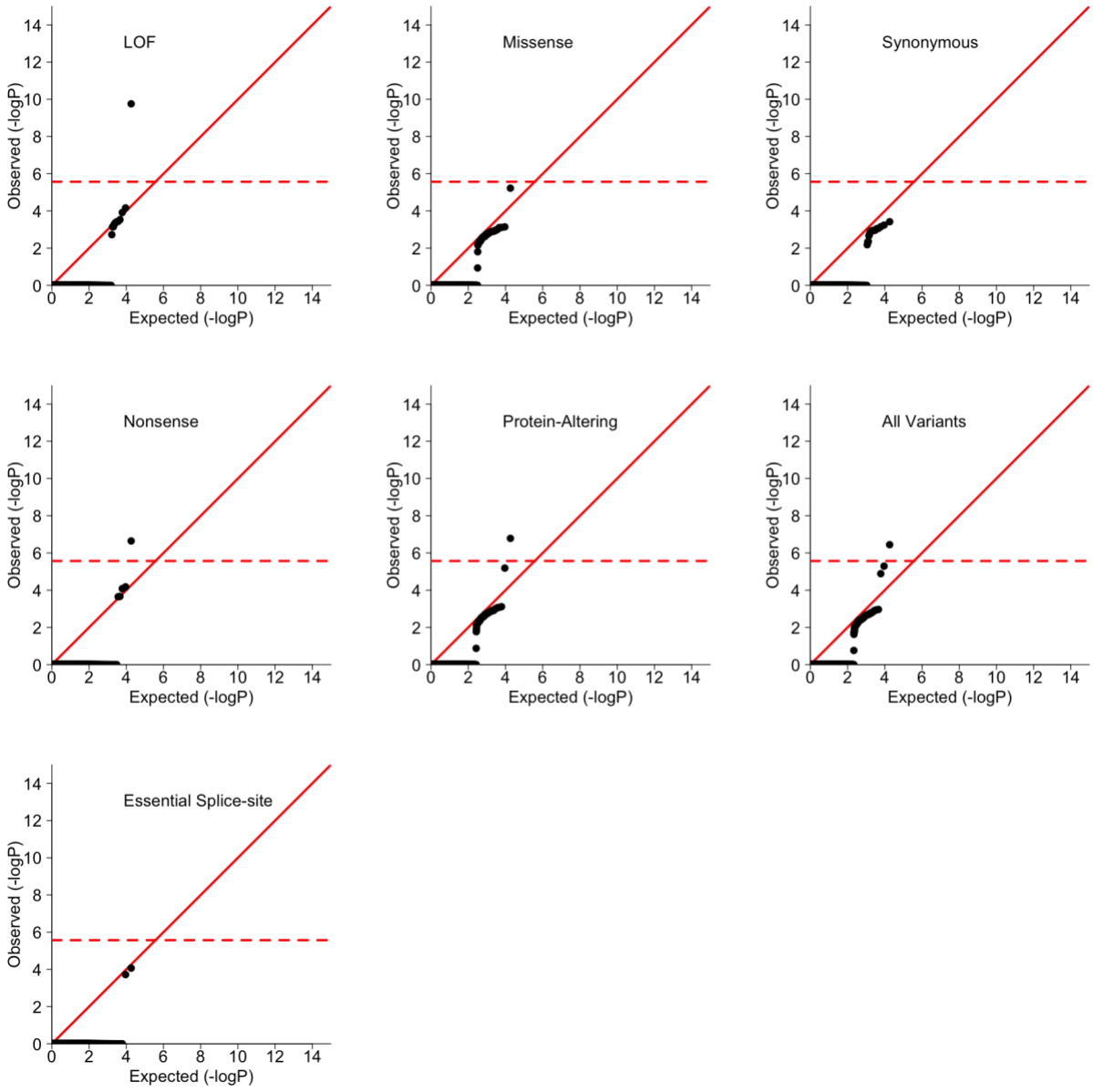


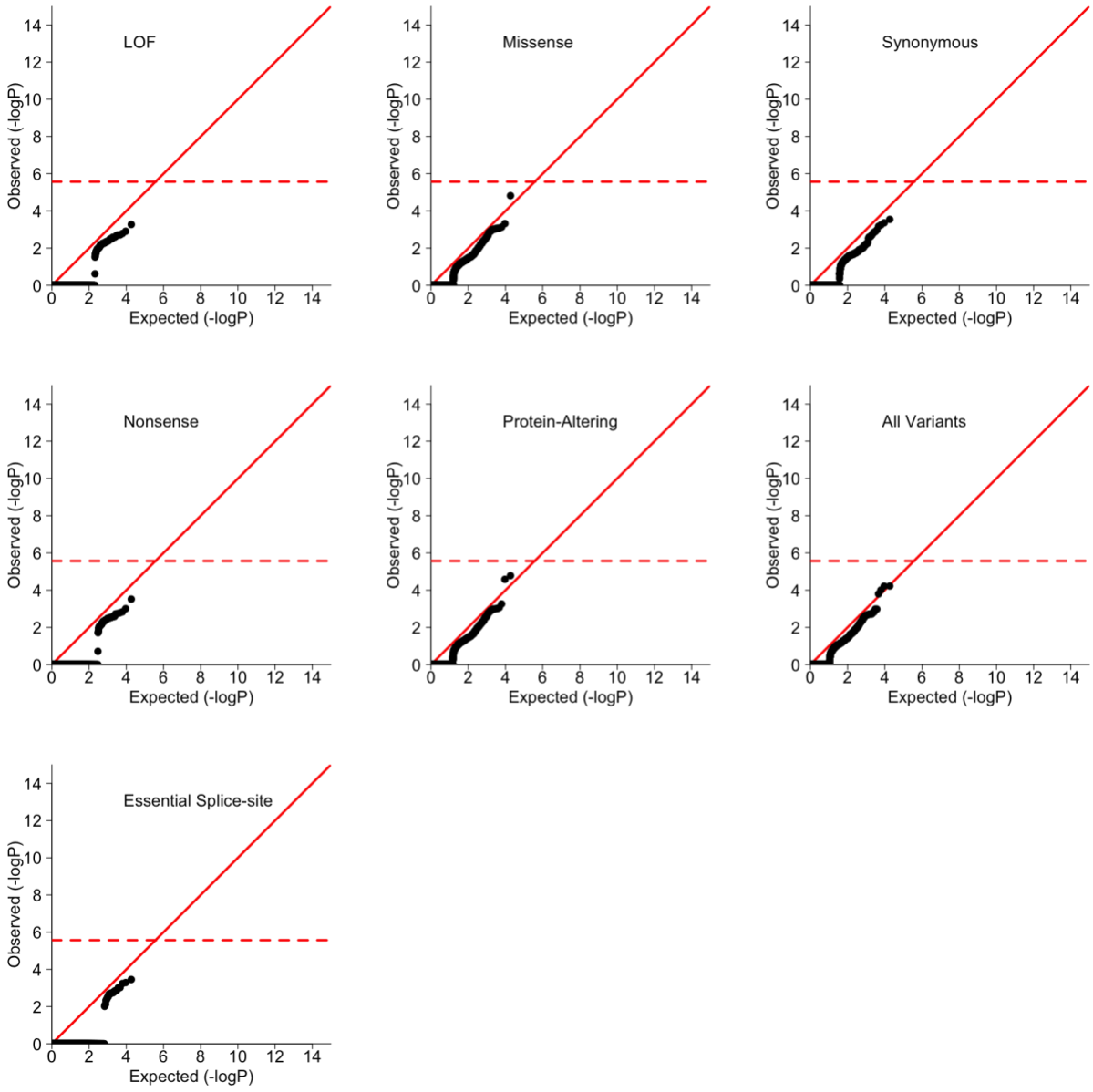
Supplementary Figure 1. Distribution and Poisson Expected Distributions for the number of De Novo Mutations (DNMs) observed per person in CM1 trios (N=67) and Control trios (N=1911). No difference was seen between the expected distribution of DNMs per person in CM1 trios (p=0.87) or in Control trios (p=0.74).



