Does genetics of obesity overlap with pharmacogenetics of antipsychotic induced weight gain?

- A molecular pathway analysis.

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Introduction

Weight gain is a prime concern of antipsychotic drug treatment, as it is a major cause of treatment discontinuation. The genetics and mechanisms behind the antipsychotic induced weight gain is at the time of writing not completely understood. In the current study we examine individuals from the CATIE study, that gained excessive weight gain during antipsychotic treatment and look for variations in a number of genes, previously implicated in obesity.1,2

Methods

Cytoskape was instrumental to define a molecular pathway (picture 1) from a list of genes previously reported to be consistently associated with obesity in literature.1 GeneMania further enriched the original pathway. That pathway was tested for enrichment in the CATIE trial through the interrogation of reactomePA and bioconductor. Outcome was the largest increase in weight throughout the different phases of the trial. Analysis of clinical covariates was conducted prior to the genetic tests and, when found significantly associated with the phenotype under analysis were included as covariates for genetic tests. Plink and R were instrumental for the analyses. As for the genetic genome-wide analysis, quality checking were set as standard for this kind of analysis (genotype call rate > 0.95 or 0.99; maf > 0.01; hwe < 0.0001), inflation factor was controlled by lambda values and imputation was run with the use of 1000 genomes in a Plink environment. Pathway analysis was conducted at the SuperCluster PC at Aarhus University.

Results

765 individuals from the CATIE study, M=556, mean age=40.93±11.03 were included in the initial analysis. 29 genes were finally analysed as a consistent metabolic pathway. 2067 SNPs were available from the CATIE and harbored by genes belonging to the pathway under analysis. The enrichment was tested against 10E5 permutated pathways. Under a threshold of p<0.01 for significance, a permuted p of 0.005 for enrichment was retrieved from the pathway under analysis. No enrichment was detectable under a threshold of p<0.05.

Conclusion

Genes involved in obesity may compose a molecular pathway at risk of weight gain during antipsychotic treatment. A genetic test run before the drug treatment is initiated could grant the opportunity to prevent weight gain. Further independent analyses are warranted. A focus on the significant threshold to be used in enrichment analyses must be further investigated.

References