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International Congress on GERIATRICS AND GERONTOLOGY

October 18-19, 2021 | Webinar

Disentangling the genetic contribution of *IP6K3* and *IPMK* variations in LOAD and longevity: evidence for a multifaceted signaling network at the crossroad between neurodegeneration and survival

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The study of centenarians, exceptionally long-lived individuals that in most cases experienced a delayed aging, has arisen growing interest for its potential to reveal information on the combination of genes and lifestyle factors that can prevent or postpone age-related diseases (Garagnani et al., 2013).

Literature data report several genetic variants predisposing, for instance, to neurodegeneration which may also associate with human longevity diseases (Giuliani et al, 2018). In the inositol pathway, IP6K3 and IPMK regulate many crucial biological functions by mediating synthesis of inositol poly- and pyrophosphates (Tsui et al, 2010; Livermore et al, 2016). Furthermore, they regulate cellular functions non-enzymatically via protein-protein interactions. In two previous works, we demonstrate that the genetic variability of IP6K3 affected Late Onset Alzheimer Disease (LOAD) and IPMK may influence longevity (Crocco et al, 2016; De Rango et al, 2019). Then, we tested the cross-association of these genes with the two phenotypes, by replicating the study in the same sample groups, and investigating whether variants of IP6K3 may affect longevity, and variants of IPMK LOAD susceptibility. We found that: i) a SNP of IP6K3, previously associated with increased risk of LOAD, increased the chance to become long-lived, ii) SNPs of IPMK, previously associated with decreased longevity, were protective factors for LOAD. Furthermore, SNP-SNP interaction analysis highlighted phenotype-specific interactions between sets of alleles. Moreover, linkage disequilibrium and eQTL data associated to analyzed variants suggested mitochondria as crossroad of interconnected pathways crucial for susceptibility to neurodegeneration and/or longevity.

Overall, our data support the hypothesis that in complex traits interactions may be more important than single polymorphisms and prompt to a holistic view in future research questions, candidating pathways respect to single genes. In fact, interactions may contribute to the non-additive heritability of neurodegeneration and longevity and be part of the missing heritability of these traits.

Biography

Paolina Crocco has her expertise in research the impact of genetic variability on several human complex traits, including normal and pathological aging as well as longevity. She has explored various analytical approaches, from case-control studies using the candidate gene approach, to linkage disequilibrium analysis in regions involved in human longevity, up to the integration of demographic data to genetics. Currently her studies are dedicated to the analysis of large datasets of SNPs through network approaches, to the pathway-based analysis of SNPs sets related to human aging and age-related diseases, as well as to the study of the contribution of non-genetic factors, including nutrition, in the predisposition to a successful aging. In addition to genetic factors, epigenetic events are emerging as important factors in aging and longevity. In this context, she is investigating the role of specific circulating microRNAs in the development of frailty in the elderly.

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