M47. WHOLE EXOME SEQUENCING OF AFFECTED INDIVIDUALS FROM LARGE CONSANGUINEOUS PEDIGREES WITH PSYCHOTIC/AFFECTIVE DISORDERS FROM PAKISTAN

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Background For historical, religious, cultural, and social reasons, Pakistan has the highest rate of consanguineous marriage in the world, which have generated some large multiplex pedigrees clustering severely affected individuals with major psychiatric disorders. Such large consanguineous unions may offer a unique opportunity to identify, and characterize genetic risk factors associated with severe psychotic/affective disorders, as well as the mode of inheritance and underlying genetic mechanisms.

Methods 10 multiplex pedigrees aggregated with psychotic/affective disorders were included in the study. Exome capturing was performed using Agilent SureSelect™ Human All Exon Kits for 118 affected individuals, and sequenced by HiSeq2000 at McGill University and Génome Québec Innovation Centre. Sequence data was processed, aligned and variants called using standard bioinformatic pipeline, with extensive relevant annotations, including the functional effects and deleteriousness of the variants, population frequencies, and relevant phenotypic information.

Results I. Selection of potential candidate variants/genes: (1) In total, 846,266 variants were identified in 118 exomes of affected individuals from 10 large pedigrees. 10,687 potential deleterious variants were selected, including nonsense, frameshift indels, splicing variants and predicted damaging missense, comprising of 2,414 novel variants and 8273 rare and novel variants. (2) We used in-house controls to exclude false positives which were generated by sequencing platform. (3) South-Asian population minor allele frequency from public database was used as references for population-specific variants. (4) We further selected candidate variants locating in evolutionary constraint genes. (5) Genes expressed in the brain tissue were prioritized. (6) Gene-set enrichment analyses of the final candidate list identified gene sets over-representing in brain functional pathways, which may have an implication with the disease phenotypes in each pedigree. II. Validations: individual-, pedigree- and population- specific novel and rare deleterious variants have been selected for further bioinformatic characterization.

Discussion (1) rare/novel deleterious variants are mostly heterozygote variants, exclusion of monogenic recessive variant in each pedigree; (2) rare/novel deleterious variants are mostly individual, family and population specific variants; (3) aggregation of novel/rare variants in each affected individuals and pedigree; and segregation and gene-set enrichment analyses indicate polygenic mode of inheritance and specific gene network(s) involved. Genetic validation through targeted resequencing of selected variants in family and population controls through a MiSeq-
MIP (molecular inversion probe) platform and subsequent family-based statistical analyses are underway.

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