**DEVELOPMENTAL BIOLOGY MOLECULAR PATHWAYS ARE ENRICHED IN BOTH STAR*D AND CATIE PATIENTS WHO GAINED EXCESSIVE WEIGHT DURING TREATMENT.**


**Introduction**

Psychotropic induced weight gain (PIWG) may lead to increased risk for cardiologic diseases, metabolic disorders and, ultimately, treatment discontinuation. The hypothesis tested in the present contribution was that PIWG might be genetically driven. The analysis of complete molecular pathways may grant a sufficient power to tackle the biologic variance of PIWG. The identification of a genetic makeup at risk for PIWG would characterize the subjects at risk for this possible severe side effect, and helps to move a step forward in the direction of personalized treatments in psychiatry.

**Results**

CATIE: 765 individuals treated with diverse antipsychotics (27.32% females) were included in the analysis. The average age was 40.9 ± 11.03 years. The period of observation was 242.78±197.39 days. After frequency, genotyping pruning and imputation, 4268977 SNPs were available from the CATIE study. A lambda value of 1.002 allowed for the ruling out of major stratification factors. None of the SNPs under analysis revealed a genome-wide significant association with weight gain. However a trend of association was observed for the investigated phenotype. 18 genes identified: COL4A2 & COL4A3, COL6A1, CREBBP, EP300, KCNQ2, KCNQ3, NR5A2, GRIN2B, ITGA2B, KRT2, KCNQ2, KCNQ3, POLR2B, RXRA, SH3GL2, CNTN1, ROBO3. Patients gained on average 6.48 ±7.5 kg. None of the sociodemographic variables were significantly associated with weight gain after correction for multiple testing. Several molecular pathways were identified in the CATIE sample, including “Developmental biology” and molecular pathways enrolling genes coding for proteins involved in the insulin - related molecular events (pathways 2-11).

Developmental biology molecular pathway had a higher frequency of genes found to harbor variations associated with the investigated phenotype. 18 genes identified: CATIE: 765 individuals treated with diverse antipsychotics (27.32% females) were included in the analysis. The average age was 40.9 ± 11.03 years. The period of observation was 242.78±197.39 days. After frequency, genotyping pruning and imputation, 4268977 SNPs were available from the CATIE study. A lambda value of 1.002 allowed for the ruling out of major stratification factors. None of the SNPs under analysis revealed a genome-wide significant association with weight gain. However a trend of association was observed for the investigated phenotype. 18 genes identified: COL4A2 & COL4A3, COL6A1, CREBBP, EP300, KCNQ2, KCNQ3, NR5A2, GRIN2B, ITGA2B, KRT2, KCNQ2, KCNQ3, POLR2B, RXRA, SH3GL2, CNTN1, ROBO3.

*genes marked in bold, have previously been associated with weight gain.*

**Methods**

The sample under analysis is the NIMH CATIE sample (NIMH contract NO1 MH90001). Schizophrenic patients were enrolled between 1/2001-12/2004. CATIE was a multi-phase randomized controlled trial of antipsychotic medications involving 1,460 persons with schizophrenia (SCZ) followed for up to 18 months. The main focus of the CATIE investigation was to test the tolerability of a number of antipsychotic treatments in the “real world” conditions. 51% of CATIE participants donated a DNA sample. This sub-sample is the core of the present investigation. Main outcome: Weight was a continuous variable measured from the Hardy-Weinberg equilibrium were accepted under a P-threshold of 0.0001. Lambda values served to exclude inflation factors. The sample under analysis is the NIMH CATIE sample (NIMH contract NO1 MH90001). Schizophrenic patients were enrolled between 1/2001-12/2004. CATIE was a multi-phase randomized controlled trial of antipsychotic medications involving 1,460 persons with schizophrenia (SCZ) followed for up to 18 months. The main focus of the CATIE investigation was to test the tolerability of a number of antipsychotic treatments in the “real world” conditions. 51% of CATIE participants donated a DNA sample. This sub-sample is the core of the present investigation. Main outcome: Weight was a continuous variable measured from the Hardy-Weinberg equilibrium were accepted under a P-threshold of 0.0001. Lambda values served to exclude inflation factors.

**Conclusion**

Results from the current contribution correlates with previous evidence and it is consistent with our earlier result on the STAR*D sample. Furthermore the result from the study stresses the relevance of the peripheral tissue rearrangement in the biologic modifications that follow psychotropic treatment and may lead to PIWG. Further research is warranted.