p-281

Friday

Methylome analysis of FTLD patients with TDP-43 pathology (FTLD-TDP) implicates the hexosamine biosynthetic pathway in disease

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State of the art: In the last decade, numerous studies have highlighted the importance of DNA methylation in the functioning of the central nervous system, yet the genome-wide contribution of epigenetic changes to the development of FTLD remains largely unexplored.
Methodology: We performed the largest FTLD methylation study to date focused on patients with TDP-43 pathology (FTLD-TDP). We included 192 matched pairs of frozen post-mortem tissue samples from cerebellum (CER) and frontal cortex (FCX) regions (N=394; Mayo Clinic Brain Bank), divided into 6 groups: FTLD-TDP types A (N=25), B (N=25) and C (N=25), *GRN* mutation carriers (N=25), *C9ORF72* repeat expansion carriers (N=25); and controls (N=42). For each sample, DNA methylation was measured using reduced representation bisulfite sequencing. Bioinformatic analyses using MethylKit, DMRFinder and EdgeR tools were employed to compare methylation profiles of patient groups *versus* controls, either including all genomic locations or focusing specifically on promoter regions.
Results: We identified 102 significant loci in FCX (FDR<0.05; 59 hypomethylated; 43 hypermethylated *versus* controls) and 153 significant loci in CER (95 hypomethylated; 58 hypermethylated *versus* controls). Hits identified in these analyses were prioritized for further functional follow-up using an in-house built scoring system, which highlighted an important role for the hexosamine biosynthetic pathway in FTLD-TDP. Functional validation of the top hits as well as integration of the methylome data with already existing genome and transcriptome data is currently ongoing.
Conclusion: Overall, our results suggest that epigenetics plays a role in FTLD-TDP pathophysiology and highlights an important role for the hexosamine biosynthetic pathway.

Conflicts of interest

N/A