

# **The Role of Gene Therapy in Psychiatry**

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With the latest advancements of CRISPR (clustered regularly interspaced short palindromic repeats) and other gene therapies on the scientific horizon, such as next-generation sequencing and genome-wide association studies (GWAS), a certain degree of scientific focus has turned to psychiatric disorders with renewed interest (Zhuo et al. 2019). Although research is still in its infancy and human trials are years away, recent experiments carried out postmortem and in mice have proven fruitful. Using CRISPR technologies, deletions of target genes and insertions of others has repeatedly been shown to lower certain traits and tendencies associated with psychiatric disorders such as depression, bipolar disorder, and schizophrenia. Specific challenges arise in both monogenic and polygenic disorders, but gene editing technologies for psychiatric disorders are no longer a distant dream.

Psychiatric disorders are highly debilitating patterns of behavior, or thought, that cause significant impairment and decreased functionality. While countless studies have sought to find a single source of mental illness, the causes of psychiatric disorders are often unclear. Most commonly stress, abuse, trauma, and life experiences give rise to psychiatric disorders, as development is a complex combination of biological, psychological, and environmental factors. They are also extremely heritable; zygotic twin-based studies have shown that anxiety disorders, including PTSD and OCD, are 20-25% heritable, alcohol dependence and eating disorders are 50-60% heritable, and bipolar disorder, autism spectrum disorders, ADHD, and schizophrenia are around 80-85% heritable (Deans 2019; Trubetskoy et al. 2022; Legge et al. 2021). Many treatments for psychiatric disorders are unsatisfactory and decades old. Gene therapy aims to change that. The role of gene editing, or gene therapy, is to introduce a corrected version of a gene into the genome, or to delete a mutated or affected gene, as treatment of a condition (Vidyasagar 2022).

CRISPR is just one of the techniques used in gene therapy, and it excels in precision. A few recent additions to the CRISPR toolbox, base-editors, are able to edit single nucleotides and induce point-mutations. This is important as around 50% of disease-causing mutations are single-nucleotide substitutions (Wong et al. 2021). However, administering gene therapy in the brain is not a simple procedure. Current research on treatment of psychiatric disorders with gene editing is hindered by the body's natural defenses; the blood-brain barrier prevents many foreign macromolecules, such as toxins and pathogens, from entering the brain (Wong et al. 2021). This also means, unfortunately, that CRISPR systems are inhibited from entering the brain. Viral delivery and nanoparticles offer possible, but still underdeveloped modes of transmission (Wong et al. 2021). This is only exacerbated by the polygenic nature of hereditary psychiatric and neurodevelopmental disorders.

In recent years, many genes associated with psychiatric disorders have been identified. However, as with many other diseases, no known psychiatric disorder yet follows defined Mendelian inheritance with a single distinguishable gene or locus (Thome et al. 2012). In fact, there are only a handful of complex polygenic disorders for which linkage analysis has identified chromosomal regions and genes contributing to them; most notably, the apolipoprotein E on chromosome 19 in Alzheimer's disease, and *NOD2* in Crohn's disease (Sklar 2002). It is unlikely, therefore, that CRISPR will be able to, in the near future, simply exchange a mutated gene with a fixed one and cure mental illness. It is important to note that a few psychiatric and neurodevelopmental disorders are monogenic, with specific genes identified on the genome as being responsible for them. Most, however, are not. The complexity of these psychiatric disorders calls for similarly complex technology and imaging. Polygenic disorders, those caused

by a multitude of genes, are among the most complex of disorders. Unfortunately, for polygenic conditions, gene therapy is a distant reality (Foulkes et al. 2020).

