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Genetic Link Between Obsessive-Compulsive Disorder and Anorexia Nervosa

Introduction

Several clinical studies and epidemiological studies have consistently shown that the majority of people with eating disorders experience one or more anxiety disorders, with obsessive-compulsive disorder (OCD) being the most common in individuals with anorexia nervosa (AN) and bulimia nervosa (BN).¹ Many studies, both individual and twin, have shown that the majority of participants report the onset of OCD well before they developed an eating disorder, suggesting that those with OCD are more susceptible to developing an eating disorder.² According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), OCD is diagnosed by a presence of “recurrent and persistent thoughts, urges, or images...and that in most individuals cause marked anxiety or stress” and/or the presence of “repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.”³ Anorexia nervosa is diagnosed by a presence of “restriction of energy intake relative to requirements, intense fear of gaining weight, and a disturbance in the way in which one’s body weight is shape is experienced.”⁴ Given the nature of behavioral symptoms between OCD and AN, it is not surprising that the former can lead to the development of the latter.

¹ Kaye et al., “Comorbidity of Anxiety Disorders with Anorexia and Bulimia Nervosa.”

² Kaye et al., “Comorbidity of Anxiety Disorders with Anorexia and Bulimia Nervosa.”

³ “Obsessive-Compulsive and Related Disorders.”

⁴ “Feeding and Eating Disorders.”

While these two mental disorders share many of the same behavioral qualities, I wondered whether or not they shared a genetic link that may cause such a strong connection between the two. This paper will explore the genes responsible for each of the mental disorders, any similarities they share, and any studies that can shed light on a possible genetic link between the two disorders.

Genes Responsible for Obsessive-Compulsive Disorder⁵

A UniProt search for obsessive-compulsive disorder gave three significant genes. The first gene is a sodium-dependent serotonin transporter (SLC6A4), whose primary function is the regulation of serotonergic signaling via transport of serotonin molecules from the synaptic cleft back into the pre-synaptic terminal for re-utilization. The main GO terms for SLC6A4 are related to neurotransmitter transport, and post-translational modifications include glycosylation and phosphorylation. The second gene is 5-hydroxytryptamine receptor 2B (HTR2B). This gene is a G-protein coupled receptor for serotonin and functions as a receptor for various ergot alkaloid derivatives and psychoactive substances. The process affects neural activity and plays a role in perception of pain, possibly even impulsive behaviors as well. Many of the GO terms include G-protein coupled receptor, and post-translational modification sites include disulfide bonds, glycoproteins, and lipoproteins. The last gene that came up in the search is a brain-derived neurotrophic factor (BDNF). During development, BDNF promotes the survival and differentiation of selected neural populations of the peripheral and central nervous system. BDNF plays a role in axonal growth and regulates synaptic transmission

⁵ www.uniprot.org

and plasticity at adult synapses. GO terms include growth factor, and post-translational modifications include cleavage on basic residue pairs and disulfide bonds.

Genes Responsible for Anorexia Nervosa⁶

After doing a UniProt search for anorexia nervosa, two genes were linked to the disorder. The first is an Agouti-related Protein (AGRP) that plays a large role in weight homeostasis. The gene is involved in controlling feeding behavior through the central melanocortin system by inhibiting cAMP production . GO terms associated with AGRP include neuropeptide hormone activity, adult feeding behavior, and hormone-mediated signaling pathway and can be post-translationally modified at the disulfide bonds. The second gene that the search included was BDNF, as previously mentioned in the OCD search.

The BDNF Gene

A search on this gene specifically reveals that common genetic variations in the BDNF gene have been associated with an increased risk of developing psychiatric disorders such as anxiety and eating disorders.⁷ Since the protein is found in regions of the brain that control eating, drinking, and body weight, a variation in the gene can result in behaviors associated with that particular location in the brain.⁸ An Online Mendelian Inheritance in Man (OMIM) search provided a few studies that link the BDNF gene to both OCD and AN.⁹ A study in 2003 found 164 individuals with OCD and genotyped several single-nucleotide polymorphisms (SNPs). The results of the study revealed significant evidence of association to the disease between alleles from heterozygous parents and affected

⁶ www.uniprot.org

⁷ “BDNF Gene.”