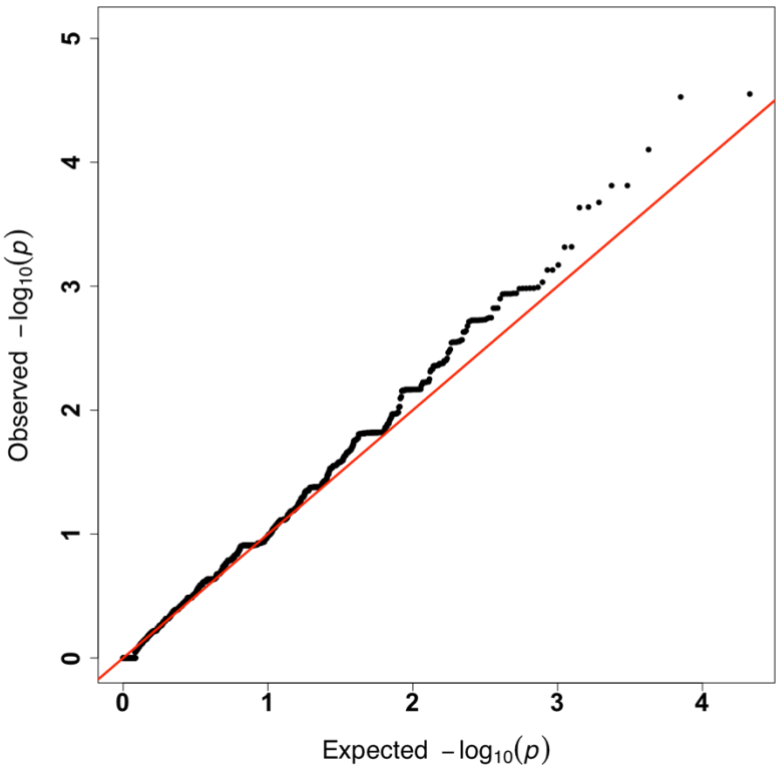
Supplementary Figure 2. Enrichment of DNMs in SSC Controls (N=1911) within gene classes. All enrichment tests presented in this figure were not significant in a two-sided Poisson test. Error bars are 95% CI.



