Genetic pleiotropy in neurodegeneration

https://neurodegenerationresearch.eu/survey/genetic-pleiotropy-in-neurodegeneration/

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Genetic pleiotropy in neurodegeneration

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Alzheimer's disease & other dementias

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Research Abstract

Alzheimer’s disease, frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS are severely disabling and fatal
neurodegenerative diseases. Although they have very characteristic phenotypes (Alzheimer’s disease: progressive memory

loss, ALS: progressive weakness), there are also many commonalities. They are late onset, progressive diseases in which
there is aggregation of specific proteins. The etiology of most neurodegenerative diseases remains poorly understood, but
there is mounting evidence that genetic risk factors play a large role.
Interestingly patients affected by neurodegenerative disorders may also develop (features of) other neurodegenerative
diseases. For instance FTD patients may develop ALS, ALS patients can show signs of parkinsonism, etc. Recently several
genes have been identified that seem to cause multiple neurodegenerative disorders of which C9orf72 is perhaps the most
spectacular and has been implicated in FTD, ALS, parkinsonism, ataxia and psychosis. Other examples of pleiotropic genes
are ANG, FUS, MAPT and TARDBP. Most neurodegenerative disorders can present as familial or sporadic disease. Even
within families, where the disease is assumed to be due to a single mutation, there is high phenotypic variability and
non-penetrance is frequently observed. The main hypothesis underlying this proposal is that there are genes that predispose to
neurodegeneration in general and that it is the sum of mutations across multiple genes that determine phenotype. Recently
there have been several publications describing patients with mutations in multiple neurodegenerative genes. I propose that
phenotypic variability, overlap between disorders and non-penetrance are due to oligogenic inheritance of pleiotropic genes.
This hypothesis will be tested by analyzing whole exome sequencing data from large cohorts of Alzheimer’s, FTD, ALS patients
and controls. We will search for multiple risk factors within diseases as well as across different disorders

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