⁸ “BDNF Gene.”

⁹ McKusick, “OMIM ENTRY – BDNF.”

offspring.¹⁰ More importantly, the study revealed that a variation at BDNF's codon 66 was highly associated with OCD.¹¹ At this codon, a methionine substitutes for a valine, either affecting the processing of the mature form of BDNF or by modulating apoptotic signaling.¹² The OMIM database also provided a study regarding codon 66 but with anorexia nervosa. In 2003, a study screened for the BDNF gene in 95 patients with eating disorders and identified four sequence variants, one of them being the amino-acid substitution Val66Met.¹³ Further investigation of SNPs in a sample of 143 eating disorder patients and 112 controls found a strong association of restricting AN with the Met allele of the Val66Met BDNF polymorphism, suggesting that the variant may be a susceptibility factor to anorexia nervosa.¹⁴ The same scientists performed the same tests on 1142 Caucasian patients with eating disorders from six different European Centers in France, Germany, Italy, Spain, and the United Kingdom.¹⁵ This study was the first to identify a susceptibility gene involved in the etiology of eating disorders across different populations.¹⁶

Studies Linking OCD and AN

While the BDNF gene has proven to link the two disorders genetically, I came across another genetic link of interest. In 1997, a study genotyped three independent sets of

¹⁰ Hall et al., "Sequence Variants of the Brain-derived Neurotrophic Factor (BDNF) Gene Are Strongly Associated with Obsessive-compulsive Disorder."

¹¹ Hall et al., "Sequence Variants of the Brain-derived Neurotrophic Factor (BDNF) Gene Are Strongly Associated with Obsessive-compulsive Disorder."

¹² Hall et al., "Sequence Variants of the Brain-derived Neurotrophic Factor (BDNF) Gene Are Strongly Associated with Obsessive-compulsive Disorder."

¹³ Ribasés et al., "Met66 in the Brain-derived Neurotrophic Factor (BDNF) Precursor Is Associated with Anorexia Nervosa Restrictive Type."

¹⁴ Ribasés et al., "Met66 in the Brain-derived Neurotrophic Factor (BDNF) Precursor Is Associated with Anorexia Nervosa Restrictive Type."

¹⁵ Ribases, et al. "Association of BDNF with Anorexia, Bulimia and Age of Onset of Weight Loss in Six European Populations."

¹⁶ Ribases, et al. "Association of BDNF with Anorexia, Bulimia and Age of Onset of Weight Loss in Six European Populations."

unrelated participants: 68 anorectics and 69 controls from the USA, 20 anorectics from Italy, and 62 patients with OCD and 144 controls without OCD from the USA.¹⁷ The results showed that a hypothalamic serotonin (5-HT) receptor promoter polymorphism, -1438G/A, was more common in anorectics than in controls as well as in patients with OCD than in controls.¹⁸ This suggests that the 5-HT_{2A}-1438G/A promoter polymorphism may contribute to a behavioral trait that is common to both AN and OCD, such as perfectionism or obsessionality.¹⁹ The exact function of the receptor is unknown, but it is thought to contribute to eating behaviors and anxiety.²⁰ Another study genotyped men and women with OCD for the same 5-HT_{2A} promoter polymorphism and found that it is strongly associated with OCD in women, but not in men.²¹ This implies that there may be a fundamental gender difference in genetic susceptibility to OCD and possibly even AN.²²

In 2006, one study found that a functional serotonin promoter polymorphism, HTTLPR, can alter the risk of disease and brain morphometry and function.²³ One of its variants, Val425, leads to a gain in function, increasing behavioral problems common in

¹⁷ Enoch et al., "5-HT_{2A} Promoter Polymorphism -1438G/A, Anorexia Nervosa, and Obsessive-compulsive Disorder."

¹⁸ Enoch et al., "5-HT_{2A} Promoter Polymorphism -1438G/A, Anorexia Nervosa, and Obsessive-compulsive Disorder."