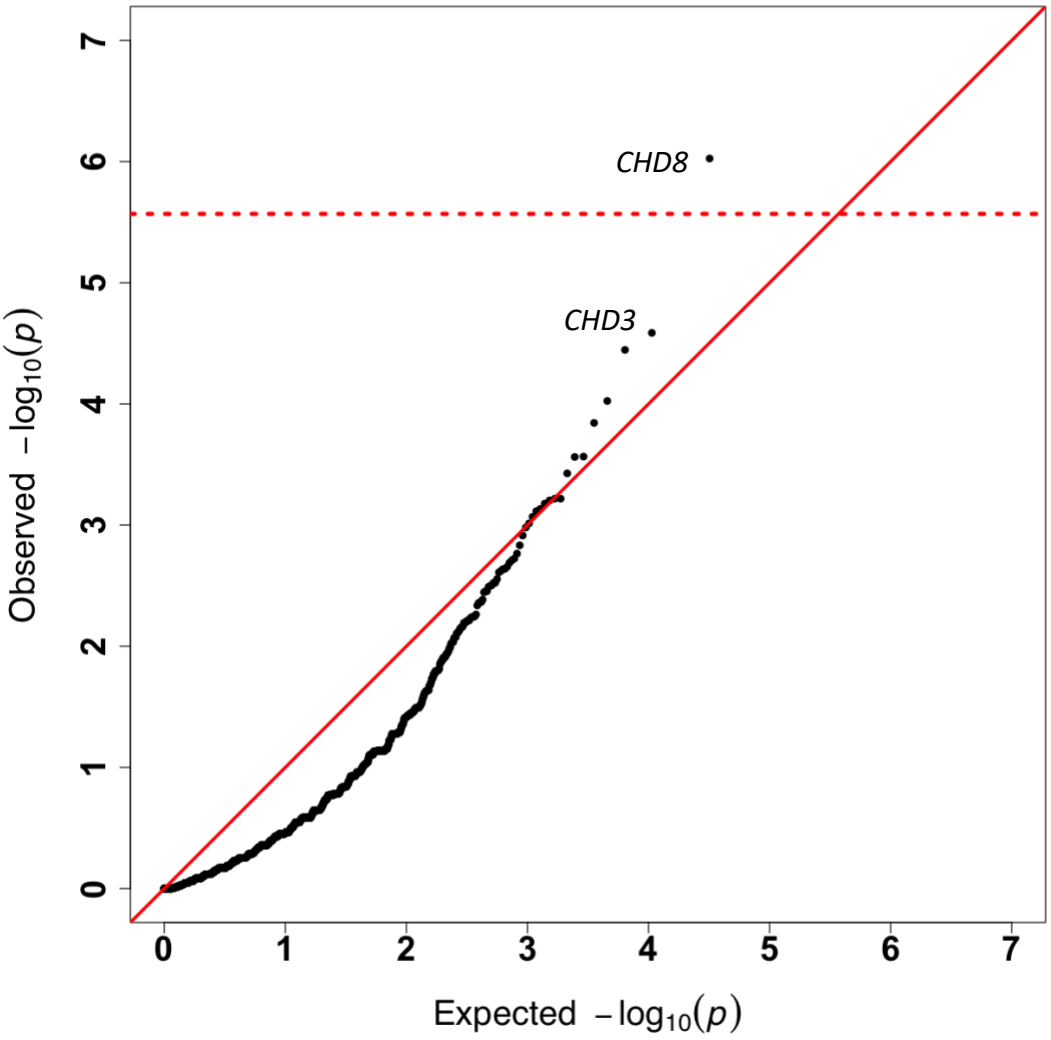
Supplementary Figure 3. QQ plots for denovolyzeR association of per gene *de novo* mutations (DNMs) in CM1 trios (N=67). See Supplementary Table 7 and Supplementary Table 8 for results for all data presented in this figure.



Supplementary Figure 4. QQ plots for denovolyzeR association of per gene *de novo* mutations (DNMs) in SSC Control trios (N=1911).



Supplementary Figure 5. Q-Q Plot for Gene-burden analysis of rare synonymous variants. See Supplementary Table 10 for summary statistics for all data presented in this figure. Lambda = 0.79, SE=0.00105.



Supplementary Figure 6. QQ plots for meta-analysis using per gene enrichment of *de novo* mutations (DNMs) in CM1 trios and gene burden analysis. For each, only protein-altering (missense, nonsense, splice-site, frameshift) variants were used. See Supplementary Table 7 for results for all data presented in this figure. Lambda = 0.31, SE=0.0018.

Table S1. Cohort Information, Quality Control, and Sequencing Metrics. Two exome library kits were used for the case/control cohorts with different target sizes and, therefore, varying coverage of RegSeq hg19 coding regions. To control for these factors, we determined the number of ‘‘callable’’ bp, or the number of bp that have coverage >10x. We then intersected these coordinates with RefSeq hg19 coding exons to determine the ‘‘total callable exome,’’ or the number of bp within RefSeq coding exons that had sufficient coveragefor de novo variant calling. Picard Tools (https://broadinstitute.github.io/picard/) generated capture, sequencing, alignment, and variant level quality metrics, and GATK DepthOfCoverage generated coverage metrics for the exome intervals. Where applicable, sequencing metrics include ±95% confidence intervals. For SSC Sibling Trios, data was not combined across capture methods so all captured bases were interogated and utilized when calculating the DNM probabilities.

