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Integrative analysis of shared genetic pathogenesis by obsessive-compulsive and eating disorders

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Abstract. A number of common pathological features have been observed in obsessive-compulsive disorder (OCD) and eating disorders (EDs). The present study examined the association between OCD and EDs at the genetic level in order to gain an improved understanding of the shared genetic basis of the diseases and identify novel potential risk genes for the two diseases. An integrated analysis using large-scale disease-gene association data and gene expression data was conducted. Disease-gene association data were acquired from the Pathway Studio Mammalian database. Gene expression data were acquired from samples of 133 subjects, including 15 ED cases, 16 OCD cases and 102 normal controls. Genes associated with OCD and ED presented significant overlap (21 genes, $P=6.70x10^{-34}$), serving roles within multiple common genetic pathways (top 10 pathway enrichment $P<4.30x10^{-7}$) that were implicated in the two diseases. A genetic network of 17 genes was constructed, through which OCD and ED were observed to influence each other. Expression analysis revealed four novel common significant genes for OCD and ED (oxytocin receptor, glutamate decarboxylase 2, neuropeptide Y and glutamate ionotropic receptor kainate type subunit 3). These genes demonstrated a strong functional association with the two diseases. The results of the present study supported the presence of complex genetic associations between OCD and ED. Genes associated with one disease are worthy of further investigation as potential risk factors for the other. The findings of the present study may provide novel insights into the understanding of the pathogenesis of OCD and ED.

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Introduction

Obsessive-compulsive disorder (OCD) is a mental health disorder characterized by obsessive and compulsive thoughts and behaviors. OCD typically arises in late adolescence or early adulthood and can lead to chronic illness if it is left untreated (1,2). Although there is no consensus regarding its etiology, genetic studies have indicated that heritability is associated with 26-61% of cases (3-5).

Eating disorders (EDs) are a group of mental health syndromes characterized by significant disturbances in eating behavior, and by distress or excessive concern with body shape or weight. The most studied sub-types of EDs are anorexia nervosa (AN) and bulimia nervosa (BN). The lifetime prevalence rates for EDs are higher among women than men (6). Although the cause of EDs remains unclear (7), it is hypothesized that genetic factors have a significant role in the development of the disease (8,9).

A number of clinical symptoms of EDs have also been observed in OCD (10). In addition, shared genetic liability and brain circuitries have been identified among the obsessive psychiatric syndromes of AN, BN and OCD (11). Additionally, genetic analysis using genome-wide association studies and gene expression data have revealed a number of genetic risks associated with ED and OCD (12,13). However, thus far, no systematical study has been performed to investigate the genetic risks shared by the two diseases.

The present study integrated gene expression data and a large-scale literature database to investigate the association between OCD and ED at the genetic level, with the aim of gaining an improved understanding of their common genetic basis and identify novel potential genes associated with the two diseases. In recent years, Pathway Studio (PS; pathwaystudio.com) has been widely used to study modeled associations between proteins, genes, complexes, cells, tissues and diseases (14). Updated weekly, the PS relation database is the largest database among known competitors in the field (15).

The present study intended to examine the hypothesis that OCD and ED present significantly shared pathogenesis at the genetic level. If the hypothesis was verified, then the aim was to determine if risk genetic factors associated one disease were worthy of study into its potential association with the other disease.

Materials and methods

Data collection summary. Initially, large-scale ED-gene and OCD-gene relation data were analyzed to identify shared genes and genetic pathways. Then, expression data acquired from patients with OCD and ED, and healthy controls, were used to identify potential novel common risk genes for ED and OCD. Subsequently, gene-disease-drug-relation network analysis was conducted to study the potential pathogenic significance of the novel common genes to ED and OCD. The network analysis was conducted using the 'Shortest Path' function module of the PS database. The purpose of the network analysis was to identify possible functional association and pathological pathways between the novel common risk genes and OCE/ED.