¹⁹ Enoch et al., "5-HT_{2A} Promoter Polymorphism -1438G/A, Anorexia Nervosa, and Obsessive-compulsive Disorder."

²⁰ Enoch et al., "5-HT_{2A} Promoter Polymorphism -1438G/A, Anorexia Nervosa, and Obsessive-compulsive Disorder."

²¹ Enoch et al., "Sexually Dimorphic Relationship of a 5-HT_{2A} Promoter Polymorphism with Obsessive-compulsive Disorder."

²² Enoch et al., "Sexually Dimorphic Relationship of a 5-HT_{2A} Promoter Polymorphism with Obsessive-compulsive Disorder."

²³ Hu et al., "Serotonin Transporter Promoter Gain-of-Function Genotypes Are Linked To Obsessive-Compulsive Disorder."

OCD, AN, and Asperger syndrome.²⁴ This gain-of-function was approximately twice as common in 169 whites with OCD than in the 253 matched controls, and when compared to the probands of parents, the allele was twofold overtransmitted to patients with OCD.²⁵ This reinforces the idea that OCD and AN have genetic links that after the onset of one, can lead to the susceptibility of developing the other.

Increased family heritability can also suggest genetic links between OCD and AN. A study looked at 26 women with AN, 47 women with BN, and 44 control women with no history of an eating disorder.²⁶ First-degree relatives of each participant were interviewed according to the DSM-III-R Axis I disorders.²⁷ The results showed a common familial vulnerability for AN and BN, and more specifically, every AN proband interviewed had a lifetime history of an anxiety disorder.²⁸ The study discusses the possibility that it is necessary to have a risk for both OCD and an eating disorder to develop restricting-type AN.²⁹ Another familial study interviewed 574 first-degree relatives of 152 probands with AN and compared them to rates observed in 647 first-degree relatives of 181 never-ill control probands and found common familial liability

²⁴ Hu et al., "Serotonin Transporter Promoter Gain-of-Function Genotypes Are Linked To Obsessive-Compulsive Disorder."

²⁵ Hu et al., "Serotonin Transporter Promoter Gain-of-Function Genotypes Are Linked To Obsessive-Compulsive Disorder."

²⁶ Lilenfeld et al., "A Controlled Family Study of Anorexia Nervosa and Bulimia Nervosa: Psychiatric Disorders in First-Degree Relatives and Effects of Proband Comorbidity."

²⁷ Lilenfeld et al., "A Controlled Family Study of Anorexia Nervosa and Bulimia Nervosa: Psychiatric Disorders in First-Degree Relatives and Effects of Proband Comorbidity."

²⁸ Lilenfeld et al., "A Controlled Family Study of Anorexia Nervosa and Bulimia Nervosa: Psychiatric Disorders in First-Degree Relatives and Effects of Proband Comorbidity."

²⁹ Lilenfeld et al., "A Controlled Family Study of Anorexia Nervosa and Bulimia Nervosa: Psychiatric Disorders in First-Degree Relatives and Effects of Proband Comorbidity."

factors between AN and OCD.³⁰ This case-control study found that relatives of probands with AN have a threefold greater risk of OCD, and other anxiety disorders, compared to those without AN, suggesting common genetics between eating disorders and anxiety disorders.³¹

Conclusion

Obsessive-compulsive disorder and anorexia nervosa share many of the same behavioral qualities and, through my own findings, share a few genetic similarities. Both share a common gene brain-derived neurotrophic factor, BDNF, that when varied, can cause an increase in risk of developing psychiatric disorders. In addition, several studies have discovered polymorphisms that link the two disorders. Much still has to be learned about both disorders, but from the evidence shown, there seems to be a strong genetic link between OCD and AN.

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³⁰ Strober et al., "The Association of Anxiety Disorders and Obsessive Compulsive Personality Disorder with Anorexia Nervosa."

³¹ Strober et al., "The Association of Anxiety Disorders and Obsessive Compulsive Personality Disorder with Anorexia Nervosa."

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