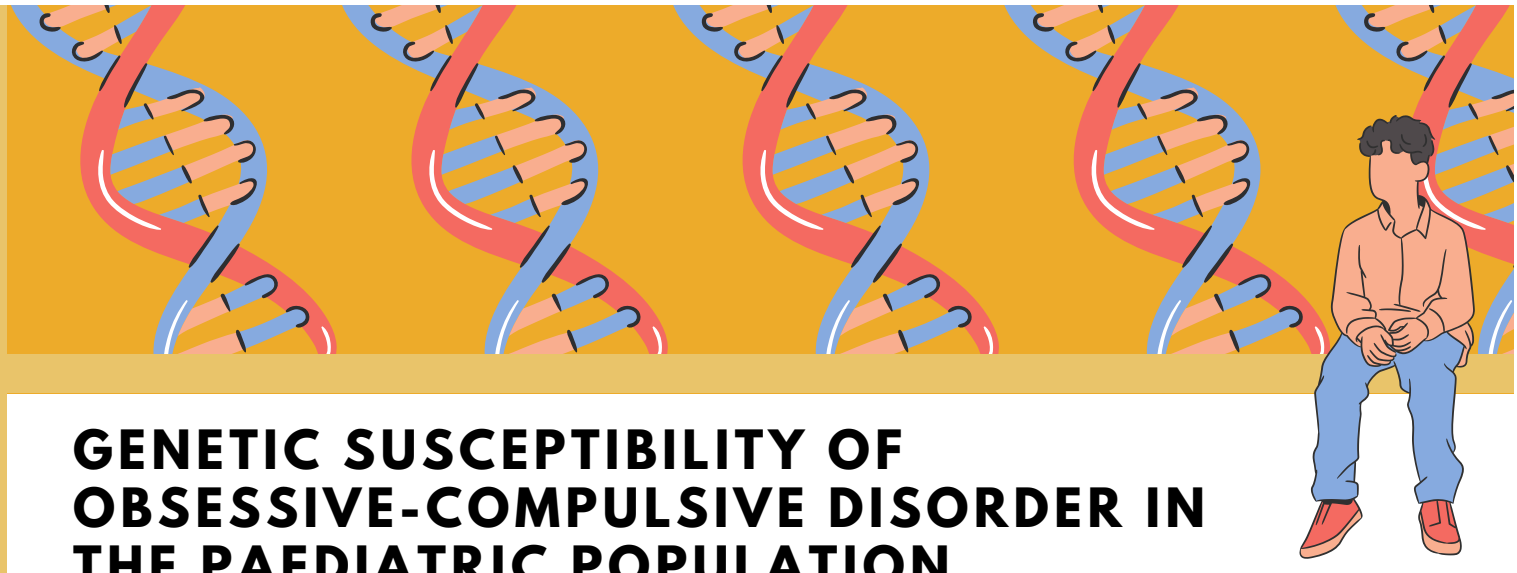

GENETIC SUSCEPTIBILITY OF OBSESSIVE-COMPULSIVE DISORDER IN THE PAEDIATRIC POPULATION

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a psychiatric disorder involving recurring, unwanted thoughts followed by eliciting ritualistic behaviours to alleviate feelings of distress. Two onsets of OCD exist: early and late. Early-onset (also known as paediatric or childhood) OCD shows greater rates of comorbidities and symptom severity, as well as stronger links to genetics, which are a developing field in OCD etiopathogenesis. An extensive number of twin and family studies have demonstrated heritability of OCD and clustering in families. Although genome-wide association studies (GWAS) are a relatively new addition to the progression of OCD genomics, they have provided initial results on specific candidate genes involved. Currently, the serotonergic, early glutamatergic, and dopaminergic systems possess the main genes implicated in OCD. An epigenetic contribution has also been recently considered in paediatric populations. This review of existing literature primarily focuses on the genetic factors of OCD, particularly its early-onset form.

INTRODUCTION

I. OCD

Obsessive-compulsive disorder (OCD) is a mental illness defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as the presence of unwanted, intrusive, and upsetting thoughts (obsessions) that may lead to repetitive behaviours or mental acts (compulsions).[1] In those with OCD, compulsions are actions the individuals perform to soothe their obsessions, disturbing day-to-day functioning. The severity of symptoms range from obsessive-compulsive traits to overt OCD.[2]

Although there is no standardized test to diagnose OCD, a series of criteria in the DSM-5 is used for diagnosis by clinicians.[3] First, there must be the presence of recurrent, anxiety-inducing obsessions alongside compulsions in response to those thoughts. These obsessions and compulsions must be time-consuming to the degree that they interfere with day-to-day life or impair work or social functioning. Further, these involuntary thoughts and behaviours should not be attributed to substances, medical conditions, or symptoms of another mental disorder.[4]

