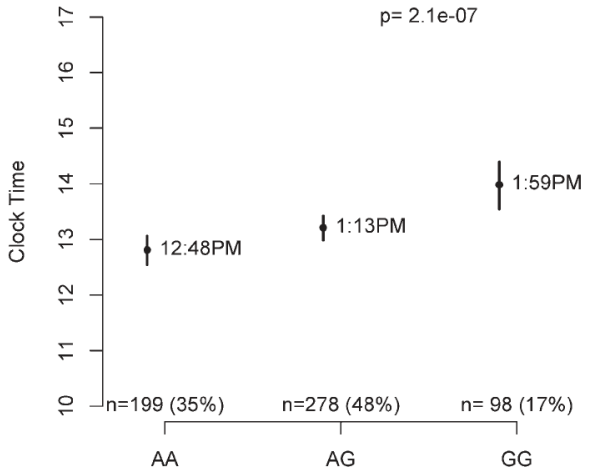
***PER1*: a clock gene that regulates circadian rhythms**

Physiological and behavioral patterns such as the sleep-wake cycle that repeats every 24 hours are called circadian rhythms. A number of genes known as "clock genes" are involved in setting an individual's circadian rhythm; different alleles of clock genes have been associated with variations in circadian rhythms in organisms as diverse as plants, fruit flies, and humans. These variations can range from individuals lacking a circadian clock entirely, so that their physiological and behavioral patterns fail to cycle in any particular timeframe, to individuals whose clock is shifted, so that peaks in their activity are either earlier or later in the day. For example, in humans, mutations in the clock gene *PER2* are associated with advanced sleep phase syndrome (ASPS), characterized by an extreme early shift in an individual's circadian rhythm (Toh KL, et al., 2001). Individuals with ASPS both fall asleep and wake early – their average day begins between 1:00 and 3:00 am, and ends between 6:00 and 8:00 pm. Mutations like the one that causes ASPS are relatively rare, but common variants have been identified in other clock genes that are associated with less extreme variations in circadian rhythms. For example, different alleles of the *PER1* gene are found in individuals with "early" circadian clocks as compared to individuals whose circadian clocks are shifted slightly later (Lim, ASP, et al., 2012). This shift is not as extreme as that observed in individuals with ASPS – as shown in the figure to the right, individuals homozygous for the "A" allele at the rs7221412 SNP at the *PER1* locus are active about an hour earlier than individuals homozygous for the "G" allele at this site. Researchers were able to detect a correlation between the genotypes of individuals at this SNP and the timing of their activity throughout the day. The researchers measured individuals' behavioral patterns using actigraphs (activity monitors) that were worn by study participants to provide a direct readout of their activity. The researchers calculated the time of acrophase for each individual by identifying the midpoint of the eight consecutive hours that each participant was most active (y-axis in figure). There was some overlap in the measured circadian rhythms of individuals with different genotypes, which could be due to the involvement of other genes and/or the environment in determining an individual's behavior. Despite this variability, the correlation between an individual's genotype at this SNP and his or her phenotype is quite strong. Additionally, there is a correlation between an individual's genotype and the time of day at which they died – individuals homozygous for the "G" allele died, on average, nearly seven hours later than individuals homozygous for the "A" allele or heterozygous.



The A/G SNP is not in the coding region of the *PER1* gene, but there is evidence that different alleles have different levels of *PER1* expression, which could explain why people with different circadian rhythms have different genotypes at this locus (Lim, ASP, et al., 2012).

***ACTN3:* a gene important for muscle function**

Skeletal muscle, which controls voluntary motion, is made of two main types of fibers. These fibers contract and relax to move the skeleton and thus, the body. The two types of fibers that comprise skeletal muscle can be distinguished both by their structure and function. Fast twitch fibers undergo rapid, powerful contractions, and generate the type of explosive power that is required for sprinting and other short, intense bouts of exercise. These fibers can generate a great deal of power, but only for a limited time – they fatigue relatively quickly. The contractions

of slow twitch fibers are longer and more sustained. These contractions are important for endurance exercise, such as marathon running and long-distance swimming. Most people have approximately equal numbers of fast and slow twitch muscle fibers, but elite athletes with different specialties have different ratios of fast:slow twitch muscles. Top marathoners often have a higher proportion of slow twitch muscle fibers (up to 80%), while athletes for whom power is most important can have up to 80% fast twitch muscle fibers.