OCD and ED-gene data acquisition. Disease-gene relation data for ED (all types) and OCD were acquired from PS, as described previously (14). A genetic database, termed OCD_ED, was developed through a complex analysis of the identified association data. Besides the full lists of genes linked to the two diseases (OCD_ED, OCD Related Genes; and OCD_ED, ED Related Genes), the database also presented the supporting references for each disease-gene relation (OCD_ED, Ref for OCD Related Genes and OCD_ED Ref for ED Related Genes), including titles of the references and the related parts of the study where a disease-gene association was identified. The OCD_ED database is online available at 'Bioinformatics Database' (gousinfo.com/database/Data_Genetic/OCD_ED.xlsx). The information can be used to locate the detailed description of how a candidate gene is associated with OCD and/or ED.

Common risk genes. A gene expression dataset (GSE60190) of 133 subjects (15 patients with ED, 16 patients with OCD and 102 non-psychiatric controls) was used to test the genes associated with one of the two diseases but not the other. The expression data is available online at www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE60190. For a gene associated with only OCD, one-way analysis of variance was performed to compare the expression between healthy controls and ED cases, in order to determine association with ED. Similarly, the genes associated with only ED were tested for their potential association with OCD. The Benjamini-Hochberg procedure was employed to control the false discovery rate (FDR), and FDR-corrected P-values were used to identify potential significant genes for further analysis. All analyses were conducted using Matlab (R 2017a; The MathWorks, Inc., Natick, MA, USA).

Pathway analysis of potential risk genes. For the target common risk genes identified through expression analysis as described above, a shortest-path based network analysis was performed to identify pathogenic pathways between the target genes and the disease (ED/OCD). The analysis was performed using PS.

Results

Shared genetic basis between OCD and ED. Within the curated OCD_ED database, there were 81 genes associated with OCD, supported by 450 scientific references (OCD_ED→OCD Related Genes and OCD_ED→Ref for OCD Related Genes). For ED, there were 71 associated genes supported by 204 references (OCD_ED, ED Related Genes and OCD_ED, Ref for ED Related Genes). A significant overlap ($P=6.80x10^{-34}$; right-tail Fisher's Exact test) of 21 genes were identified between the two groups of genes, as shown in Fig. 1. More information concerning these 21 genes is in OCD_ED, 21 cross genes.

To test the functional profile of the 21 common genes associated with OCD and ED, a Pathway Enrichment Analysis (PEA) was conducted using PS. The 10 most significantly enriched pathways ($P<4.30x10^{-7}$; q=0.001 for FDR) are presented in Table I. In total, 60 pathways/gene sets were enriched with $P<1.00x10^{-3}$ including all 21 genes (OCD_ED, Common Pathways).

The PEA approach revealed 7 pathways (13 overlapped genes) associated with behavior, 5 (14 overlapped genes) with neuro system, 4 (17 overlapped genes) with drug effects, 3 (5 overlapped genes) with neuro transmitter, 2 (8 overlapped genes) with brain function development, 1 (9 overlapped genes) with cell proliferation, and 1 (6 overlapped genes) with protein phosphorylation. For detailed information of these significantly enriched pathways, please refer to OCD_ED, Common Pathways. The results of the present study suggested that OCD and ED share multiple genetic pathways, through which these 21 genes serve various functions affecting the pathogenic development of the two diseases.

Potential co-regulations between OCD and ED. Functional network analysis using PS demonstrated that 17 out of the 21 common risk genes exhibit down- and upregulation associated with OCD and ED (influenced by and influencing OCD and ED), as presented in Fig. 2. Detailed information concerning the network presented in Fig. 2 is in OCD_ED, Co-Regulation Network; including the type of the association, supporting references and related excerpts from the references where an association has been identified. Fig. 2 demonstrates that OCD and ED may influence the pathogenic development of each other through these genetic pathways.

Gene expression analysis. Although there was a significant overlap between ED-genes and OCD-genes (21 genes; $P=6.80x10^{-34}$), certain genes were linked to one disease only (60 for OCD and 50 for ED; Fig. 1). These results were from literature data analysis. The present study analyzed the correlation between the 60 OCD-genes and ED, and the correlation between 50 ED-genes and OCD, using a gene expression dataset (GSE60190; 15 patients with ED, 16 patients with OCD and 102 non-psychiatric controls). Fig. 3 presents the '-log10' transferred P-values (q=0.001 for FDR) for each gene tested. The detailed results are presented in OCD_ED, 50 ED Genes for OCD and OCD_ED, 60 OCD Genes for ED, including the P-values and FDR correction status. Note that 3 out of 50 ED-genes and 2 out of 60 OCD-genes are not included in the expression dataset utilized in the present study and thus, the corresponding results were not available.

