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SHORT REPORT

Genetic factors underlying insomnia and ovarian insufficiency

M. Moysés-Oliveira[a*], A. M. C. Scaff[a*], L. N. G. Adami[a,b*], H. Hachul[a,b], M. L. Andersen[a,b] and S. Tufik[a,b]

[a]Sleep Institute, AFIP, São Paulo, Brazil; [b]Departamento de Psicobiologia, Universidade Federal de São Paulo, São Paulo, Brazil

ABSTRACT

Premature ovarian insufficiency (POI) is characterized by a loss of regular hormone production and egg release in women below the age of 40 years, which often leads to infertility, vaginal dryness and dysfunctional sleep. Acknowledging the common co-occurrence of insomnia and POI, we tested the overlap between POI and insomnia-associated genes, which were implicated in previous large-scale populational genetics efforts. Among the 27 overlapping genes, three pathways were found as enriched: DNA replication, homologous recombination and Fanconi anemia. We then describe biological mechanisms, which link these pathways to a dysfunctional regulation and response to oxidative stress. We propose that oxidative stress may correspond to one of the convergent cellular processes between ovarian malfunction and insomnia pathogenic etiology. This overlap might also be driven by cortisol release associated with dysregulated DNA repair mechanisms. Benefiting from the enormous advances in populational genetics studies, this study provides a novel outlook on the relationship between insomnia and POI. The shared genetic factors and critical biological nodes between these two comorbidities may lead to identification of putative pharmacological and therapeutical targets, which can leverage novel approaches to treat or alleviate their symptoms.

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Premature ovarian insufficiency (POI) is characterized by loss of regular ovarian function before age 40 years [1], with dysfunctions including sleep disturbances [1]. Although hormone therapy can alleviate some manifestations, for example vasomotor symptoms and sleep quality [2], sleep problems have been reported as persistent [3]. Among factors which contribute to POI's multifactorial etiology, genetic components are well established (e.g. Turner syndrome) [4] and continue to be leveraged by recent genome-wide association studies [5]. Here, we aim to pinpoint genetic factors underlying the convergence between insomnia and ovarian failure, identifying biological pathways that drive this clinical overlap.

To assess the overlap between POI and insomnia genetic architectures, we curated one gene list for each of those traits (see Supplementary Table 1). Our gene list for insomnia was gathered from the two largest-scale genome-wide association studies for this trait ever performed [6,7], whose inclusion criteria were: difficulties initiating or maintaining sleep, daytime complaints at least three times a week for 3 months (which could not be attributed to inadequate sleep conditions), increased sleep-onset latency, and frequent and prolonged night awakenings. The POI gene list was based on the compilation of a pre-established set of POI-associated genes [8] with genome-wide association study-implicated genes [9]. The latter corresponds to a large-scale genetic assessment of a cohort composed by women with amenorrhea; elevated gonadotropin levels with menopausal levels of follicle stimulating hormone (FSH), estradiol and anti-Müllerian hormone (AMH); and disappearance of menstrual cycles, defective folliculogenesis and/or absent pubertal development [5]. Following the statistical assessment of the overlap between those two gene lists (Fisher's exact test), we used the newfound intersect list to identify enriched biological pathways (Benjamini–Hochberg test, adjusting for multiple comparisons). We considered as relevant those pathways with $p < 0.05$ and at least three genes involved.

There were 27 overlapping genes (Figure 1; see Supplementary Table 2) between the lists associated with insomnia and the gene list associated with POI, indicating a significant overlap ($p = 2.5 \times 10^{-3}$, odds ratio = 1.9). Significantly enriched terms were the 'DNA replication', 'homologous recombination' (HR) and 'Fanconi anemia' pathways (Table 1). These three pathways revolve around DNA repair processes. When considering the interplay between the investigated phenotypes and DNA repair, oxidative stress (OS) might correspond to a central player in this association. In accordance with this hypothesis, we observed OS-related terms with nominal statistical significance in our pathway enrichment analysis (see Supplementary Table 3).

The connection between OS and POI is based on the fact that the latter has been reported as accompanied by ovarian inflammation and, consequently, ovarian stroma deficiency [9]. Consistently, lower levels of inflammation biomarkers have been described in women with POI [10]. Regarding the association between OS and insomnia, lower levels of oxidative imbalance indicators have been found in patients with

