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PERIOD3 gene P415A/H417R polymorphism-linked familial advanced sleep phase

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Evidence of transcriptional investigations in human medicine showed that significant segments of the genome are regulated by the circadian clock, and more than half of protein-encoding genes exhibit circadian oscillation in different forms across tissues [1]. There is a strong association between the circadian clock gene *PERIOD3* (*PER3*) P415A/H417R variants and familial advanced sleep phase (FASP) [2]. The P415A and H417R are rare variants *of PER3* gene. The *PER3*-P415A/H417R polymorphism may alter the period of circadian clock oscillation. FASP is a rare autosomal dominant trait and human behavioral phenotype [3]. One feature that differentiates FASP from advanced sleep phase disorder is its robust familial trend and lifetime expression. Genetic sequencing analysis of affected lineages revealed that nearly 50% of related family members have FASP [4]. Individuals with FASP usually have a short circadian period, an advanced circadian phase, phase-advanced plasma melatonin levels and body core temperature rhythms, and a typical morning chronotype [3]. Individuals with FASP experience constant early evening sleep onset and early morning awakening [5].

Ever since Dr Zhang and colleagues [2] showed a robust association between *PER3*-P415A/H417R variants, FASP, and related seasonal affective disorder (SAD), no other scientific investigation has been carried out to unravel more information regarding the underlying pathophysiology, and relationship between *PER3*-P415A/H417R polymorphism, FASP, and mood disorders. The *PER3*-P415A/H417R polymorphism was detected in genetic sequencing analysis, and SAD was also diagnosed in individuals with FASP. Moreover, SAD is a seasonal pattern of recurring major depressive periods that frequently occur during autumn or winter and drops in spring [6]. Dr Zhang and colleagues infused the *PER3*-P415A/H417R variants on mice, and the mice showed symptoms of depression and poor sleep quality, suggesting an association between the P415A/H417R missense mutations and mood disorders, hence demonstrating a relationship between poor sleep quality and depression.

The P415A and H417R missense mutations in the *PER3* gene occur on the same allele, a C-to-G transversion resulting in the substitution of proline for alanine at position 415, and an A-to-G transition resulting in the substitution of histidine for arginine at position 417 [2]. The two missense heterozygous mutations in the *PER3* gene were mapped at chromosome *1p36.23*. The *PER3*-P415A/H417R variants function as a link, connecting the regulatory processes of circadian rhythms with those of mood, and it partakes in the modulation of these processes to adjust to the short photoperiods during winter. Expression of the variant allele in transgenic mice resulted in a longer circadian period under constant light, and phase shifts of the sleep-wake cycle in a shorter light period, as detected in winter, and increased depression. The mutant protein was also expressed at levels lower than the control values, due to decreased stability, and the failure to stabilize the *PERIOD1* and *PERIOD2* proteins, which play vital roles in circadian timing. There are few studies that reported on the prevalence of *PER3* gene polymorphism in different ethnic groups worldwide. According to the outcome of a study conducted in Brazil, the allele frequency of 4 repeats in the *PER3* gene was much higher in Asians than Caucasians, and this might be attributed to evolutionary processes that have reformed these genetic patterns in diverse ethnic groups [7]. However, Nadkarni et al. did not observe any significant variation in the pattern of *PER3* allele frequencies among European American, African American, and East

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Asian populations [8]. One study that examined the association between sleep duration and mood traits in *PER3* genotype groups among Brazilian families living in Baependi, a small rural town in Brazil, showed an association between *PER3* genotype, sleep duration and depression symptoms [9].

In conclusion, genetic testing to detect *PER3*-P415A/H417R polymorphism during genetic sequencing analysis in individuals and families with symptoms of advanced sleep phase disorder or SAD is important in the diagnosis of FASP. However, further studies on FASP-related *PER3*-P415A/H417R variants will offer more clue on the association between sleep-wake cycle, extreme diurnal preference in arousal and activity, and mood regulation. Furthermore, advanced laboratory and clinical investigations on *PER3*-P415A/H417R polymorphism-linked FASP may present evidence on how to develop pharmaceutical agents to target depression associated with poor sleep quality due to the disruption of the circadian clock. Moreover, there is a need to conduct large experimental studies concerning *PER3* gene polymorphism in different ethnic groups around the world.

Abbreviations

PER3: *PERIOD3*; FASP: Familial advanced sleep phase; SAD: Seasonal affective disorder

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Author's contributions

CEO did the literature search, wrote the manuscript, drafted the manuscript, and revised the manuscript critically. The author read and approved the final manuscript.

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Competing interests

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