Of the 50 ED-genes, 3 [oxytocin receptor (*OXTR*), glutamate decarboxylase 2 (*GAD2*) and neuropeptide Y (*NPY*)] and out of the 60 OCD-genes one [glutamate ionotropic receptor kainate type subunit 3 (*GRIK3*)] passed the FDR correction

Table I. Genetic pathways enriched with 21 genes associated with obsessive-compulsive disorder and eating disorder.

Name	GO ID	Number of genes	Overlap	P-value (following FDR)	P-value (prior to FDR)
Response to drug	0017035	509	12	2.57×10^{-10}	8.78×10^{-15}
Grooming behavior	0007625	16	5	2.66×10^{-8}	2.60×10^{-12}
Response to cocaine	0042220	44	6	2.66×10^{-8}	3.15×10^{-12}
Feeding behavior	0007631	45	6	2.66×10^{-8}	3.64×10^{-12}
Synaptic transmission	0007268	472	10	4.20×10^{-8}	8.51×10^{-12}
Locomotory behavior	0007626	108	7	4.20×10^{-8}	8.60×10^{-12}
TC 2.A.22.1	None	3	3	1.46×10^{-7}	3.98×10^{-11}
Positive regulation of ERK1 and ERK2 cascade	0070374	134	7	1.46×10^{-7}	3.98×10^{-11}
Positive regulation of peptidyl-serine phosphorylation	0033138	77	6	3.38×10^{-7}	1.04×10^{-10}
Response to ethanol	0017036	161	7	4.27×10^{-7}	1.46×10^{-10}

For each pathway/GO term, the P-value was calculated using Fisher-Exact test against the hypothesis that a randomly selected gene group of same size (21) can generate a same or higher overlap with the corresponding pathway/GO term. All these pathways/GO terms passed the FDR correction (q=0.001). GO, Gene Ontology; FDR, false discovery rate; ERK, extracellular signal-regulated kinase.

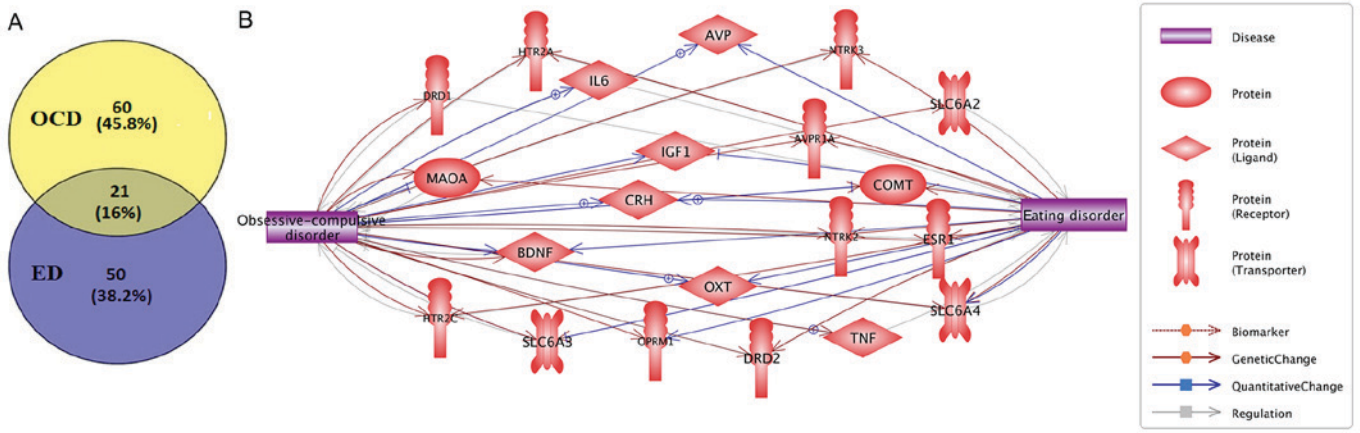

Figure 1. Genetic association between OCD and ED. (A) Venn diagram between OCD-genes and ED-genes. (B) The 21 cross genes associated with OCD and ED. OCD, obsessive-compulsive disorder; ED, eating disorder.

