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Brief Report: Genetic Links between Autism and Suicidal Behavior: A Preliminary Investigation

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Abstract

Evidence suggests there may be increased risk for suicidal behavior among individuals with autism spectrum disorder (ASD). An emerging body of research explores social factors that may contribute to increased risk, however little is known about the potential role of biological factors.

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Compliance with Ethical Standards

The authors have no conflicts of interest. The data analyzed in this study was from publicly-available databases and existing published literature; no direct research was conducted with human participants nor animals. No informed consent procedures were used.

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The current project addresses this knowledge gap through a preliminary study of genes associated with both ASD and suicidal behavior. Gene set enrichment tests of eight genes strongly associated with both ASD and suicidal behavior revealed overrepresentation of nine biological processes, including cognition and synapse function, and 14 cellular components, including the neuron, the synapse, and the synaptic and postsynaptic membrane. These results can be used to inform future investigations of the biological underpinnings of suicidal behavior and ASD.

Keywords

autism; suicide; genetic; gene set enrichment

Introduction

A growing body of research points to increased risk of suicidal behaviors (i.e. suicidal ideation, suicide attempts, and suicide death; Turecki and Brent 2016) among individuals with autism spectrum disorder (ASD). Evidence with clinical and convenience samples indicate that there are high rates of suicidal ideation and attempts in ASD groups relative to comparison groups (Hedley and Uljarević 2018; Zahid and Upthegrove 2017). Further, recent population-based studies suggest higher rates of suicide death among individuals with ASD compared with the non-ASD populations both in Sweden and in Utah, USA (Hirvikoski et al. 2016; Kirby et al. 2019). Results from both of the existing population-based studies also reveal that females with ASD were at significantly greater risk for suicide death than females without ASD. Other studies have looked more broadly at dimensional autism phenotypes (i.e., behavioral characteristics of ASD, but not a diagnosis), finding that autistic traits such as social communication difficulties are significantly associated with suicidal behavior (Culpin et al. 2018; Pelton and Cassidy 2017).

Despite mounting evidence of the association, little is known about specific risk factors and potential causes of suicidal behavior in ASD. Much like ASD, the science of suicide is complex and evidence suggests a myriad of factors that contribute to elevated risk (Franklin et al. 2017). Emerging research has begun exploring social factors and co-occurring psychopathology (e.g., depression, anxiety) that may connect suicidal behavior and ASD (e.g., Cassidy et al. 2018); however, there has not yet been exploration into biological factors associated with suicidal behavior and ASD. In particular, there is a need to examine the potential role that genetics may play in risk of suicidal behavior in ASD.

Large bodies of genetic research exist for both ASD and suicidal behavior, distinctly, and have established high heritabilities of both (see Robinson et al. 2015 for a review of genetic research in ASD; see Sokolowski et al. 2015 for a review of genetic research in suicidal behavior). Heritability is a measure of the extent to which genetic differences account for variation in traits among individuals; heritability estimates range from zero to one. Estimates near zero indicate little influence of genetic factors and a large influence of environmental factors (e.g., life events, trauma, stress, nutrition, pollution) whereas heritability estimates close to one indicate that most of the differences in individuals can be attributed to genetic factors. The most recent estimates of ASD heritability are high, at 0.74 (Tick et al. 2016) and

heritability of suicidal behavior is also estimated to be substantial, ranging from 0.17 – 0.55 depending on the specific behavior (Pedersen and Fiske 2010). Thus, variability in ASD and risk of suicidal behavior in individuals is due to both genetic and environmental factors, and both have strong genetic underpinnings.

Most psychiatric phenotypes, including ASD and suicidal behavior, have complex genetic compositions (Sullivan et al. 2012), where risk is influenced by hundreds of genetic differences throughout an individual's genome as opposed to one mutation in a single gene. Furthermore, there is often significant genetic overlap across psychiatric disorders (Gandal et al. 2018). Overlap of genetic risk can exist between the same genes or between broader gene interaction networks. Most genes do not act in isolation but rather affect the function of other genes. Gene interactions can be grouped into gene networks that are assigned biological meaning, establishing molecular and biological pathways. If genetic overlap exists between ASD and suicidal behavior, we would expect to find the same genes or similar gene networks influencing risk.

Once individual genes have been associated with a diagnosis, gene set enrichment analyses can be used to identify groups of these genes that are statistically significantly enriched, or over-represented in biological function. Enrichment analyses in ASD have implicated pathways involving inhibitory neuron expression and synapse development (Parikshak et al. 2015; Wang et al. 2018). Enrichment analyses in suicidal behavior have implicated signal transduction pathways and synaptic genes in brain development as important biological processes (Sokolowski et al. 2018, 2015). Gene set enrichment using the intersection of genes associated with both ASD and suicidal behavior will allow us to begin to understand potential biological aspects of the increased risk of suicidal behavior to those with ASD. This exploration is possible using well characterized gene lists for ASD and suicidal behavior-associated genes from the literature. The examination of significant genetic overlap between disorders allows for prioritization of genes and gene pathways and a better understanding of biological processes contributing to ASD and suicidal behavior. Increased understanding of biological risks that may put some individuals with ASD at greater risk for suicidal behavior will enable better identification of those at risk, and future development of targeted personalized interventions.