Age of OCD onset has a bimodal distribution with peaks at adolescence, and early adulthood.[5] Early-onset OCD, also known as paediatric-onset OCD, is grouped around a mean age of 11 years old, with a mean cut-off of 21 years old.[6] Compared to its adult-onset counterpart, the early-onset form is shown to be more strongly correlated with genetics and associated with greater symptom severity.[5-7] Additionally, the subtype of OCD involving symmetry and ordering is more likely to be found in early-onset patients.[5]

II. Etiology and pathophysiology

There are many factors that contribute to the etiology of OCD. Neuroimaging studies have consistently identified the orbitofrontal cortex, the anterior cingulate area, and the caudate nucleus as primary structures responsible for the manifestation of OCD.[8,9] In early onset cases of OCD, Busatto et al. determined reduced regional cerebral blood flow in the right thalamus, left anterior cingulate cortex, and the inferior prefrontal cortex in comparison to late-onset cases.[10] The neurobiological etiology is still being researched but may involve changes to brain pathways such as the cortico-striato-thalamo-cortical (CSTC) circuit, which is thought to be the pathway that relays “worry thoughts.”[11] In individuals with OCD, this pathway experiences an excess of glutamate levels, which leads to cerebral hyperactivity. In addition to

glutaminergic pathways, serotonin receptors are also commonly implicated due to the successful application of selective serotonin reuptake inhibitors (SSRIs). SSRI's have greatly resulted in symptom improvement in both adult and paediatric OCD populations. Conversely, the administration of certain serotonin receptor agonists exacerbate some OCD symptoms.[12] Dopamine is another closely studied neurotransmitter as researchers have found a higher concentration of dopamine receptors in the basal ganglia of individuals with OCD.[12] In combination with neurobiological structures and pathways, genetic and environmental factors are illustrated in many twin studies of OCD.

III. Twin and family studies

Twin and family studies have examined the critical role of genetic factors in the onset of OCD. One of the earliest twin study on OCD was conducted in 1965, and since then, evidence has repeatedly demonstrated a significant concordance rate among monozygotic twins of 0.57, as compared to 0.22 in dizygotic twins.[2,13-14] Among the paediatric population, overall heritability from twin studies for early-onset OCD has mostly ranged between 41-74%, with few studies demonstrating heritability as low as 7%.[5]

Likewise, first-degree relatives of OCD patients have demonstrated a relatively high recurrence risk for lifetime OCD, in comparison to second-degree relatives and control groups. The majority of these studies found values ranging from 10-20% in comparison to the lifetime prevalence of OCD in the general population of 0.7-3%.[14] In a meta-analysis observing familial aggregation in various psychiatric disorders, a risk ratio of 4.0 was determined for OCD among first-degree relatives.[15] Thus, first-degree relatives have a significantly increased risk of OCD diagnosis compared to comparison relatives by a factor of four. In a multigenerational family clustering study of OCD, 24,000 individuals along with their available first- to third-degree relatives were matched with controls. First-degree relatives were found at highest risk of OCD diagnosis, followed by second- and third- degree relatives, demonstrating the significant role of genetic relatedness in OCD.[16] Furthermore, early-onset OCD has been suggested to have a higher association with familial aggregation in comparison to adult-onset OCD. A recent study comparing paediatric-onset to adult-onset OCD patients concluded that the risk of OCD in a first-degree relative for paediatric cases is approximately two times greater, and up to 26% in comparison to the 12% risk among adult-onset cases.[17] As such, the current understanding of OCD genetics can be greatly attributed to a plethora of family and twin studies.

IV. Genetics in the paediatric population

Although there are many intersectional factors such as adverse childhood events and family history that contribute to the progression of OCD, this review will focus on genetics as it has gained a renewed focus in the field due to greater exploration of candidate genes, animal models for behavioural neuroscience, and genome-wide association studies (GWAS). Through these, research has identified potential genes relevant to OCD diagnosis and treatment. Previously, few GWAS and genome-wide analyses investigating the genomics of OCD have been carried out since the first study by Stewart et al. in 2013; however, there is progress in using this approach to study OCD, as demonstrated by a recent 2021 GWAS in the paediatric population, which had larger sample sizes than previous GWAS on OCD.[5,18] Research into genetics can also incorporate the potential impact of environmental factors through the investigation of epigenetics, which is grossly understudied thus far in children and youth due to ethical and logistical constraints.impact of environmental factors through the investigation of epigenetics, which is grossly understudied thus far in children and youth.

GENETIC INFLUENCES IN OCD

Three main signaling pathways that have been proposed to be related to pathogenesis of the disease: serotonergic, glutamatergic, and dopaminergic.[19] Related to genetics is the study of epigenetics, which examines the impact of gene and environmental interactions.

