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Susceptible genes and disease mechanisms identified in frontotemporal dementia and frontotemporal dementia with Amyotrophic Lateral Sclerosis by DNA-methylation and GWAS.

Frontotemporal dementia (FTD) is a neurodegenerative disorder predominantly affecting the frontal and temporal lobes. Genome-wide association studies (GWAS) on FTD identified only a few risk loci. One of the possible explanations is that FTD is clinically, pathologically, and genetically heterogeneous. An important open question is to what extent epigenetic factors contribute to FTD and whether these factors vary between FTD clinical subgroup. We compared the DNA-methylation levels of FTD cases (n = 128), and of FTD cases with Amyotrophic Lateral Sclerosis (FTD-ALS; n = 7) to those of unaffected controls (n = 193), which resulted in 14 and 224 candidate genes, respectively. Cluster analysis revealed significant class separation of FTD-ALS from controls. We could further specify genes with increased susceptibility for abnormal gene-transcript behavior by jointly analyzing DNA-methylation levels with the presence of mutations in a GWAS FTD-cohort. For FTD-ALS, this resulted in 9 potential candidate genes, whereas for FTD we detected 1 candidate gene (ELP2). Independent validation-sets confirmed the genes DLG1, METTL7A, KIAA1147, IGHMBP2, PCNX, UBTD2, WDR35, and ELP2/SLC39A6 among others. We could furthermore demonstrate that genes harboring mutations and/or displaying differential DNA-methylation, are involved in common pathways, and may therefore be critical for neurodegeneration in both FTD and FTD-ALS.