PLIN1 gene: fat keeper and prevention switcher

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IT HAS LONG BEEN RECOGNIZED that the ability to become an elite athlete has a strong genetic basis. Support for this notion does not require the use of sophisticated laboratory genetic analyses, but just being a passive spectator of sporting events. When it comes to athletics (specifically, track and field), the world record for short distance is currently held by a Jamaican, on the other hand, for endurance races such as the marathon, it is almost expected that a Kenyan or an Ethiopian will rise to the podium. These differences suggest that it is not only a matter of global physical performance, but, in addition, there seems to be a strong genetic specialization that enables athletes to excel in different types of races. This is even more evident in light of comparisons among more dissimilar sports such as swimming or gymnastics, activities that seem to favor other ethnic groups. Whereas cultural and environmental factors play an important role, it is undeniable that a very strong genetic predisposition is needed to become an elite athlete and that this predisposition or set of genes will be different for a runner, a swimmer, or a gymnast. Therefore, since the first mention of the phrase "genetics of fitness and physical performance" over 25 years ago, considerable effort has been directed toward identifying the specific genetic basis determining the interindividual variability of physical performance as well as response to training (1). This knowledge could be used to identify those predisposed to become elite athletes and, moreover, guide the training to allow them to reach their peak, either in sports or in other types of activities requiring physical performance, such as the military. It was more than a decade ago when Montgomery et al. (6) published a series of findings describing the first gene associated with physical performance. Specifically, the I allele of the angiotensin-converting enzyme (ACE) I/D polymorphism was associated with lower ACE activity and endurance performance; an excess occurs in elite distance runners, rowers, and mountaineers, perhaps secondary to enhanced muscle efficiency. Conversely, the D allele is associated with training-related strength gain and elite power-oriented performance secondary to increased ACE and angiotensin II, a growth factor and regulator of blood pressure. Since these initial findings, additional supporting evidence has been accumulating linking differences in physical performance and response to training with genetic markers within chromosomal and mitochondrial DNA. Consolidation and solidification of this knowledge should open multiple possibilities ranging from identification and training of elite athletes to personalized prevention of common diseases in the general population.

Similar to physical performance and response to training, most of the common ailments affecting modern society have a genetic component, including cardiovascular diseases, cancer, diabetes, and obesity, with the latter reaching epidemic proportions in the last few decades in both the industrialized world and in developing countries. Obesity is also the result of a complex web of hundreds of genes and scores of environmental factors potentially implicated in its expression. Among the environmental/behavioral factors involved in obesity, the most significant are probably diet and physical activity. Both excess caloric intake and insufficient physical activity contribute to the accumulation of energy in the body in the form of adipose tissue. However, the rate of accumulation and/or release of that excess of energy stored in the adipocyte varies dramatically among individuals and several genes have been suggested to be involved in these processes. Among them, we can highlight the perilipin family of genes, encoding for the most abundant proteins surrounding the lipid droplet in the adipocyte (5). We and others have demonstrated that common genetic polymorphisms at the PLIN1 gene are associated with risk of obesity (7–9) as well as response to weight loss interventions (2). Moreover, we have found significant gene-diet interactions with several dietary components (3, 10). Therefore, the PLIN1 locus is becoming a candidate gene for obesity in humans supported by both genetic evidence as well as the evidence from experimental animal models. Moreover, given the previously indicated dietary interactions, PLIN1 could be used to guide therapeutic approaches toward more personalized and successful dietary recommendations and treatments for obesity as well as other components of the metabolic syndrome. However, diet is only one of the main factors involved and the current widespread sedentary lifestyle contributes as much as diet to the current prevalence of obesity.

The data presented by Jenkins et al. (4) unravel a new connection between the PLIN1 gene and the interindividual differences in the response of obesity and other cardiovascular disease-related phenotypes to exercise training. The genetic variants investigated by these authors were the most commonly occurring single nucleotide polymorphisms (SNPs) reported in Whites [6209 T>C (rs2289487); 11482 G>A (rs894160); 13041 A>G (rs2304795) and 14995 A>T (rs1052700)] and they were examined in a small sample of apparently healthy men (n = 46) and women (n = 55) aged 50 to 75 yr and with BMIs <37 kg/m². The investigators focused their efforts on two of these SNPs, namely 13041 A>G and 14995 A>T, previously reported as PLIN5 and PLIN6, names that should be discontinued to avoid confusion with the newly recommended nomenclature suggested for the perilipin family of genes. Using haplotype analyses defined by the 13041 A>G and the 14995 A>T SNPs, these investigators defined two relatively evenly sized groups, those who carried the most common AA alleles at both SNPs (n = 57) and those who did not (n = 44). Despite the small sample size, the data for these individuals replicated previous reports associating the minor alleles at these two SNPs with increased obesity risk. However, the most innovative finding came from the differences in response to a 6-mo endurance exercise training program. Although both subgroups benefited from the exercise training, fatness remained higher in the non-AA carriers, which could have reduced their maximal oxygen uptake (VO2max) adaptation to exercise training. In addition to fatness and VO2max training also affected lipid and glucose related parameters and some of these outcomes differed according to haplotype and sex. Most intriguing was the sex-specific response in insulin area under the curve (AUC) with training. Only non-AA male carriers
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significantly improved their insulin AUC with training. Interestingly, the previously reported associations between the PLIN1 gene and obesity-related parameters were also sex specific, as were gene-diet interactions reported for the HOMA-IR index, although in those instances the main effects and the diet interactions were noted exclusively in women.

These results add to the body of evidence in support of PLIN1 as an important obesity candidate gene in humans. Moreover, in addition to its potential usefulness in identifying those predisposed to obesity, this locus could be instrumental as a genetic “switcher” to facilitate the definition of more personalized recommendations to reduce obesity using behavioral (diet and physical activity) approaches. Nevertheless, the data should be interpreted cautiously given the limitations of this study. Several of them have been identified by the investigators, the most limiting being the small sample size which may be barely enough to detect main effects but clearly insufficient to investigate complex three-way interactions such as those presented in the paper. An additional caveat is the fact that none of the SNPs examined appears to be functional and although we and others have hypothesized that they may be in linkage disequilibrium with other functional variants, these have yet to be identified and reported. Despite the stated caveats and limitations, this paper supports previous findings related to associations of PLIN1 with obesity in humans. Moreover, it should foster some interest in replicating these findings in other populations to conclusively demonstrate the solidity of these observations.

The potential benefits of personalized medicine are remarkable; and this work contributes to the body of information that may lead us toward this goal; however, we should be careful about concluding that we can start identifying potential elite athletes or establish the ideal exercise program to decrease an individual’s cardiovascular disease risk based on the current genetic knowledge. After all, it has been more than a decade since the first “performance gene” was identified (6) and this knowledge has yet to be translated into practical applications. The development of reliable predictive genetics will have to rely on properly designed experimental studies emphasizing sample size and quality of the phenotypes, which represent major challenges limiting our ability to make adequate progress in this field.

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