Methods

We first examined gene overlap between ASD and suicidal behavior by cross-matching prioritized lists of genes implicated, distinctly, by research studies in both traits. For ASD-associated genes, we used The Simons Foundation Autism Research Initiative (SFARI) database (SFARI Gene; <https://gene.sfari.org/>). To date, SFARI has listed 1,079 genes implicated in ASD. Of these, 91 are considered “high ranking” ASD risk genes—these have been prioritized as “high confidence” or “strong candidate” genes using their expert-established ranking criteria. Over 755 genes have been associated with suicidal behavior with varying levels of statistical support (Coon et al. 2018). Currently there has been no centralized effort to prioritize genes in suicidal behavior as in ASD. To identify genes strongly associated with suicidal behavior, we used the most comprehensive review article prioritizing genes of interest (Sokolowski et al. 2015) and top results from genome wide

association studies (GWAS) that mapped to genes from the GWAS catalog (Buniello et al. 2019). Next, we performed gene set enrichment tests with FUMA GENE2FUNC software (Watanabe et al. 2017) with overlapping genes identified to be strongly associated with both autism and suicidal behavior. In FUMA, Gene Ontology (GO, <http://geneontology.org/>) gene sets that have specific functional interpretations can be compared to all genes in the genome as well as to our selected gene set of interest. We therefore used FUMA to test our selected gene set against all genes and against the GO biological processes and the GO cellular components gene sets. Gene sets with a Bonferroni-adjusted p -value of < 0.05 in FUMA were considered significant. The GO biological processes gene sets encompass broad biological functions established from the literature; these processes encompass many molecular pathways. The GO cellular components gene sets encompass the cellular location of the gene products and are also established from the literature.

Results

When comparing the 91 highly ranked autism-associated genes from SFARI against 285 highly ranked suicidal behavior-associated genes (see Table S1), we identified eight overlapping genes associated with both ASD and suicidal behavior (see Table 1; Table S2).

Two of the eight genes (*GRIN2B* and *PTEN*) have the highest ranking for autism association in SFARI Gene. Gene set enrichment tests in FUMA showed overrepresentation of nine GO biological processes gene sets and 14 GO cellular compartment gene sets involving six of the eight genes. Figure 1 displays the significantly enriched gene sets.

GO biological processes

Four genes (*PTEN*, *GRIN2B*, *SLC6A1*, *GRIA1*) were overrepresented in biological processes relating to cognition (GO Cognition, $p = 1.71\text{E-}07$), behavior (GO Single Organism Behavior, $p = 9.39\text{E-}07$; GO Behavior, $p = 3.05\text{E-}06$) and synapse function (GO synaptic signaling, $p = 1.39\text{E-}06$). *PTEN*, *SLC6A1* and *GRIA1* were implicated in regulation of neural communication across a synapse (GO Negative Regulation of Synaptic Transmission, $p = 0.0012$) and *PTEN* and *GRIA1* were also associated with synaptic plasticity (GO Long Term Synaptic Depression, $p = 0.0211$). *PTEN*, *GRIPI* and *CTNND2* were found to be involved in formation of a neuronal extension called a dendrite (GO Dendrite Development, $p = 0.0027$). *PTEN* and *CTNND2* were also implicated in formation of the dendritic spine, which is a specialized protrusion of a dendrite (GO Dendritic Spine Organization, $p = 0.0273$; GO Dendritic Spine Development, $p = 0.0343$).

GO cellular components

Six genes (*CTNND2*, *GRIA1*, *GRIN2B*, *GRIPI*, *PTEN* and *SLC6A1*) were found to overlap in their cellular location of gene products at the neuron (GO neuron part, $p = 3.28\text{E-}05$; GO Neuron Projection, $p = 5.67\text{E-}06$). Of these genes, all but *SLC6A1* were found to have gene products localized at cellular synapses (GO Postsynapse, $p = 4.38\text{E-}06$; GO Synapse Part, $p = 8.25\text{E-}08$; GO Synapse, $p = 0.0001$). Nine other cellular component gene sets involving less than five genes were also significant. All gene set enrichment results are listed in Table S3.

Discussion

This preliminary study involved examination of genetic overlap in ASD and suicidal behavior, contributing to our understanding of the observed associations between increased risk of suicidal behavior and ASD. Results are consistent with shared biological processes that influence genetic risk for ASD and for suicidal behavior (Parikshak et al. 2015; Sokolowski et al. 2018, 2015; Wang et al. 2018). Eventually, understanding genetic and social influences—as well as how they interrelate—will advance the field toward potential targeted mental health treatments for individuals with ASD. In the current study, we were able to compare genes with strong evidence from both research areas and identify eight genes and multiple biological processes of interest shared across six of these genes.

