

APOE4 is a risk-factor gene associated with the metabolic syndrome

The *metabolic syndrome* (MetS) is a cluster of risk factors that may lead to diabetes and heart diseases. Symptoms related with the MetS are obesity, high blood pressure, and elevated glucose or lipids in the plasma. The main lipid (fat) species in the human plasma are triglycerides, phospholipids and cholesterol. As fat does not mix well with water, to be transported in plasma these lipids have to be complexed with proteins. Some of these proteins are apolipoproteins and the particles resulting from conjugating these apolipoproteins with lipids are known as lipoproteins. The different proportion of lipids and proteins in the lipoproteins gives characteristic density properties, so that particles acquire a greater density and smaller size with increasing protein content compared to lipid. According to their density, we distinguish: chylomicrons (Qm), very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL).

The apolipoprotein E (APOE) associates with Qm, VLDL and HDL, and it is the main ligand of lipoprotein receptors. Due to genetic variation, the human APOE has three different forms called APOE2, APOE3 and APOE4. APOE3, the most common form, is present in the 70-80% of the population while the less common, APOE2 and APOE4 are present in the 10-15% and 20-25% of the population, respectively. These forms only differ in two positions of their DNA sequence. Yet, this small change radically alters the protein behavior. APOE4 presence is a confirmed risk factor for important morbidities such as Alzheimer's disease and cardiovascular disease. We hypothesize that it also contributes to the development of the MetS as it may affect all the MetS components. APOE4 carriers have increased plasma levels of triglyceride- and cholesterol-rich lipoproteins. Some studies have also proven an APOE4 effect on blood pressure and glucose metabolism. Furthermore, obesity is a prominent aspect of the MetS and, and APOE is also produced in the adipose tissue where it plays an important role regulating its functionality.

Considering this background, we studied individuals enrolled in the Aragon Workers Health Study (AWHS) in Spain and the Coronary Artery Risk Development in Young Adults (CARDIA) in the USA, to determine the relationship between APOE4 and prevalence of the MetS in subjects with different body mass index (BMI).

Our analysis revealed that there was an association between APOE4 presence and the MetS, and that this association was stronger in overweight subjects. For these individuals, the MetS risk was 30 % higher in APOE4 carriers than in non-carriers. We know that adipose tissue dysfunction is of paramount importance in the development of obesity-associated complications, including the MetS.

Consequently, we explain these results as the presence among the APOE4 carriers of a dysfunctional adipose tissue which caused, at least partially, the augmented MetS risk. This association was not observed in individuals with normal weight, because they had little fat, or in obese individuals because the mild increase of the MetS risk caused by the APOE4 presence may

be masked by the dramatic effect that an excessive expansion of the adipose tissue *per se* has on increasing the risk of developing the MetS. Thus, there is an elevated risk of the MetS when the dysfunctional APOE4-expressing adipose tissue enlarges moderately, as we observed in the overweight AWHs and CARDIA subjects.

Considering that the disturbances of the MetS are preventable and even reversible by early detection, we hope that the characterization of individual's APOE genotype may help identify at-risk overweight persons for preventive intervention.

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Publication

[Apolipoprotein E4 association with metabolic syndrome depends on body fatness.](#)

Torres-Perez E, Ledesma M, Garcia-Sobreviela MP, Leon-Latre M, Arbones-Mainar JM
Atherosclerosis. 2016 Feb