***Whole and targeted exome sequencing JPSS trios***

Genetic samples from the JPSS trios were sent to MC King’s laboratory for next generation sequencing. Exons were captured using the NimbleGen Se Cap EZ SR v2 and Illumina sequencing technology and run Multiplex, 4 libraries per lane on v3 HiSeq flowcell. The median depth of coverage was >100x, with 93% of base pairs covered at ≥ 10× per sample. Sequences were aligned and SNVs and indels were identified with in-house scripts, filtered for variants that were present in the proband but neither parent, which were potentially disruptive and were frameshift or nonsense mutations, splice mutations + 3 bp, or missense mutations with a Polyphen-2 score >0.5. The events were validated based on filtering set of >800 in-house unrelated exomes for point mutations that were novel.

***Targeted exome capture in replication sample***

In the replication sample, all annotated exons of the de novo JPSS genes were sequenced using the following methodology. 500ng of DNA from each sample were sheared to an average of 150 bp in a Covaris instrument for 360 seconds (Duty cycle - 10%; intensity - 5; cycles/Burst - 200). Barcoded libraries were prepared using the Kapa Low-Throughput Library Preparation Kit Standard (Kapa Biosystems). Libraries were amplified using the KAPA HiFi Library Amplification kit (Kapa Biosystems) (8 cycles) and quantified using Qubit Fluorimetric Quantitation (Invitrogen) and Agilent Bioanalyzer. An equimolar pool of the 4 barcoded libraries (300 ng each) was used as input to exon capture using one reaction tube of the custom Nimblegen SeqCap EZ (Roche) with custom probes target the coding exons of the genes of interest. Capture by hybridization was performed according to the manufacturer’s protocols with the following modifications: 1 nmol of a pool of blocker oligonucleotides (complementary to the barcoded adapters), and (B) post-capture PCR amplification was done using the KAPA HiFi Library Amplification kit instead of the Phusion High-Fidelity PCR Master Mix with HF Buffer Kit, in a 60 ul volume, since we found that the Kapa HiFi kit greatly reduced or eliminated the bias against GC-rich regions. The pooled capture library was quantified by Qubit (Invitrogen) and Bioanalyzer (Agilent) and sequenced in on an Illumina MiSeq sequencer using the 2x150 paired-end cycle protocol, or on an Illumina HiSeq 2500 using a 2 X 100 run, according to the desired depth of sequencing. Reads were aligned to the hg19 build of the human genome using BWA with duplicate removal using samtools as implemented by the Illumina MiSeq Reporter. Variant detection was performed using GATK UnifiedGenotyper. Variants were annotated with Charity annotator to cross-reference against known dbSNP, 1000 Genomes, COSMIC mutations and Schizophrenia Genebook entries. Only rare variants (MAF < 0.01 in 1000Genomes Browser) and new mutations, which were not described in any reported database were considered to be positive findings in this study and were analyzed by Polyphen-2.