I. Serotonergic genes

The serotonergic system has been extensively studied in the genetics of OCD because the primary pharmacological treatment for OCD involves the use of SSRIs.[17] SSRIs inhibit the reuptake of serotonin by slowing the mechanism of action of the serotonin transporter, allowing more serotonin to remain in the synaptic cleft.[20] The serotonin transporter is coded for by the SLC6A4 gene which has been the primary focus of OCD genetic research. This gene has consistently been associated with OCD.[19,21] Numerous studies have found that the LA allele of the single nucleotide polymorphism (SNP) rs25531, found within the serotonin transporter-linked polymorphic region, increases the risk of OCD.[19] Additionally, the serotonin 2A receptor (HTR2A) gene is another candidate gene for OCD. Recently, the HTR2A gene has shown nominally significant [odds ratio (OR) = 1.219; 95% confidence interval (CI), 1.037–1.433; P = 0.003] results for the involvement of rs6311 SNP in the development of OCD, indicating that changes to this receptor could be a genetic basis for OCD pathogenesis.[21] In addition to the aforementioned polymorphisms, other serotonergic genes including monoamine oxidase A (MAOA), tryptophan hydroxylase (TPH1 and 2), and serotonin 1D-beta receptor (HTR1B) have also been reported to play a role in genetic etiology of OCD.22 Overall, the vast majority of evidence supports the involvement of serotonergic genes in OCD etiology, however, the exact variants and their degree of influence is still relatively unclear.[23] Further research should seek to stratify the involvement of different genes to help explain past inconsistencies and the lack of significant results.[23] The elucidation of the underlying genetic risk

factors of OCD, including the role of serotonergic genes, will serve to inform future treatment studies, and potentially allow for the modification of genotypic and phenotypic characteristics.[23]

II. Glutamatergic genes

Alterations, such as disturbances of the CSTC circuit of the glutamatergic system, have also been implicated in the pathogenesis of OCD.[24] The abnormal activation within the CSTC circuit has been shown to lead to the hyperactivation of the orbitofrontal-subcortical pathway which increases concerns related to symmetry, danger, harm, and contamination that are seen in individuals with OCD, regardless of the age of onset.[24] Further, the rs301443 and rs12682897 SNPs present on the SLC1A1 gene that codes for the glutamate transporter, a biochemical molecule involved in intracellular trafficking of glutamate between mitochondria and cytosolic compartments, have been shown in some studies to lead to OCD.[25-27] However, other studies have also shown no significant association between the SLC1A1 gene and OCD.[28] Due to these inconsistent findings, the involvement of the SLC1A1 gene in the development of OCD is still largely inconclusive. Additionally, clinical trials of glutamatergic agents, magnetic resonance spectroscopy studies, and knock-out mouse models have implicated the glutamatergic system in the pathogenesis of OCD, however the exact mechanisms and genes involved are still relatively unclear.[29]

III. Dopaminergic genes

The dopaminergic system has also been examined for its role in OCD pathogenesis due to the effects of antipsychotics as an adjunct medication to antidepressants for the treatment of OCD.[24] Numerous studies have found that the low activity Met allele of the catechol-O-methyltransferase (COMT) rs4680 was overrepresented in males with OCD.[30] Moreover, it was determined that this change was disorder-specific in males with OCD when compared to other psychiatric disorders such as depression, bipolar disorder, and schizophrenia.[31] This sex-based difference was significant; $\chi 2(1) = 7.43$, $P = 0.005.31$ Additionally, studies using animal models, neuroimaging, and neurochemical approaches also implicate dopaminergic dysfunction in the pathophysiology of OCD by inducing or aggravating the symptoms that are indicative of OCD. [32] Despite these studies, further research is needed to implicate the dopaminergic system in OCD pathogenesis.

IV. Other genes

Other notable candidate genes include brain-derived neurotrophic factor (BDNF) and those involved in the oxytocin system. BDNF aids in the development of serotonergic and dopaminergic neurons, among others.7 SNP rs6265, which has been associated with several neuropsychiatric disorders, was found to be linked to gender, age at onset, symptom severity, and/or subpopulations in people with OCD within at least nine studies.[33-41] Alternatively, five other studies found no association between rs6265 and OCD.7 Three other BDNF polymorphisms, rs2883187, rs1519480, and rs7124442, have been identified, but too few studies have been conducted for any conclusions to be drawn.[7]

Additionally, oxytocin is hypothesized to play a role in OCD due to its involvement in prosocial behaviours, and connection to anxiety and depression.[7] When the molecule binds to its receptor, which is coded by the OXTR gene, a cascade of intracellular signaling pathways that affect physiological responses, such as mood regulation, is triggered.[7,42] Although few studies have looked into relationship between OCD and OXTR, Kang et al. found polymorphisms rs2268493 and rs13316193 to have significant linkages to the disease's age at onset, with subjects possessing the minor allele for both polymorphisms being more likely to develop adult-onset OCD, as compared to early-onset OCD.[43]

