Response by Giuliani et al to Letter Regarding Article, "genetics of Human Longevity Within an Eco-Evolutionary Nature-Nurture Framework"

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RE: Circulation Research Response Letter MS#CIRCRES/2018/314440
Title: Response to Letter to the Editor

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We thank Professor Brian Morris to have brought to our attention on studies linking FOXO3 genetic variability and CHD mortality, stroke and hypertension that we did not cited in our review. In particular four papers [1–4] are candidate-gene studies and two of them have been performed in the same group of individuals [1,2] and not validated in different populations and in an adequate number of cases.

In order to understand such a decision we like to stress the following:

1. the main purpose of our review was *"to describe the genetics of longevity as a highly context-dependent phenomenon, within a new integrated, ecological, and evolutionary perspective.... The available literature has been scrutinized within this perspective, paying particular attention to factors (sex, individual biography, family, population ancestry, social structure, economic status, and education, among others) that have been relatively neglected"* rather than to provide a detailed report of all the studies present in the literature on the genetic variants involved in both longevity and in cardiovascular diseases (CVD). Accordingly, we have given priority to GWAS studies with respect to studies on single SNPs in candidate genes, being aware that many interesting results, including those on FOXO3, would not have been considered owing to our focus on the most robust genetic features shared by longevity and CVD.
2. To identify genes involved in both longevity and CVD we interrogated the GenAge [5] and CardioGenBase databases [6] and the Venn diagram (Figure 9) depicted those genes shared by the two conditions. The result showed that FOXO3 gene was not present at the intersection, indicating that FOXO3 genetics is not yet recognized as a major heritable component of CVD phenotypes.
3. To further verify this result we have performed a scan of additional GWAS and reviews on the genetics of CVD (not reported in our review) [7–10] and still FOXO3 do not emerge. The reason for such a negative result can be: i) the gene variants are not involved in CVD; ii) FOXO3 plays a role in the last decades of life poorly investigated in most studies on CVD genetics.
4. The above-mentioned arguments explain our sentence "As far as we know, no evidence has been reported for FOXO3 and cardiovascular disease" that has been questioned by Professor Morris.

5. In order to support the role of FOXO3 variants in CVD, Professor Morris provides evidence from a mixture of human and preclinical studies. To this regard we clearly stated in our review that we did not cover studies on animal models.
6. It is not clear to us the reference about the correlation between FOXO3 and intelligence. Even if the field of the genetics of human behavior should be considered in longevity this topic was out of the purpose of our review.

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Disclosures

None

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