CONTACT Mariana Moysés-Oliveira mariana.oliveira@afip.com.br Sleep Institute, AFIP, Rua Marselhesa, 500, São Paulo, SP 04020060, Brazil
*These authors contributed equally to this work.
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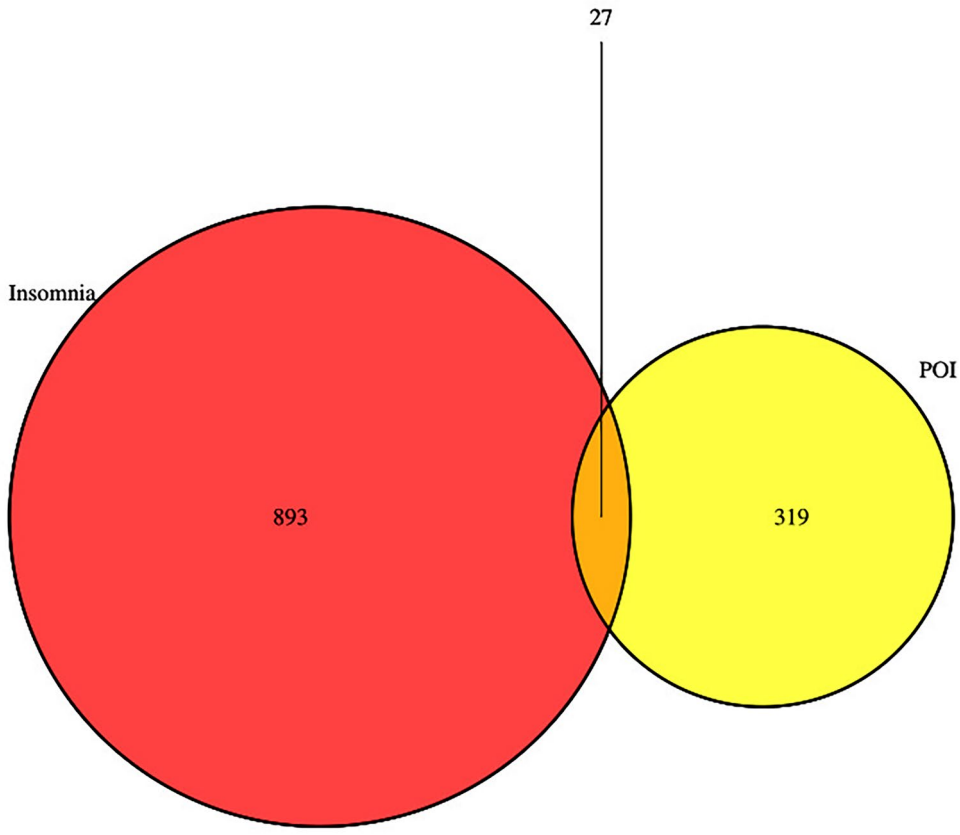

Figure 1. Venn diagram of overlapping insomnia and premature ovarian insufficiency (POI) gene lists. A subset of 27 genes were found after the intersection between 893 insomnia-related genes and 319 POI-related genes.

Table 1. Significantly enriched pathways for insomnia versus premature ovarian insufficiency (POI) gene intersect.

Term	*Overlap*	p-*Value*	*Adjusted* p-*value*	*Odds ratio*	*Associated intersect genes*
DNA replication (GO:0006260)	3/108	4.08×10^{-11}	4.0×10^{-2}	23.65	*TOP3A, CDKAP1, POLG*
Homologous recombination (KEEG)	3/41	2.26×10^{-11}	8.14×10^{-11}	65.58	*TOP3B, UIMC1, TOP3A*
Fanconi anemia pathway (KEEG)	3/54	5.20×10^{-10}	9.36×10^{-11}	48.83	*FANCI, TOP3B, TOP3A*

GO, Gene Ontology; KEEG, Kyoto Encyclopedia of Genes and Genomes.

this condition [11]. Populations at a higher OS risk have also presented increased sleep insufficiency, with lower mean levels of oxidative imbalance markers [12].

HR and OS share an important connection, since the latter has been associated with induction of chromosomic recombinogenic damage, responsible for triggering HR, which minimizes cell death due to oxidative DNA damage [13]. Fanconi anemia, an autosomal (MIM #227650, #227646, #227645) or X-linked (MIM #300514) recessive disorder responsible for hypogenitalism, hypogonadism and ovarian alterations, has been related to dysfunctional DNA repair mechanisms, with components under the Fanconi anemia pathway coordinating the HR process [14]. Therefore, Fanconi anemia pathogenesis may cause cells to be hypersensitive to OS [15], and less effective at repairing DNA damage.

Several biological processes can culminate in cellular OS, one of which is the activation of the hypothalamic–pituitary–adrenal (HPA) axis [16]. Stress-induced HPA mechanisms are relevant to insomnia [16] through decreased rapid eye movement sleep [17], arousal and sleeplessness [18]. Corticosterone, the rodent glucocorticoid analog to cortisol, initiates a cascade of reactions increasing the cellular metabolic rate, spiking ATP and superoxide (O_2^-) production, which is converted to hydrogen peroxide and, subsequently, to hydroxyl radical, the most deleterious free radical. Superoxide effects include DNA fragmentation, protein carbonyl formation and membrane lipid peroxidation [16]. The hypothalamic–pituitary–ovarian axis is strongly linked to ovulatory behavior and acts as an HPA regulatory target. The decrease of HPA and hypothalamic–pituitary–ovarian biomolecules, estradiol and progesterone has been observed in the context of psychological stress [16,19], and the imbalance of the neuroendocrine-immune biomolecular network leads to POI development [16].

DNA repair is one of the main biological processes for oocyte homeostasis. Expressed by oocytes, the 8-hydroxy-2′-deoxyguanosine (8OHdG) enzyme acts upon potential DNA damage in the sperm nuclei, after fertilization [20]. Besides being an OS biomarker, 8OHdG activity is related to preservation of the fertilization rate and embryo quality [20]. In POI pathogenesis, a disruption in the aforementioned pathways might affect this repair mechanism, leading to a disrupted axis, hormonal imbalance and ovarian failure.

Upon verification of the highlighted pathways, we can hypothesize the following path: cellular stress and cortisol release can induce OS, prompt DNA repair process, and impair sleep quality and proper ovarian cell functioning. OS caused by dysfunctional cortisol release may trigger the HR pathway and might be relevant for the overlap between insomnia and POI. Shared genetic factors between POI and insomnia may lead to a deeper understanding of biological mechanisms underlying both traits and point toward future research on more effective approaches to treat or alleviate their symptoms.

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ORCID

M. Moysés-Oliveira http://orcid.org/0000-0002-3233-932X
L. N. G. Adami http://orcid.org/0000-0002-5123-9236
H. Hachul http://orcid.org/0000-0002-3661-582X
M. L. Andersen http://orcid.org/0000-0002-1894-6748

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