EPIC4ND

Disease prediction for Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis using methylome profiling

Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are progressive neurodegenerative disorders (NDs) showing growing prevalence in industrialized, aging populations. Despite all three disorders having a genetic basis, it is becoming increasingly evident that variants of the DNA sequence alone do not fully explain the phenotypic picture of these NDs.

This means that non-genetic mechanisms, such as environmental/lifestyle factors and other factors related to transcriptional regulation of gene expression likely make substantial contributions to disease development. Specifically, this relates to epigenetic markers in blood, e.g., DNA methylation, which likely reflect the combined effects of disease-specific pathophysiological processes, exposure to environmental and lifestyle factors, and genetics. Thus, the investigation of their potential to serve as molecular biomarkers for AD, PD, and ALS is highly promising. However, while epigenetics research has gained momentum in recent years owing to the advent of high-throughput technologies, thus far, DNA methylation biomarker studies in AD, PD or ALS are typically limited to testing prevalent disease cases, which does not allow inferences on pathophysiological processes or risk prediction due to potential reverse causation. The only remedy is to conduct large prospective studies where biosamples of unaffected individuals are collected at baseline and these individuals are then followed longitudinally over many years. This is difficult to achieve and, as a result, there is a severe lack of sufficiently sized and appropriately characterized datasets with available predisease biomaterials for systematic biomarker identification. In this project, we propose to make use of one of the largest prospective cohorts ever assembled worldwide (i.e., the European Prospective Investigation into Cancer and Nutrition, EPIC) for biomarker identification in pre-disease blood samples of future AD, PD and ALS patients. In EPIC, blood samples were collected at baseline in 521,000 healthy individuals in a highly standardized fashion, then aliquoted and stored in liquid nitrogen. During the more than 20 years of follow-up, a substantial fraction of the participants has been diagnosed with neurodegenerative diseases, including AD, PD, and ALS. The main aim of our project ("EPIC4ND") will be to assess whether DNA methylome profiles derived from blood samples prior to disease onset in EPIC participants (n=6,900) can predict a later conversion to AD, PD and ALS. To this end, we will generate DNA methylation profiles in pre-disease biosamples of EPIC individuals who later developed AD (n=900), PD (n=900) or ALS (n=300) and will compare them to equivalent profiles of matched controls (n=4,800) randomly drawn from within the EPIC cohort. These data will be analyzed together with other "-omics" data generated in separate projects from the same individuals (i.e. genome-wide SNP genotyping, transcriptomics, and proteomics) as well as variables from the extensive EPIC database, including questionnaire-based pre-disease exposure/lifestyle and medical data. In a subset of individuals (n~100 AD patients), we will assess longitudinal changes of methylation markers possibly reflecting pathological processes. In summary, EPIC4ND is in the unique position to use pre-disease biosamples to build novel multivariate and multi-omics disease prediction models allowing for an earlier detection, therapy and ultimately prevention of these three devastating diseases.

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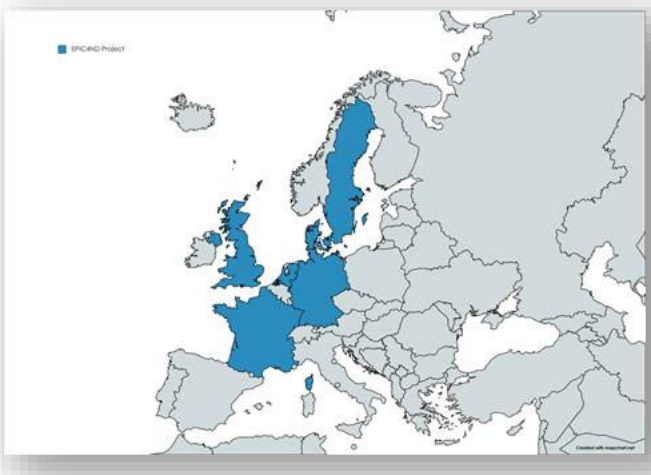

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