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RESPONSE TO LETTER

Link Between Alzheimer's Disease, Obsessive-Compulsive Disorder, and ApoE Gene Polymorphisms [Response to Letter]

Ayse Dondu[1], Seda Orenay-Boyacioglu[2]

[1]Department of Psychiatry, School of Medicine, Aydin Adnan Menderes University, Aydin, 09010, Türkiye; [2]Department of Medical Genetics, School of Medicine, Aydin Adnan Menderes University, Aydin, 09010, Türkiye

Correspondence: Ayse Dondu, Department of Psychiatry, School of Medicine, Aydin Adnan Menderes University, Aydin, 09010, Türkiye, Email aysdnd@hotmail.com

Dear editor

Firstly, we would like to express our gratitude to Xu and Mei for sharing their insightful comments regarding our paper titled "The Association Between Obsessive-Compulsive Disorder and ApoE Gene Polymorphisms".[1,2] We appreciate the opportunity to address the points raised in their letter.

To begin with, we would like to address their concerns regarding the inclusion criteria. In our study, we utilized age at onset (15 years) as a criterion to differentiate between early- and late-onset subtypes of obsessive-compulsive disorder (OCD). This age threshold was based on previous studies that identified age at onset as a significant factor in classifying OCD subtypes. In distinguishing between early- and late-onset OCD, we paid particular attention to an onset age closer to childhood to strengthen our hypothesis. According to the literature, early-onset OCD is thought to be more closely related to neurodevelopmental processes during childhood and may involve different mechanisms compared to late-onset OCD. However, we acknowledge the limitations of relying solely on age criteria. In this context, considering Taylor's findings on OCD subtypes, adjusting the age threshold in larger sample groups and incorporating various factors could provide a more detailed classification.[3] We plan to address this in more detail in our future research.

Secondly, we appreciate Xu and Mei's attention to the genetic relationship between OCD and Autism Spectrum Disorders (ASD). The shared neurobiological mechanisms and overlapping symptoms between OCD and ASD have become a growing topic of interest. Given that the *ApoE* gene is implicated in both disorders, investigating genetic and epigenetic interactions, such as abnormal methylation of *ApoE*, could shed light on this complex relationship. In future studies, we aim to further explore the impact of *ApoE* on neurodevelopmental and neurodegenerative disorders.

Previous research has suggested a potential genetic link between OCD and ASD, indicating that certain symptoms of OCD resemble core features of ASD, and both disorders often co-occur clinically. Abnormal methylation of the *ApoE* gene, which is associated with Alzheimer's disease (AD), might also play a role in ASD through similar mechanisms.[4] Therefore, further investigation into shared epigenetic mechanisms and the effect of *ApoE's* abnormal methylation on both disorders is warranted. These genetic commonalities could help explain why OCD and ASD display similar symptoms and frequently occur together.

Lastly, we welcome Xu and Mei's suggestion to investigate the role of mitochondrial function and homeostasis in the context of *ApoE* gene polymorphisms and OCD. The effects of *ApoE4* on mitochondrial respiration and autophagy are emerging as important areas of research that could illuminate the pathophysiology of OCD and its connection to neurodegenerative diseases. A deeper understanding of these mechanisms may offer valuable insights into the etiology of OCD and its relationship with the *ApoE* gene.

Studies have shown that *ApoE4* disrupts mitochondrial function and oxidative phosphorylation by causing lysosomal cholesterol accumulation in astrocytes. These dysfunctions may play a significant role in the pathophysiology of AD.

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Mitochondrial dysfunction underlies many neurodegenerative processes, and *ApoE4* carriers may be more vulnerable to disruptions in energy balance and cellular repair mechanisms in brain cells.[5] Several studies suggest that obsessive-compulsive symptomatology could be a risk factor for Alzheimer's-type dementia, and OCD may be linked to cognitive impairments associated with neurodegenerative processes.[6,7] Thus, individuals with OCD symptoms might be at higher risk of developing AD. We believe that future research focusing on the molecular basis of pathogenic mechanisms between OCD and dementia could contribute to the development of novel therapeutic strategies. Mendelian randomization analyses have highlighted that genetic liability to depression and schizophrenia increases the risk of AD, but consistent findings for other psychiatric disorders are still lacking.[8,9] These data offer clues to the genetic and biological mechanisms through which psychiatric disorders may contribute to AD development.

In conclusion, we once again thank Xu and Mei for their valuable feedback. Their suggestions will play an important role in guiding our future research on understanding the relationship between *ApoE* gene polymorphisms and OCD.

Disclosure

The authors report no conflicts of interest in this communication.

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