An individual's athletic performance is dependent on a number of different factors, including their genetic makeup, training, diet, and other variables. While training does not change the number of each type of fiber an individual has, it can influence fiber subtypes and the efficiency with which an individual can use different energy sources. For example, fast twitch fibers come in two subtypes based on how they obtain energy. Fast glycolytic fibers are specialized to power short bursts of muscle activity, and are anaerobic - they generate force without relying on the use of oxygen. As a consequence, they fatigue quickly. In contrast, fast oxidative fibers use aerobic respiration – by using oxygen in their energy-harvesting reactions, they are able to resist fatigue. Training can alter the ratio of glycolytic:oxidative fibers that an individual has, to make them better at either power or endurance sports. For example, an individual training for a marathon may convert some of their fast glycolytic fibers to fast oxidative fibers, thus improving their ability to maintain their performance for an extended period of time.

Athletic performance is also influenced by genetics. A number of different genes have been identified that contribute to an individual's muscle performance, and thus their athletic ability. Therefore, it is a complex trait. For example, the ACE gene, which encodes a protein known as angiotensin converting enzyme, is involved in regulating blood flow throughout the body. Some individuals have an insertion in the ACE gene that reduces its expression level. In some, but not all, studies, this "I" allele is found more commonly in elite endurance athletes than in power athletes or non-athletes. The mechanism by which a reduction in angiotensin converting enzyme activity leads to improved performance in endurance sports is still not well understood, and the association is stronger in some populations than others. However, it is an interesting candidate for further study.

Other genes are required for the function of different types of muscle fibers. For example, a-Actinin 3 is a protein that is found in fast-twitch muscle fibers and is involved in muscle contractions. When a muscle contracts, actin and myosin filaments in the muscle fiber slide past each other. a-Actinin 3 helps to stabilize the actin filaments in fast twitch muscles. Individuals homozygous for the R577X mutation in the gene for a-Actinin 3, ACTN3, have two copies of a nonfunctional allele that changes the CGA arginine codon at rs1815739 to a TGA stop codon. This mutation acts as a deficiency, resulting in a lack of a-Actinin 3 protein production. The absence of a-Actinin 3 in the fast-twitch muscle fibers of these individuals reduces their performance at athletic activities that rely on power. However, this T allele is overrepresented in endurance athletes because the lack of a-Actinin 3 enhances their performance in activities like long-distance running or cycling. Muscle cells in mice that have been genetically modified to lack a-Actinin 3 activity show an increase in fast oxidative fibers (and a reduction in fast glycolytic fibers), suggesting that individuals with the T allele may be better at endurance sports because their muscles rely more on the oxidative pathway to release energy, and fatigue more slowly (MacArthur, DG et al., 2007). The frequency of the T and C alleles vary in different populations, though the C allele is more common in most, if not all, populations.

TAS2R38: **a gene encodes for a bitter taste receptor**

Genetic variation can also cause differences in individuals' perceptions of taste and odor. The human genome encodes approximately 400 different odorant receptors, each of which is responsible for detecting a different type of odorant. Individuals with different alleles of these receptors show different sensitivities for different odorant molecules, and due to the large number of odorant receptors and alleles, there is great variation in odor perception from one

person to another. The number of taste receptors is lower, but genetic variation in the genes that encode these receptors can have a dramatic effect on how different people taste particular foods. For example, the TAS2R38 locus encodes a taste receptor that is largely responsible for an individual's ability to taste bitter things. Individuals homozygous or heterozygous for the valine (C) allele at the rs10246939 SNP are able to taste compounds like propylthiouracil or phenylthiocarbamide (PTC), which make cabbage, coffee, and other foods taste bitter. These individuals are considered "tasters" because of their ability to taste these compounds. Individuals homozygous for the T allele have an isoleucine at this site and are insensitive to these molecules, and thus they do not taste bitter (Kim, UK, et al., 2003). Other bitter taste receptor genes can compensate for the "taste blind" allele of TAS2R38. For this reason, approximately 20% of individuals homozygous for the T allele are still able to detect bitter compounds – they have a second gene whose function is redundant with TAS2R38. The alleles that "tasters" have at these and other loci influence their ability to detect bitter compounds as well as the severity of their response to them (Bufe, B, et al., 2005).

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