



Commentary

Untangling the knot: Lifetime physical exercise and amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is now recognized as a complex disease, characterized by the interaction between genetic and environmental factors. However, unlike prototypic multifactorial disorders, such as Alzheimer disease and multiple sclerosis, the genetic footprint in ALS is more marked. In fact, depending on the methodologies utilized, the heritability of ALS has been estimated to range between 20 to 60 percent [1]. Nevertheless, in the clinical setting the frequency of patients with a clear-cut family genetic origin of ALS or frontotemporal dementia (FTD) is about 10%. The gap between this latter figure and those derived by genetic approaches is likely due to gene variants with a reduced expressivity or penetrance.

The two last decades have seen an incredible development in our understanding of ALS genetics. Genetics has been instrumental to determine with confidence the strict link between ALS and FTD as a clinical and pathological continuum. At least 40 'Mendelian' genes have been proposed to be related to ALS, but for some of these genes, as well for certain variants of more established genes (eg, *SOD1*, *TARDBP* and *FUS*), there is still a large degree of uncertainty [2]. In addition, a few genetic variants have emerged as risk factors with non-Mendelian effect (for example, CAG intermediate expansions of *ATXN2* gene) or as modifiers of ALS genotype (such as the rs12608932A>C variant of *UNC13A* gene).

Among exogenous detrimental factors proposed in ALS, physical activity was initially reported in relation to participation in specific sports. In 2005, it was reported that Italian professional soccer players had a more than 6-fold increased risk for ALS compared to the general population. Even more importantly, their age at onset was more than 20 years younger than non soccer-playing individuals with ALS, and bulbar onset was disproportionately more frequent

than expected [3]. Both increased risk and anticipation effect have been subsequently described in retired American National Football League players with ALS [4]. Recently, an international case-control study showed robust evidence for a positive association between history of physical activity, both in leisure time (including sport) and/or occupational activities, and the risk of developing of ALS [5].

A major criticism to cohort and case-control studies is that they cannot determine the direction of causality. This flaw has been solved by the use of two novel techniques, the linkage disequilibrium score regression (LDSR) and Mendelian randomization (MR) which allow to test distinct aspects of the genetic architecture underlying a disease. Specifically, LDSR investigates whether polygenic risk contributing to a phenotype of interest might also contribute to the risk of ALS, and MR uses genetic data to assess whether an exposure exerts a causal effect on a particular outcome. Using both methodologies, it has been demonstrated that ALS shares polygenic risk genetic factors with a number of traits and conditions, including positive correlations with smoking status and moderate levels of physical activity, and negative correlations with higher cognitive performance, higher educational attainment, and mild levels of physical activity [6]. In addition, a recent paper showed that the relationship between ALS risk and exogenous factors (namely smoking habits, alcohol consumption, energy intake, physical activity, and body mass index) date back several decades before ALS onset and partially depends on C9orf72 status [7]. In the same direction, another paper demonstrated the presence of a functional motor reserve related to lifetime sport practice in ALS through brain ¹⁸F-FDG-PET [8].

The paper by Julian et al, [9] published in this issue of *EBioMedicine*, has examined the relationship between ALS and physical exercise using three different approaches, greatly enhancing our understanding of this interaction and adding important novel information. First, using MR the paper confirmed a causal relationship between genetic liability to frequent and strenuous leisure-time exercise and ALS. Second, transcriptomic analysis revealed that genes with altered expression in response to acute exercise are enriched with known ALS risk genes including C9ORF72, and with ALS-associated rare variants of unknown significance. Third, using a validated physical activity questionnaire in a small cohort of genetically selected ALS patients, the authors reported that age of onset is inversely

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proportional to historical physical activity for C9ORF72-ALS but not for non-C9ORF72-ALS. Furthermore, the variability in average physical activity was lower in C9ORF72-ALS compared to both non-C9ORF72-ALS and neurologically normal controls, a finding consistent with a homogeneous effect of physical activity in C9ORF72-ALS patients.

Taken together, these studies support the role of strenuous physical activity in the development of ALS, and highlights the notion that a patient's genetic background plays an important role in the modulation of this interaction. The study of other ALS-related genes, as well as of genetic modifiers of the phenotype in relation with lifetime expositions will probably reveal relevant mechanisms of the pathologic process of this disease, bridging the gap toward a personalized approach to patients' management.

Contributors

AC and GM co-wrote this commissioned Commentary.

Declaration of Competing Interest

Adriano Chiò and Gabriele Mora declare no competing interests.

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