Epistasis, physical capacity-related genes and exceptional longevity: FNDC5 gene interactions with candidate genes FOXOA3 and APOE

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Background: Forkhead box O3A (FOXOA3) and apolipoprotein E (APOE) are arguably the strongest gene candidates to influence human exceptional longevity (EL, i.e., being a centenarian), but inconsistency exists among cohorts. Epistasis, defined as the effect of one locus being dependent on the presence of 'modifier genes', may contribute to explain the missing heritability of complex phenotypes such as EL. We assessed the potential association of epistasis among candidate polymorphisms related to physical capacity, as well as antioxidant defense and cardiometabolic traits, and EL in the Japanese population. A total of 1565 individuals were studied, subdivided into 822 middle-aged controls and 743 centenarians. Results: We found a FOXOA3 rs2802292 T-allele-dependent association of fibronectin type III domain-containing 5 (FDNC5) rs16835198 with EL: the frequency of carriers of the FOXOA3 rs2802292 T-allele among individuals with the rs16835198 GG genotype was significantly higher in cases than in controls (P<0.05). On the other

hand, among non-carriers of the APOE 'risk' ?4-allele, the frequency of the FDNC5 rs16835198 G-allele was higher in cases than in controls (48.4% vs. 43.6%, P<0.05). Among carriers of the 'non-risk' APOE ?2-allele, the frequency of the rs16835198 G-allele was higher in cases than in controls (49% vs. 37.3%, P<0.05). Conclusions: The association of FDNC5 rs16835198 with EL seems to depend on the presence of the FOXOA3 rs2802292 T-allele and we report a novel association between FNDC5 rs16835198 stratified by the presence of the APOE ?2/?4-allele and EL. More research on 'gene*gene' and 'gene*environment' effects is needed in the field of EL.

Ageing

APOE

Centenarians

Exceptional longevity

FNDC5

FOXO3A

apolipoprotein E

complementary RNA

cyclin dependent kinase inhibitor 2B

fibronectin

fibronectin type III domain containing 5

glutathione peroxidase 1

manganese superoxide dismutase

unclassified drug

apolipoprotein E

fibronectin

FNDC5 protein, human

FOXO3 protein, human

transcription factor FKHRL1

ACTN3 gene

aged

APOE gene

Article

ASCL1 gene

CDKN2B AS1 gene

controlled study

energy metabolism

epistasis

exceptional longevity

female

FNDC5 gene

FOXOA3 gene

gene

gene frequency

gene interaction

genetic association

genetic polymorphism

genotype

GPX1 gene

human

Japanese (people)

longevity

male

physical capacity

PTK2 gene

SOD2 gene

TRHR gene

very elderly

adult

exercise

genetics

longevity

middle aged

single nucleotide polymorphism

young adult

Adult

Apolipoproteins E

Epistasis, Genetic

Exercise

Female

Fibronectins

Forkhead Box Protein O3

Gene Frequency

Genotype

Humans

Longevity

Male

Middle Aged

Polymorphism, Single Nucleotide

Young Adult