GENETIC PREDISPOSITION TO GENERALIZED ANXIETY DISORDER

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ABSTRACT: Generalized Anxiety Disorder (GAD) is a subset of anxiety disorders and recently has been investigated by researchers worldwide due to a potential genetic predisposition. Researchers have consulted a variety of potential factors that could lead an individual to develop GAD, including familial structures, peer stimulus, age, living/schooling environments, and genetics. Of all of these factors, a genetic predisposition is the one factor that can be observed globally. This paper is an extensive literary review from international researchers looking at the potential for a genetic predisposition to GAD. This paper identifies a serotonin transporter gene polymorphism (5-HTTLPR) as the genetic variant which is thought to predispose an individual to GAD. Finally, this paper looks at how identifying this genetic predisposition can lead to advancements in medicine and therapy and ultimately lead to curbing the amount of diagnosable cases of GAD worldwide.

Introduction

Within the field of psychology, researchers seek to find whit might predispose someone to GAD. Both environmental and biological factors have been investigated in search of an answer. However, when taking into account all of the contradicting data claiming to know the greatest risk factors for GAD, the most compelling data backed with minimally debated research is a genetic predisposition. This literature review walks through worldwide evidence on the genetic variation identified as the potential predictor of GAD; also providing background on the variation and an explanation as to why it is thought to be a predictor. Additionally, alternative views are presented to show the breadth of information about GAD and the vast variety in potential influencers in the development of this mental illness. This research is important to know because when a genetic predisposition can be identified, prevention plans can be put in place in order to deter an individual from developing a diagnosable case of GAD. Furthermore, side effects of medications used to treat GAD can be predicted if the genetic predisposition of one person matches that of another.

KEYWORDS: Generalized Anxiety Disorder (GAD), Serotonin Transporter Gene Polymorphism (5-HTTLPR), Anxiety Sensitivity (AS), Stressful Life Event (SLE).

Review of Literature

Researchers have investigated a specific serotonin transporter gene polymorphism (5-HTTLPR) and observed how this polymorphism, when found at high levels in the body, makes people more anxiety sensitive (Stein, Schork, & Gelernter 2007). Anxiety sensitivity (AS) is when a person is at greater risk for developing GAD after experiencing a Stressful Life Event (SLE). SLEs are the precipitating event of this mental illness but only with the preexistence of high levels of 5-HTTLPR. The presence of high levels of 5-HTTLPR is found through blood sampling (Hemmings et al., 2015). This par-

ticular genetic variation contains a long L allele and a short S allele (HUGO Gene Nomenclature Committee [HGNC], 2017, 2017).

Even though studies indicate higher levels of 5-HTTLPR predisposes a person to GAD, a specific haplotype (another word for polymorphism) called the L-G haplotype must be found within the variation in order to make this statement accurate. This haplotype, unlike other ones found in the body, can "be found cross-culturally" (Hemmings et al., 2015). This is significant because many disorders are thought to be products of culture and manifest within a particular context; examples of this being both bulimia and ataques de nervios, a term used in Spanish-speaking countries, primarily Puerto Rico, for a person going through a nervous breakdown but here is actually a diagnosable mental illness (Oltmanns & Emery, 2015). Research has shown the presence of the L-G haplotype at high levels will make people more likely to develop GAD, and people who develop GAD across all cultures have shown high levels of the L-G haplotype (Hemmings et al., 2015).

Research has looked closely at the correlation between 5-HTTLPR and SLEs, particularly in regards to child maltreatment. When a child has higher levels of 5-HTTLPR and lives in a abusive or neglectful environment, GAD is likely to develop (Stein et al. 2007). Additionally, Stein et al. (2007) discovered that when two or more individuals have comparable levels of 5-HTTLPR, they will react to antidepressant medications in a similar way. The study showed multiple pairs of patients with comparable levels of 5-HTTLPR. These patients were given identical doses of antidepressant medications and found both positive and negative reaction were the same within each patient pair. This finding has led to more accurate antidepressant medication prescriptions and less negative effects on behalf of the patient. Now patients can rely on the results from previous patients and know what to expect when taking new medications instead of the old method of trial and error.