EPIGENETIC & ENVIRONMENTAL RISK FACTORS

Increasing evidence has led to hypotheses that epigenetic modulation of certain genes is associated with the development and characterization of OCD, either through repressing or activating gene expression.44 The serotonin transporter gene SLC6A4 has also been extensively investigated for its relevance to OCD. Grünblatt et al. explored potential epigenetic mechanisms associated with OCD, including DNA methylation.44 Their preliminary data demonstrated that SLC6A4 DNA methylation levels within an amplicon at the first intron were significantly higher in the saliva of paediatric patients compared to controls and adult patients. Morning awakening salivary cortisol levels were also positively associated with methylation levels.44 The findings of this study support the connection between the SLC6A4 gene through epigenetic and genetic mechanisms; however, the finding needs to be corroborated in larger sample sizes.

Existing research has also identified a link between OCD and increased methylation in the OXTR gene. OXTR hypermethylation has also been previously associated with a worse treatment response to cognitive behavioural therapy.45 In an attempt to replicate these findings, Bey et al. conducted a study that also intended to apply previous findings to gene hypermethylation, environmental stressors, as well as OCD diagnosis and treatment response.45 Childhood stressful life events and adversity were measured using the Life Experience Survey and Childhood Trauma Questionnaire, respectively.45 The study found that individuals with OCD displayed significant hypermethylation at CpG site cg04523291 as compared to controls, and this increased methylation was associated with reduced treatment response.45 Hypermethylation at cg04523291 was also associated with stressful life events in OCD patients, demonstrating a potential epigenetic linkage.45

With regards to environmental risk factors, a review conducted by Bellia et al. identified the perinatal and adolescent time periods as critical for the development of OCD.[7] Early adverse life events, such as physical abuse, negative emotionality, and perinatal insults, have been related to an increased risk of OCD.[7] Further research must be conducted in order to better highlight potential areas for intervention, both genetically and within the broader community.

PSYCHIATRIC GENOMICS

Burton et al. conducted a GWAS in an effort to determine genetic risk factors for OCD in children and youth.[18] The findings of this study have implications in earlier diagnosis and improved treatment for youth with OCD.[18] Previous studies have revealed that OCD has a familial link; however the identification of specific OCD-related genes are a considerable gap in the literature.[46] Through the "Spit for Science Study," researchers at SickKids generated a diverse sample of 23,000 participants to determine specific genes with a role in the presentation of OCD symptoms within the paediatric population.[18] Study participants provided a DNA sample, completed a cognitive task, as well as a questionnaire on their health, lifestyle, and behaviours.18 Using the Toronto Obsessive-Compulsive Scale and saliva samples from roughly 5,000 children and youth, researchers identified the gene PTPRD, with a locus tagged in an intron of the gene to be significantly associated with OC traits at the genome-wide significance level.[18] This discovery led to the conclusion that children and youth with this genetic variant may have a greater risk of presenting obsessive-compulsive traits.[18]

CONCLUSION

I. Implications of findings

As was explored throughout this paper, OCD can present heterogeneously for different individuals and age groups, making it difficult for healthcare practitioners to administer a universal treatment. Understanding the genetic component of OCD will advance the field of mental disorders towards developing precise medical approaches for affected individuals. Indeed, advancements in treatment inspired by the role of genes in OCD have already occurred, such as the development of memantine, a drug that modulates glutamine, and which a meta-analysis has demonstrated positive effects in the course of treatment for the disease.[5] With a clearer understanding of how genetics influences the onset and course of OCD, early and more efficacious interventions can be designed to reduce disease burden for the paediatric patient.

II. Future directions

Due to the complex nature of OCD, the development of treatments for this disorder has been a difficult task, as there are multivaried genetic components in the etiopathogenesis of early-onset OCD. Looking into the genetic influences of OCD in terms of the candidate serotonergic, glutamatergic, and dopaminergic genes may enable researchers to develop a method of treating each OCD patient with targeted therapies in the future.[19] Additionally, a major limitation present in several GWAS is the lack of diversity present in the sample populations.[5] An example of this restriction is found in the study conducted by SickKids and the University of Calgary, in which children and youth of non-Caucasian background were excluded.18 This must be taken into consideration as the results may not be generalizable to the wider population. Presently, the majority of GWAS samples have come from Caucasian cohorts. Increasing diversity among study populations is key to advancing our understanding of OCD, and ensuring that research findings are broadly applicable. Further consideration to genomic studies in children and youth includes attention to sex differences, as well as relationships between OCD and comorbid disorders, as the majority of current studies are mostly conducted in the adult population.[5]

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