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### The importance of gene – environment interactions in Alzheimer disease and the emerging role of epigenetics

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Although a minority of Alzheimer's disease (AD) forms are single-gene disorders, showing an autosomal dominant inheritance pattern, most AD cases appear to be a complex disorder that is likely to involve multiple susceptibility genes and environmental factors. Much work has been done to identify susceptibility genes in AD, however the contribution of individual genes to the increase or decrease in risk appears generally low, as evidenced by the odd ratio values found.

Twin studies represent traditional methods to reveal the importance of environmental and genetic influences in complex traits/diseases. A plethora of studies on monozygotic or dizygotic twins discordant for numerous complex diseases, including AD, was performed, many of which came to the same conclusions: in twins discordant for a complex-age-related disease what differs is not the genome, but the epigenome.

Epigenetic modifications are common in complex diseases, including neurodegenerative diseases. For AD the most robust disease biomarkers resulting from candidate gene approach and epigenome-wide association studies (EGWAS) in post-mortem cortical samples and peripheral blood cells, will be reported.

Moreover epigenetics has been explaining us since the beginning of this century, how environmental factors such as diet, lifestyle, alcohol, smoking, pollutants, can interact with our genome. In recent years, more and more evidence has been accumulated confirming that experiences and the environment leave epigenetic marks on genes. These epigenetic modifications are similar to those found in pathological tissue samples, and in some cases a specific correspondence between environmental exposures and epigenomic alterations was found. Environmental factors, mainly nutrients but also life style factors, are key effectors towards epigenetic modifications.

Emerging evidence indicating that epigenetic changes are important cellular and molecular correlates of neurodegenerative diseases resulting from chronic neurotoxic chemical exposure will be reported, as well as specific environmental exposures linked to epigenetic modifications of AD-related genes.

Finally the periods most vulnerable for our epigenome to the effects of environmental factors as well as the importance of the reversibility of epigenetic modifications will be highlighted, in view of therapeutic strategies but also of potential primary prevention strategies.

#### **Keywords:**

Genetic factors; environmental factors; epigenetic biomarkers; Alzheimer disease.