	CM1 Cohort	CM1 Trios	In-house Unrelated Controls (IDT Subset)	In-house Unrelated Controls (Agilent Subset)	SSC Sibling Control Trios
Samples Sequenced (Families)	900 (668)	201 (67)	4437	527	5733 (1911)
Proband Male:Female (sex ratio)	257:411 (0.38)	35:32 (1.1)	2211:2226 (0.99)	240:287 (0.83)	900:1011
Paternal Age (95% CI)	-	32.4 (±1.78)	-	-	33.32 (±0.25)
Exome capture platform	IDT xGEN Exome Research Panel (v1.0)	IDT xGEN Exome Research Panel (v1.0)	IDT xGEN Exome Research Panel (v1.0)	Agilent SureSelect v5	Nimblegen EZ Exome V2
Size of Capture Region	39086460	39086460	39086460	50330201	44001748
RefSeq hg19 coding region covered	33418881	33418881	33418881	33048750	32586393
% Refseq hg19 coding region covered	97.81%	97.81%	97.81%	96.72%	96.33%
Intersection IDT/Agilent Capture Region	34236596	34236596	34236596	34236596	-
RefSeq hg19 coding region covered by Intersection	32622227	32622227	32622227	32622227	-
% Refseq hg19 coding region covered by Intersection[a]	95.47%	95.47%	95.47%	95.47%	-
Mean callable exome (million bp with >10x reads)	29.75 (±2.12)	33.81 (±3.34)	31.24 (±1.56)	28.97 (±2.56)	25.80 (±1.06)
Mean total reads per sample (million)	71.95 (±1.34)	89.9 (±3.56)	75.51 (± 1.22)	56.32 (± 2.48)	92.4 (±1.12)
Read length	76	76	76	76	76
Passing unique aligned reads (million)	65.41(±1.14)	81.6 (±3.24)	67.54 (± 1.22)	52.1 (± 2.34)	87.8 (±0.52)
% passing, unique reads aligned	99.23% (±0.23%)	99.33% (±0.38%)	99.31% (±0.06%)	99.21 (±0.31%)	99.78% (±0.38%)
% Duplicate reads	6.83% (±0.26%)	8.63% (±0.40%)	10.31% (±0.15%)	7.21% (±0.37%)	8.52% (±0.40%)
Mean coverage in target	71.25 (±1.89)	90.94 (±3.55)	78.72 (±0.87)	50.72 (±1.45)	90.47 (±0.54)
Median coverage in target	65.61 (±1.60)	88.34 (±3.42)	67.31 (±0.69)	41.72 (±1.23)	88.56(±0.56)

% target at 10x	98.35% (±1.56%)	99.32% (±0.21%)	99.12% (±0.25%)	97.13% (±0.26%)	99.56% (±0.07%)
% target at 15x	88.35% (±1.31%)	96.06% (±0.34%)	92.27% (±0.51%)	87.52% (±0.53%)	96.67% (±0.14%)
% target at 20x	85.56% (±1.46%)	88.25% (±0.73%)	89.45% (±0.56%)	79.16% (±0.66%)	88.11% (±0.3%)
% target at 30x	72.34% (±1.69%)	79.92% (±1.05%)	75.23% (±0.91%)	73.12% (±0.21%)	72.14% (±0.63%)
Het SNP quality	11.36 (±0.07	10.97 (±0.06)	10.94 (±0.03)	10.84 (±0.08)	11.54 (±0.02)
Base pair error rate	0.0035 (±0.0001)	0.0042 (±0.0001)	0.0043 (±0.0001)	0.0041 (±0.0001)	0.002 (±0.0001)
Novel transition/transversion ratio	2.12 (±0.02)	2.16 (±0.02)	2.03 (±0.02)	2.21 (±0.03)	2.01 (±0.01)

Table S2. De Novo Variant Statistics

	CM1 Trios	SSC Sibling Control Trios
Samples Sequenced (Families)	201 (67)	5733 (1911)
Male:Female (sex ratio)	35:32 (1.1)	900:1011 (0.89)
Paternal Age (95% CI)	32.4 (±1.78)	33.32 (±0.25)
DNM Average SNP quality (95% CI)	97.85 (±1.62)	98.2 (±0.02)
DNM Ti/Tv	1.92	2.33
Average Read Depth at DNMs (95% CI)	80.23 (±13.6)	68.85 (±5.7)
DNM Per Person	1.20 (±0.27)	1.04 (±0.04)

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