APOE ε4 STRATIFICATION OF ALZHEIMER´S DISEASE PATIENTS DEFINES TWO DISTINCT SET OF PLASMA METABOLIC MARKERS RELATED TO LIPID OR MITOCHONDRIAL METABOLISM DYSFUNCTION

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BACKGROUND

APOE ε4 is arguably the most important genetic risk factor for late onset AD (LOAD). As a major apolipoprotein, its role in lipid metabolism is clear. Several studies show that AD patients with at least one copy of the *APOE* ε4 *allele* (*APOE* ε4 carriers) progress faster and have more severe symptoms and cognitive decline than AD patients with no copies of the *APOE* ε4 *allele* (*APOE* ε4 non carriers). Some authors have recently raised the hypothesis that AD is a heterogeneous disorder that includes several subtypes with different etiology depending on *APOE* ε4 carriership. Accordingly, metabolic differences in L-carnitine concentration in CSF (1) and plasma lipidome metabolites (2) between *APOE* ε4 carriers and *APOE* ε4 non carriers have been reported. In line with this hypothesis, we explored whether *APOE* ε4 carrier status modify the metabolomics profile of AD patients compared to normal cognition controls.

RESULTS

Metabolites selected for creation of discriminative signatures

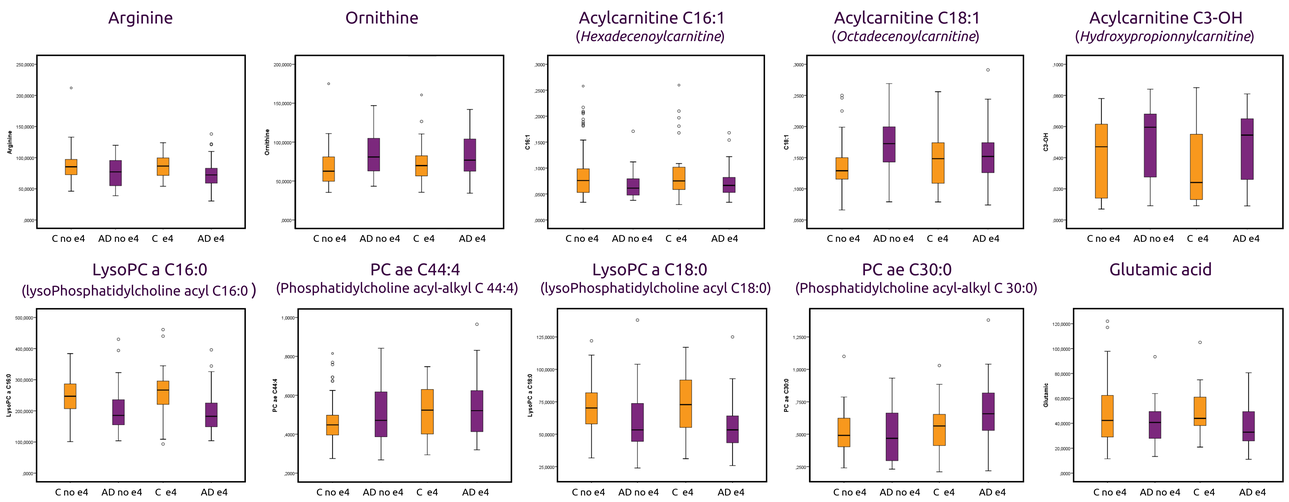

Figure 2. Box plots show metabolite concentration (μm) in each diagnostic group. Horinzontal lines within each box represent the median of the sample, while the bottom and top of each box represent the lower and upper quartiles respectively. Whiskers represent the lower and highest value of each set of data, excluding outliers. Outliers are represented as small circles.

Discriminative signatures for *APOE* ε4 carriers and *APOE* ε4 non carriers

METABOLIC BIOMARKERS	*APOE* ε4 non carrier	*APOE* ε4 carrier
Mitochondrial	Arginine Ornithine Acylcarnitine C16:1 Acylcarnitine C18:1 Acylcarnitine C3-OH	-
Membrane lipid	Lyso PC a C16:0 PC ae C44:4	LysoPC a C18:0 PC ae C30:0
Neurotransmiter	-	Glutamic acid
Accuracy (1-missclassification rate)	**0,84**	**0,71**

Our results show that different signatures for the discrimination of AD patients and controls are obtained after stratification of *APOE* ε4 status. Discriminative signature for APOE ε4 non carriers is mainly composed by mitochondrial biomarkers (metabolites involved in the urea cycle – arginine and ornithine – , and classical mitochondrial markers (acylcarnitines)). On the contrary, mitochondrial metabolites are absent in the discriminative signature for APOE ε4 carriers, which is mainly composed by lipid metabolites.

MATERIAL AND METHODS

Subjects: A total of 223 individuals classified by diagnosis as Normal Cognition (C, n=133), MCI (n=15) and Alzheimer disease (n=75) were recruited. Diagnosis was based on neuropsychological tests (MMSE) and CSF analysis of Aβ42 and tau and p-tau levels. For this work, MCI and AD patients were pooled into a single group with cognitive dysfunction (AD).
Metabolite analysis: A total of 188 metabolites were analyzed in plasma samples from patients and controls using the validated quantitative kit *Absolute IDQ® p180 kit* (Biocrates, Innsbruck). This kit comprises 40 acylcarnitines, 42 amino acids and biogenic amines, 15 sphingolipids, 90 glycerophospholipids and sum of hexoses.
Statistical analysis. An iterative model building approach (see figure 1 below) was applied to identify discriminative signatures after *APOE* ε4 status stratification (C no e4 (n=99), AD no e4 (n=36), C e4 (n=34), AD e4 (n=54).

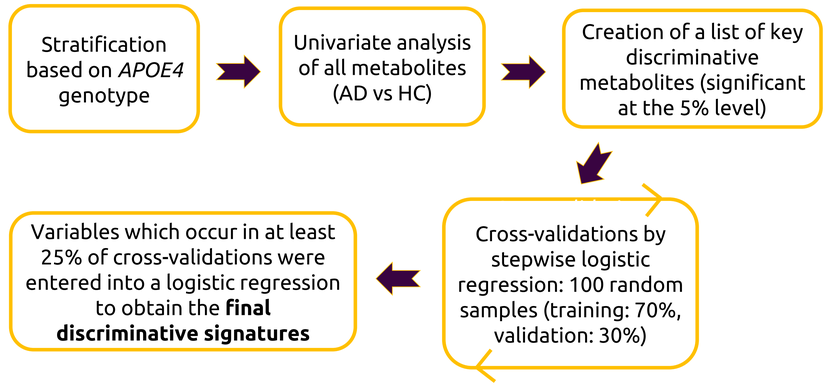

Figure 1. General model/ classification rule building process for the creation of discriminative signatures.

CONCLUSSION

APOE ε4 stratification of Alzheimer's disease patients defines two distinct sets of metabolomics markers related to lipid (*APOE* ε4 carriers) or mitochondrial (*APOE* ε4 non-carriers) metabolism dysfunction. Stratification according to *APOE* ε4 status may help to identify specific subsets of metabolomics markers for a more accurate risk prediction diagnosis and disease diagnosis.

REFERENCES

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