

Molecular Signatures of Sexual Dimorphism in Symptomatic Alzheimer’s Disease (AD)

P1-008

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Molecular signature; Sexdifference; Tyrosine; neuroinflammation

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Alzheimer’s disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid plaques (by β-amyloid peptide), and tangles of hyperphosphorylated Tau protein, leading to inflammation and neuronal death. The manifestation and progression of AD vary between sexes; women represent two-thirds of cases, exhibiting greater hippocampal atrophy and progression. At the molecular level, women present a higher burden of toxic proteins, while men present alterations in inflammation and apoptosis pathways.	Post-mortem brain proteomics identified 6,581 proteins, of which 2,344 met selection criteria (sex, age, brain region, and absence of Parkinson's disease or multiple system atrophy). Proteins were grouped by sex and diagnosis and analyzed using WebGestalt to identify neuronal pathways associated with sex-specific biological differences. 1. POST MORTEM BRAIN TISSUE SAMPLES Post-mortem brain tissue samples (PMID: 32284590) 2. PROTEIN IDENTIFICATION Intensity 6581 proteins identified m/z 3. PROTEIN SELECTION 2344 proteins selected based on criteria: • Sex • Age • Brain region • Absence of Parkinson's disease or Multiple System Atrophy 4. GROUPING Proteins grouped by sex and diagnosis SEX DIAGNOSIS Control Parkinson's disease Multiple System Atrophy 5. BIOINFORMATICS ANALYSIS WebGestalt 6. BIOLOGICAL PATHWAY ANALYSIS Identification of biological pathways involved (focus on neuronal processes) • Synaptic signaling • Neurotransmission • Axon guidance • Neuronal development • Synaptic plasticity • Neuronal survival OUTCOME → Identification of different biological protein pathways and gender differences in the human brain. In women, the main alterations involved post-translational modifications, particularly gamma carboxylation and hydroxylation, along with changes in tyrosine catabolism. In men, PTK6 activation and HIF1A stabilization were the most prominent alterations, representing a hypoxia-adaptive response associated with reduced neuroinflammation and potential β-amyloid production. Enrichment ratio 0 20 40 60 80 100 120 140 160 180 200 sexo feminino DA PTK6 promotes HIF 1A stabilization Update and function of dendrites Signaling by Overexpressed Wnt Type EGFR L Inhibition of Signaling by Overexpressed EGFR EGFR interacts with phosphatases Catenin EGFR Transactivation by G-protein PTK6 events in ERBB4 signaling Thymine biosynthesis ATF6 (ATF6-α) activates chaperone genes Bacterial Infection Pathways Enrichment ratio 0 50 100 150 200 250 300 sexo masculino DA Figura 2: sexo masculino DA The results demonstrate a dimorphism in symptomatic AD, with women presenting alterations in post-translational processes and neurotransmitter metabolism, while men present dysfunctions in pathways of response to hypoxia, signaling, and neuroinflammation. These distinct profiles indicate that the pathological mechanisms of the disease vary between the sexes. These findings reinforce the need for sex-stratified diagnostic and therapeutic strategies. doi: 10.1038/s41467-019-09613-z doi: 10.3390/biomedicines11051261 doi: 10.1038/s41591-025-03564-3 doi:10.1038/s41591-020-0815-6   			

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Figure 2: sexo masculino DA

The results demonstrate a dimorphism in symptomatic AD, with women presenting alterations in post-translational processes and neurotransmitter metabolism, while men present dysfunctions in pathways of response to hypoxia, signaling, and neuroinflammation. These distinct profiles indicate that the pathological mechanisms of the disease vary between the sexes. These findings reinforce the need for sex-stratified diagnostic and therapeutic strategies.

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