Another study (Hettema, Neale, & Kendler, 2001) investigated for common environmental and/or biological features to Obsessive Compulsive Disorder (OCD), GAD, panic disorders, and specific phobias within different sets of twins. This study was a meta-analysis and sought to observe similarities in findings in a variety of studies all looking to find what causes these disorders. The similarities found among patients OCD and specific phobias were determined to not be statistically significant. And, of all the disorders studied, GAD had the highest heritability rate with a 32% between monozygotic (MZ) twins. This finding led to the conclusion that genetics were the primary cause in the high prevalence rates of GAD and other anxiety disorders within MZ twin populations. This statistic was particularly important in male populations. In MZ male twins, the environment that the twins grew up in had virtually no effect on whether or not there was the development of GAD, however, in MZ female twins, the prevalence of GAD was highly correlated not only to 5-HTTLPR but also to shared environments. The study came to the conclusion that genetics were the most prominent feature in GADs, especially in male MZ twin populations with environmental factors following suit in terms of importance.

While most disorders are culturally bound, it is important to note 5-HTTLPR is a cross-cultural gene. In a study conducted in South Africa of "young, colored, tribal males" (Hemmings et al., 2015) the presence of 5-HTTLPR was found to be almost identical to that of people in the United States. This study revealed people in this small tribe with high levels of 5-HTTLPR were not only predisposed to have GAD, but had higher levels of AS and thus, when confronted with stressful life events, it could be predicted whether the individuals would develop GAD just by looking at the presence of 5-HTTLPR in their blood. Similarly to studies that have taken place in the United States, this study was also specific in looking for the L-G haplotype, which was found in DNA when drawing blood sam-

ples from the men. And, similar to other studies cited above, when at elevated levels, was used as a predictor for GAD with relative accuracy.

However, a study conducted by Schinka, Busch, & Robinchaux-Keene (2004), looked at the results of twenty six previous studies, all specifically looking for the genetic variance in GAD and other anxiety disorders. This study concluded there is little statistical evidence to support 5-HTTLPR variations predispose someone to GAD, stating all evidence in support of a genetic predisposition to GAD is false. However, it is important to note while this study deemed the results of previous studies to be statistically insignificant, the study still found strong correlations between 5-HTTLPR and AS.

Conclusion

The identification of 5-HTTLPR as a genetic indicator for Generalized Anxiety Disorder has furthered the field of anxiety research and has paved the way for further investigation into how to curb the diagnoses of anxiety disorders. Due to the identification of this genetic variation, prevention plans are being created for individuals prior to experiencing a Stressful Life Event, meaning an individual can have the psychological skills to handle a Stressful Life Event and not have it trigger Anxiety Sensitivity into the development of Generalized Anxiety Disorder. The identification of this genetic variation has also lead to investigation by other researchers at potential co-occurring disorders such as mood disorders and eating disorders, however, this research is far from conclusive. The identification of this variation has opened the door to a new way of studying anxiety and has provided insights into how to prevent the spread of diagnosable mental illnesses.

References

Hemmings, S. M., Martin, L. I., Merwe, L. V., Benecke, R., Domschke, K., & Seedat, S. (2015). Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents. *The World Journal of Biological Psychiatry,* 17(1), 66-75.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders. *American Journal of Psychiatry AJP*, 158(10), 1568-1578.

Hettema, J. M., Prescott, C. A., Myers, J. M., Neale, M. C., & Kendler, K. S. (2005). The Structure of Genetic and Environmental Risk Factors for Anxiety Disorders in Men and Women. Arch Gen Psychiatry. *Archives of General Psychiatry,* 62(2), 182.

HGNC. (2011, January). Symbol Report: SLC6A4. Retrieved February 27, 2017, from http://www.genenames.org/cgi-bin/gene_symbol_report?hgnc_id=11050

Oltmanns & Emery. (2015). Abnormal Psychology (8th ed.). Boston: Pearson.

Schinka, J. A., Busch, R. M., & Robichaux-Keene, N. (2004). A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. *Molecular Psychiatry Mol Psychiatry*, 9(2), 197-202.

Stein, M. B., Schork, N. J., & Gelernter, J. (2007). Gene-by-Environment (Serotonin Transporter and Childhood Maltreatment) Interaction for Anxiety Sensitivity, an Intermediate Phenotype for Anxiety Disorders. *Neuropsychopharmacology,* 33(2), 312-319.