Institute of Psychiatric Phenomics & Genomics

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Analysis of mitochondria-related genes suggests that *COA8* gene is associated with short-term memory in the PsyCourse Study

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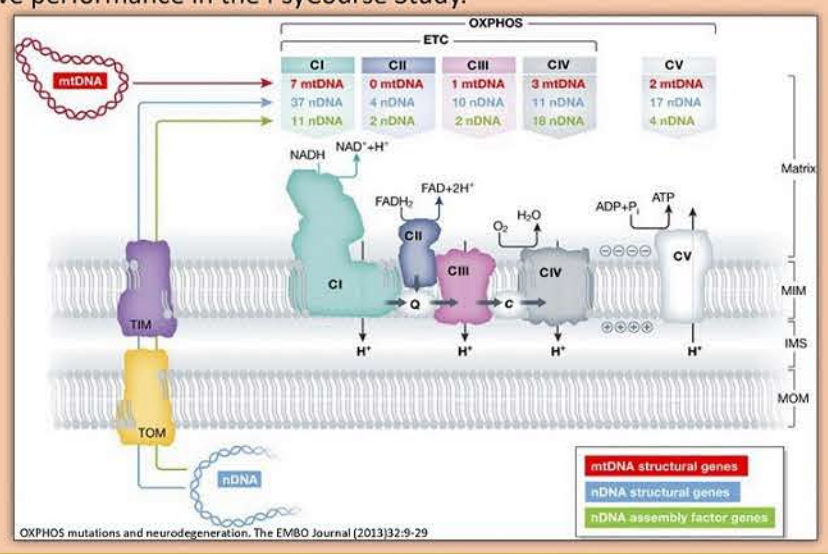
BACKGROUND

- Mitochondria are essential organelles in the cytoplasm of cells, and their dysfunction has been related to a variety of diseases.
- The main role of mitochondria is to generate energy through oxidative phosphorylation (OXPHOS), and thus to be involved in metabolism.
- Polymorphisms in mitochondria-related genes can alter the structure and expression levels of key proteins, potentially increasing the risk of mental illness.
- Changes in energy metabolism may explain previous evidence for the role of mitochondrial genes in psychiatric disorders.
- We investigated the association of genetic variants of the genes belonging to two annotated mitochondrial pathways, "OXPHOS" and "Metabolism", with cross-sectional cognitive performance in the PsyCourse Study.

