

### Reproductive Hormone Sensitivity and Obsessive-Compulsive Disorder: Are There Differences in the Genetic Predisposition Between Symptom Dimensions?

**To the Editor:** We have read with interest the recent article by Forray et al,<sup>1</sup> which provides additional evidence that pregnancy and postpartum are associated with the onset of obsessive-compulsive disorder (OCD) and the worsening of symptoms in women with preexisting OCD. The hormone-related vulnerability of some women with OCD was also pointed out by our group. We previously described that subjects with OCD and premenstrual mood symptoms more frequently reported premenstrual worsening of OCD and an onset (or worsening of previous OCD) at postpartum.<sup>2</sup> In addition, we also found that women with a history of premenstrual worsening of OCD more frequently report changes in OCD symptoms while taking oral contraceptive pills.<sup>3</sup>

As Forray et al<sup>1</sup> suggest, genes that regulate reproductive hormone signaling may play a role in this biological predisposition. The estrogen receptor  $\alpha$  gene (*ESR1*), which has been linked to premenstrual dysphoric disorder,<sup>4</sup> seems to be a good candidate. In a recent study by our group,<sup>5</sup> we genotyped 29 single-nucleotide polymorphisms (SNPs) in estrogen receptor genes (*ESR1* and *ESR2*) in 229 OCD patients and 279 controls. Although we did not find significant differences in the distribution of alleles or genotypes between controls and OCD subjects, when we analyzed OCD subphenotypes we found that the SNP rs34535804 in *ESR1* and a 5-SNPs haplotype located in the 5' end of intron 1 of *ESR1* were associated with the presence of contamination obsessions and cleaning compulsions. We observed that carriers of the rs34535804\*A-rs488133\*C-rs9478245\*C-rs2234693\*C-rs9340799\*G haplotype, a combination of functional alleles related with higher estrogen receptor  $\alpha$  expression, showed a reduced risk of suffering from these symptoms. Interestingly, in another study<sup>6</sup> that included 90 women with OCD, we concluded that the onset of the disorder in patients reporting contamination/cleaning symptoms was more frequently related to the perinatal period. In accordance with our study, Forray et al.<sup>1</sup> also found that of all obsessive-compulsive symptoms, only contamination obsessions were significantly greater in the perinatal-related subgroup when compared to the nonperinatal-related subgroup.

OCD is heterogeneous in its clinical manifestations, and patients may show distinct symptom patterns. Obsessions and compulsions are experienced within multiple overlapping symptom dimensions<sup>7</sup>: contamination/cleaning, aggressive/checking, symmetry/ordering, and hoarding. These dimensions are also mediated by different components of the frontostriatal-thalamic circuits involved in cognitive and emotion processing,<sup>8</sup> and may differ in their genetic risk.<sup>9</sup> The recent study by Alonso et al,<sup>5</sup> together with the clinical information regarding the positive relationship between contamination/cleaning symptoms and the perinatal onset of OCD,<sup>1,6</sup> suggests that women

with symptoms from the cleaning dimension may carry a genetic vulnerability that could make them more susceptible to fluctuations in gonadal steroids. Future studies need to assess whether this vulnerability to reproductive events is driven by a different genetic risk (eg, *ESR1* gene), as we hypothesize. Moreover, these studies should control for the phenotype, as the biological risk for being susceptible to changes in gonadal steroids may be greater for women with contamination obsessions or cleaning compulsions.

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