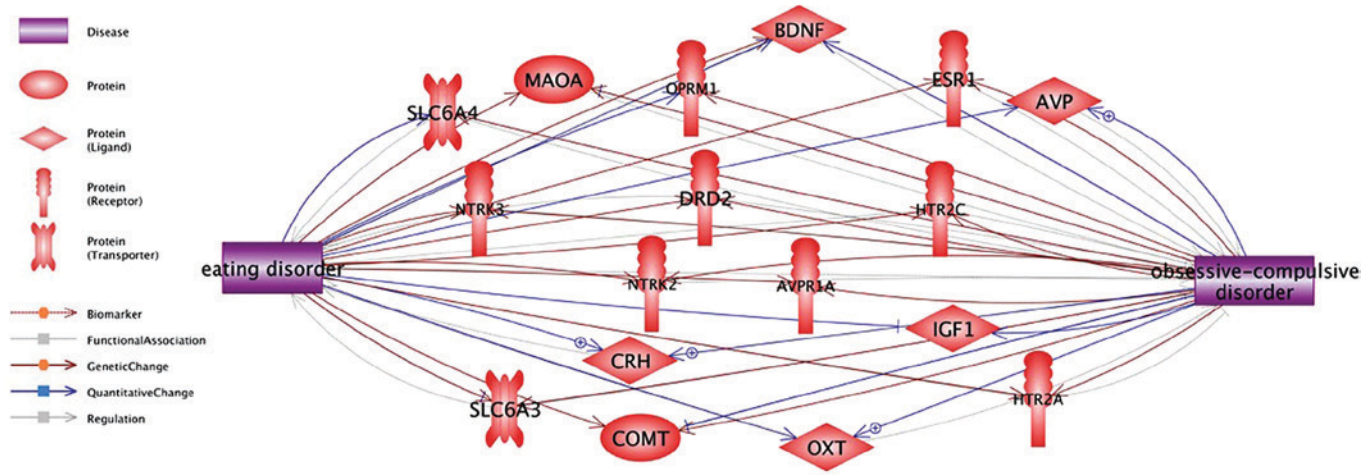

Figure 2. OCD and ED co-regulation network composed of 17 genes. The network is generated using the 'network building' module of Pathway Studio. OCD, obsessive-compulsive disorder; ED, eating disorder.