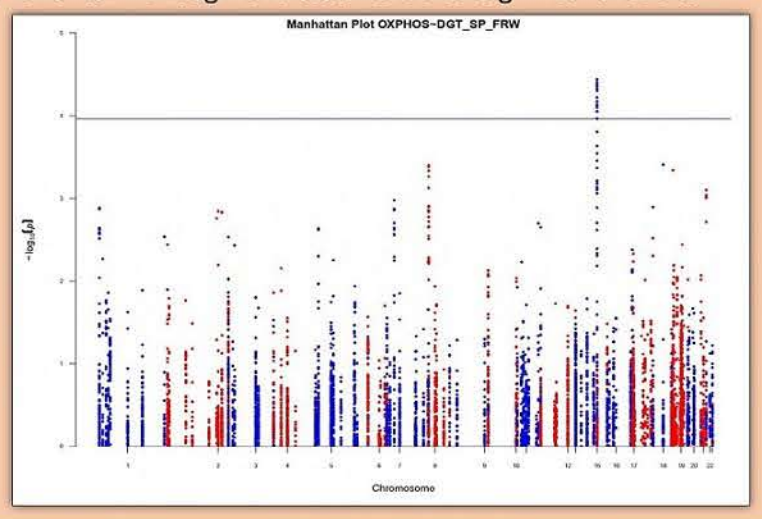


METHODS

- We used cross-sectional data from the PsyCourse Study (PMID:30070057, www.psycourse.de), including 1320 individuals with severe psychiatric disorder from the affective-to-psychotic spectrum, and 466 neurotypical individuals.
- The cognitive tests used were Trail-Making-Test (parts A and B), Verbal Digit Span (forward and backward), Digit-Symbol Test, and the Multiple-Choice Vocabulary Intelligence (MWT-B).
- DNA Genotyping (Illumina Global Screening Array v3.0) from blood samples, quality control, and imputation (Haplotype Reference Consortium [Version r1.1 2016] as reference panel) were performed.
- The SNPs of "OXPHOS" and "Metabolism" Mito-pathways genes (genes position ± 10kb) according to the "MitoCarta3.0" human inventory collection of 1136 genes (www.broadinstitute.org) were extracted from the whole dataset.
- PLINK 1.9 and R program were utilized for running association analysis between the normalized cognitive tests and the extracted SNPs.
- Association analyses were adjusted for age, sex, duration of illness, clinical center, diagnosis, medication, and principal components from population stratification analyses as covariates.
- False discovery rate (FDR) was used to adjust the results for multiple comparisons.

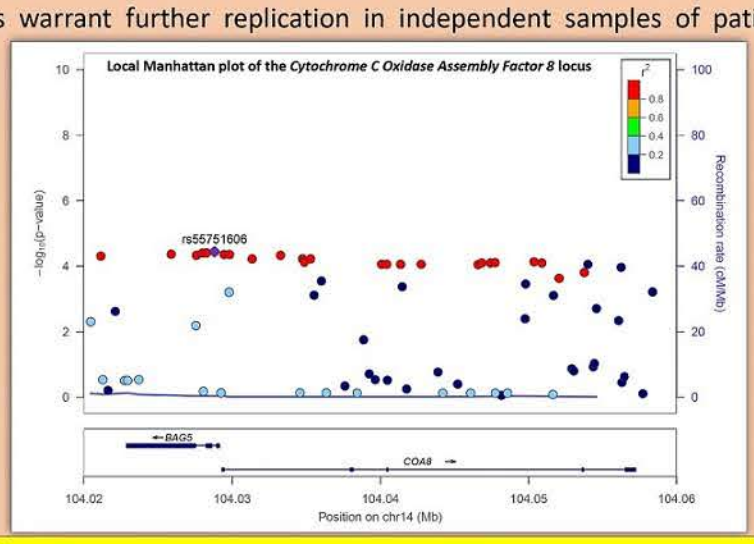
RESULTS

- After data cleaning, log-transformation, standardization, and outlier removal, a total of 1594 individuals with cognitive data (1190 cases, 404 controls) remained.
- After extracting the genetic variants, 13,386 and 60,665 SNPs, respectively related to OXPHOS, and Metabolism pathway-relevant nuclear (±10 kb) and mitochondrial genes, were included in the analysis.
- The results showed significant association (β=0.16, SE=0.04, FDR-adjusted p-value < 0.05) of 25 SNPs from "OXPHOS" pathway with the verbal digit span (forward) test.
- Specifically, nineteen of the detected significant SNPs are found in the Cytochrome C Oxidase Assembly Factor 8 (*COA8*) gene locus on chromosome 14.
- None of the other assessed associations including "OXPHOS" and "Metabolism" genetic variants with cognitive tests revealed significant results.



DISCUSSION

- *The COA8* gene, which is listed in Mito-Pathways gene list (OXPHOS>Complex IV>CIVassembly factors; OXPHOS>OXPHOS assembly factors), encodes a protein that is present in mitochondria and induces the release of cytochrome C, promoting apoptosis.
- In our analyses, *COA8* gene is associated with cognitive performance in the forward digit-span test, which evaluates short-term memory capacity by asking participants to recall a series of numerals verbally, with the sequences getting longer with each trial.
- This effect on cognitive performance aligns with a disorder related to *COA8*, the mitochondrial Complex IV Deficiency, Nuclear Type 17 (MC4DN17). In this autosomal recessive neurometabolic disease with related phenotypes such as intellectual disability and ataxia, cognitive impairment is observed in some patients.
- Our results warrant further replication in independent samples of patients/healthy controls.



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