Two of the eight genes identified are among candidate genes rated by SFARI Gene as “high confidence” suggesting that the evidence supporting their association with ASD is strong. These two genes (*GRIN2B* and *PTEN*) are associated with synaptic plasticity, brain development, and embryonic development.

We also identified numerous biological processes associated with the identified genes, including cognition, behavior, and synapse function. Prior research on suicide death and ASD suggests that cognition—specifically, presence or absence of intellectual disability—is associated with different levels of suicide death risk in ASD (Hirvikoski et al. 2016). Hirvikoski and colleagues (2016) found that individuals with ASD who did not have an intellectual disability were at much greater risk for suicide death than population controls, whereas those who did have an intellectual disability had less elevated risk (though still significantly greater than population controls). Furthermore, risk of suicidal behaviors including attempts and death was found to be highest in females with ASD without an intellectual disability (Hirvikoski et al., 2019). More research is needed to understand the role of cognition on risk of suicidal behavior in ASD.

Two of the eight identified candidate genes were not significant in the gene set enrichment tests: *MACROD2* and *SRSF11*. The functions of *MACROD2* and *SRSF11* are not well established but recent evidence suggests *MACROD2* likely plays a role in the central nervous system during brain development (Ito et al. 2018) and *SRSF11* likely plays a role in mRNA pre-processing in neurons (Gonatopoulos-Pournatzis et al. 2018).

Taken together, the eight genes identified in our analyses are related to nervous system and neuronal function. This lends support that overlap exists between ASD and suicidal behavior in fundamental biological processes.

Limitations and Future Directions

Currently, the basic genetic architecture is far from complete for both ASD and suicidal behavior (Mirkovic et al. 2016; Sullivan and Geschwind 2019); however, our identification of potential areas of genetic overlap is promising. Future studies will likely reveal many more genes and biological processes of interest. Our study, based on current knowledge of gene associations, relies heavily on *a priori* hypotheses of genes from the literature. Furthermore, the methods used in this work may exclude relevant gene information from

some publications due to the curation criteria of the tools used. Both FUMA and the GWAS catalog compile information from a large amount of published papers and relevant databases. These tools are updated regularly but include only currently known gene and pathway information, and therefore may omit results of importance. However, the genes and pathways highlighted in this paper are a logical starting point from which to initiate further research.

Planning for future research, it is important to recognize that study in this area will likely be limited by sample sizes due to the fact that both ASD and suicidal behavior are relatively rare; robust genetic research requires large sample sizes (Sullivan and Geschwind 2019). Researchers in this area are also advised to recognize the heterogeneity of ASD and suicidal behavior (Klonsky et al. 2016; Richards et al. 2019), as well as age differences in suicidal behavior risk for individuals with ASD (Kirby et al., 2019). While our definition of suicidal behavior includes suicidal ideation, attempts, and death, the nomenclature surrounding suicidal behavior as well as the approaches used to establish intent to self-harm may vary widely across the genetic suicidal behavior studies included in our analysis (Silverman, Berman, Sanddal, O'Carroll, and Joiner, 2007). These sources of heterogeneity further complicates sample size issues and may also have implications on study findings including limiting generalizability.

Conclusion

Given the overlap of strongly associated genes for suicidal behavior and for ASD, there is an apparent need for more research into genetic mechanisms leading to suicide risk among individuals with ASD. Just as how understanding the relationship between autistic behavioral traits and suicidal behavior can help shed light on social risk factors for suicidal behavior, understanding the genetic risk associations may provide new insights into the neurobiological underpinnings of risk of suicidal behavior in ASD. Understanding the complex system of factors that may contribute to suicide and suicidal thoughts and behaviors in ASD can lead to better identification of vulnerable individuals and targeted behavioral and medical treatments to prevent suicide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Gene set enrichment plots from FUMA showing significant gene sets from (a) GO biological processes and (b) GO cellular components.

Table 1

Gene overlap in autism spectrum disorder (ASD) and suicidal behavior (SB)

Gene Symbol	Relevant Gene Function	Significant in Gene Set Enrichment Analyses	Chromosome	# ASD reports ^a	# SB reports ^b
<i>CTNND2</i>	brain and eye development, neuronal development, maintenance of dendritic spines and synapses	Y	5	5	1
<i>GRIA1</i>	neurotransmission in brain, synaptic plasticity	Y	5	5	2
<i>GRIN2B</i>	brain development and synaptic plasticity	Y	12	48	4
<i>GRIP1</i>	development of neurons	Y	12	12	1
<i>MACROD2</i>	physiological role in the central nervous system during brain development	N	20	19	1
<i>PTEN</i>	regulates cell division, embryonic development	Y	10	55	3
<i>SLC6A1</i>	uptake of neurotransmitters	Y	3	19	4
<i>SRSF11</i>	pre-mRNA processing in neurons	N	1	4	1

Notes. Highest confidence genes in SFARI are bolded. Y, yes; N, no.

^a, from SFARI database

^b, references in Table S2.