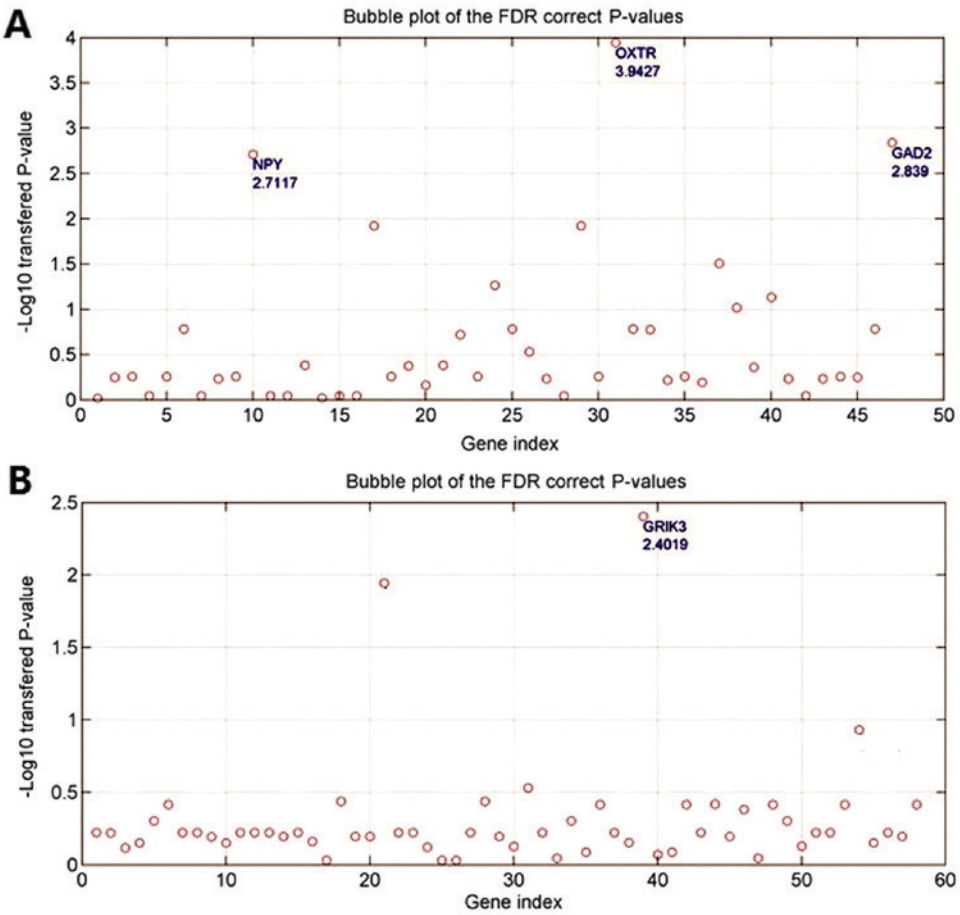

Figure 3. Gene expression analysis for OCD and ED. (A) The P-values of the 50 ED-genes for OCD case/control expression comparison. (B) The P-values of the 60 OCD-genes for ED case/control expression comparison. The P-values have been through FDR correction with q=0.001 and logic transformation using '-log10'. Names and corresponding transferred P-values of the 4 genes that passed the FDR correction (q=0.001) were marked at corresponding positions. OCD, obsessive-compulsive disorder; ED, eating disorder; FDR, false discovery rate. OXTR, oxytocin receptor; NPY, neuropeptide Y; GAD2, glutamate decarboxylase 2; GRIK3, glutamate ionotropic receptor kainate type subunit 3.

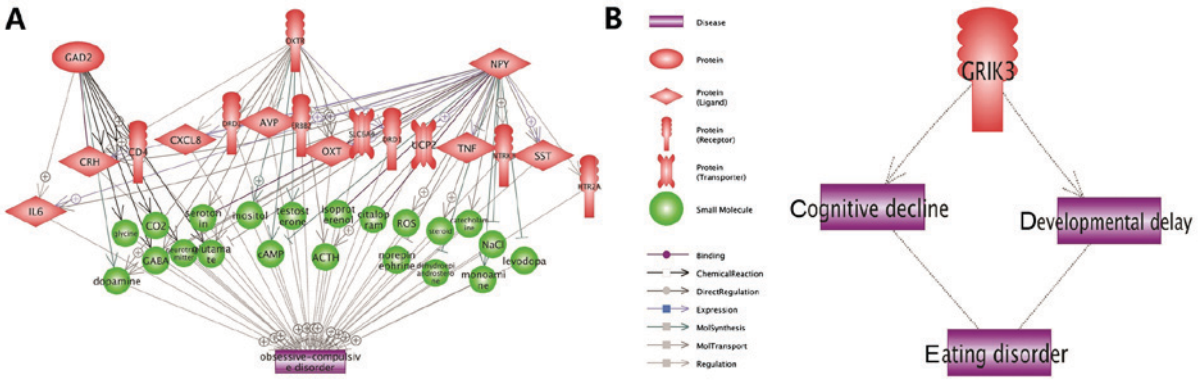

Figure 4. The functional networks between connecting three ED-genes and OCD, and one OCD-gene and ED. (A) A total of three ED genes present indirect relations with OCD. (B) A single OCD gene presents indirect relations with ED. The networks were built using 'network building' module of Pathway Studio. OCD, obsessive-compulsive disorder; ED, eating disorder.

(q=0.001). According to the PS database, *OXTR*, *GAD2* and *NPY* has no direct association with OCD, and *GRIK3* has no direct association with ED (no study has been identified that reports an association between these genes and OCE or ED).

However, *OXTR*, *GAD2* and *NPY* demonstrated strong functional linkage to OCD, through multiple genes and small molecules/drugs pathways (Fig. 4A). *GRIK3* also demonstrated an association with ED through the regulation of ED-related disorders (Fig. 4B). The detailed information of the associations in Fig. 4 is presented in OCD_EDà '3 Genes for OCD' and '1 Gene for ED', including the type of association, the underlying supporting reference, and the places in the study where these associations have been identified and described.

Discussion

Previous studies have demonstrated that ED is closely associated with OCD (16). The present study integrated large-scale disease-gene relation data and gene expression data to test the hypothesis that ED and OCD exhibit significant shared genetic bases in terms of common risk genes and pathways. Gene expression data analysis identified novel potential common risk genes for ED and OCD. Results from functional network analysis supported the association between these genes and the two diseases.

The results of the present study demonstrated that 21 genes linked to OCD and ED present significant overlap ($P=6.76x10^{-34}$). These 21 genes are significantly enriched within 60 pathways ($P<1.00x10^{-3}$; FDR-corrected, q=0.001; OCD_ED, Common Pathways). A number of these pathways have been implicated in OCD and ED, including the pathway associated with neuro system and neuro transmitter (17-21), memory [Gene Ontology (GO) ID, 0007613] (22,23), learning (GO ID, 0007612) (24,25) and response to cocaine (GO ID, 0048148) (26,27). These results suggested that OCD and ED share multiple genetic pathways. Through these pathways, a large group of genes influence the pathogenic development of the two diseases.

In addition, a 17-gene network was constructed, through which OCD and ED may affect the pathogenic status of each other. These 17 out of the 21 cross genes are downstream targets of OCD/ED and also the upstream regulators of ED/OCD. The findings of the present study supported the hypothesis that OCD and ED present significant association at the genetic level.

Closer analysis of the 50 ED only genes using gene expression data (GSE60190) demonstrated that 3 out of these 50 ED genes, *OXTR*, *GAD2* and *NPY*, were potential OCD markers (FDR-corrected $P<1.00x10^{-3}$). Functional network analysis demonstrated that these 3 three genes presented strong functional correlation with OCD, forming a genetic network reinforced by 1,406 supporting references (Fig. 4A; see OCD_ED, →3 Genes for OCD). These results supported multiple pathways between these three genes and OCD. For example, *NPY* can significantly increase arginine vasopressin (*AVP*) mRNA expression (28), while and *AVP* contributes to OCD symptoms in humans (29). This finding supports a *NPY*→-*AVP*→-OCD functional pathway. More of these pathways may be identified from the literature knowledge curated in the database OCD_ED→, 3 Genes for OCD.

On the other hand, gene expression data analysis and shorted-path based network analysis suggested that *GRIK3* may be a risk gene for ED (FDR-corrected $P<1.00x10^{-3}$; OCD_ED, 60 OCD Genes for ED). *GRIK3* presents a strong expression pattern in the central nervous system, demonstrating solid function in presynaptic neurotransmission (30). Haploinsufficiency of *GRIK3* causes severe developmental delay (30), which is associated with ED (31). *GRIK3* also serves important roles in cognitive defects (32), which are associated with ED pathogenesis (33). Therefore, by regulating the brain functions, *GRIK3* may exert an influence on the pathogenic development of ED.

Although the four genes (*OXTR*, *GAD2*, *NPY* and *GRIK3*) identified in this study are proposed as novel common risk genes for ED and OCD, and the findings were supported by data-driven indirect evidence from gene expression data and pathway analysis. Biological experiments are required to test these potential associations.

In summary, results from the present study supported the hypothesis that OCD and ED exhibit significant association at the genetic level, which helps to explain their common pathological symptoms. Additionally, four genes were suggested as novel potential common risk genes for OCD and ED. To the best of our knowledge, this is the first study integrating large-scale disease-gene association data and gene expression data for a systematical study of the associations between OCD and ED at the genetic level. The findings of the present study may add novel insights into the current field of OCD-ED correlation study, and guarantee further studies using more data sets to test novel potential risk genes for ED and OCD.

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Availability of data and materials

The datasets analyzed during the present study are available in the OCD_ED database online at 'Bioinformatics Database' (gousinfo.com/database/Data_Genetic/OCD_ED.xlsx). The expression dataset analysed during this study is available online at 'Gene Expression Omnibus' (www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE60190).

Authors' contributions

CX, HC and DL contributed to the design of the present study, acquired and analyzed the data, and wrote and revised the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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