Among the many well-known polygenic psychiatric disorders, such as bipolar disorder, major depressive disorder, and autism, the genetics of schizophrenia remain the most researched (Foulkes et al. 2020). This is, in part, because of its extremely high heritability rate. Scientists posited that genetics and gene location play a large role in the development of schizophrenia, and massive genome-wide association and linkage studies have even uncovered particular genes of interest affiliated with schizophrenia. Recent genomic studies indicate 270 distinct common genetic loci associated with schizophrenia and rare protein mutations on 10 genes (Legge et al. 2021; Trubetskoy et al. 2022; Singh et al. 2022), 8000 single nucleotide polymorphisms (SNPs) (Zhuo et al. 2019), and over 600 individual genes in 108 loci that are all significantly associated with schizophrenia (Zhuo et al. 2019). Further, studies showed that a higher polygenic risk score (PRS) that is, the higher genetic risk for developing a trait, was directly associated with a more chronic illness course, indicated by amount and duration of hospital admissions (Legge et al. 2021). The discovery of these biological mechanics of schizophrenia provides a foundation for further biological inquiry into the disorder (Ulrich 2022).

Intensive research on one specific gene, *FXR1*, has revealed it to be a regulator of many of the mechanisms behind schizophrenia (Shen et al. 2021). To study the role of this gene in mental illness, scientists deleted it from the parvalbumin interneurons (PVI) of the medial prefrontal cortex (mPFC) in mice (Shen et al. 2021). PVI generate gamma frequencies and are invaluable in modulating habitual learning and motor skills. The study went on to show that deletion of the *FXR1* gene from PVI lead to reduced PVI excitability, impaired gamma mPFC oscillation, and schizophrenia like symptoms, such as decreased locomotive activity, memory

retention, and social interaction, and increased compulsive behaviors, anxiety, and mania (Shen et al. 2021). A similar study found that deletion of FXR1 in the forebrain of mature excitatory neurons led to enhanced learning and long-term memory, suggesting that FXR1 regulation in the brain is critical, even more so in PVIs than excitatory neurons (Cook et al. 2014; Shen et al. 2021). Interestingly, FXR1 is a mutation-intolerant gene in humans (Shen et al. 2021). Mutation-intolerant genes greatly impact the rare genetic architecture of many psychiatric disorders including neurodevelopmental disorders and intellectual disability (Shen et al. 2021). Thus, research on this gene is invaluable to analysis of the genetic basis and treatment of psychiatric disorders. Despite these incredible discoveries, research, for now, is stuck at non-human clinical trials awaiting further advancements.

In another revolutionary study, scientists used CRISPR-Cas9 to isolate and induce a point mutation in the gene *GAD67* that encoded for GABA<sub>A</sub>  $\delta$  in the hippocampus of mice (Sun et al. 2018). GABA receptors react to gamma-aminobutyric acid, the chief inhibitory compound in the adult central nervous system. That is, they control brain and muscle relaxation, and have been associated with schizophrenia, depression, and bipolar disorder (Sabunciyani et al. 2016). Postmortem studies revealed that, in patients with schizophrenia, mRNA production of the gene is reduced by 15-35% (Fujihara et al. 2020). After breeding these mice, they dissected and sliced the hippocampus. Then, they stimulated neuronal cells to note the specific response of the  $\delta$  receptor (Sun et al. 2018). Subsequently, they concluded that the loss of function *GAD67* gene that codes for GABA not only caused cognitive impairments but also many behavioral alterations associated with schizophrenia, such as anhedonia and anxiety (Fujihara et al. 2020). It is the hope that future studies will confirm that activating the GABA<sub>A</sub>  $\delta$  receptors has antidepressant effects (Sun et al. 2018).

Further research has shown that an increase in mRNA production in certain individuals can give rise to disorders such as schizophrenia, bipolar disorder, and major depression; the genes that produce the RNA proteins are identifiable on the genome and distinguishable from control groups (Sabunciyan et al. 2016). Similarly, scientists are investigating the *Arc* gene as a potential treatment for individuals exposed to binge drinking in adolescence (Bohnsack et al. 2022). The scientists utilized CRISPR to manipulate methylation processes in *Arc* expression (Bohnsack et al. 2022). The gene editing normalized deficits in *Arc* regulation and led to a reduction of anxiety and excessive alcohol drinking in adult rats (Bohnsack et al. 2022). Excessive alcohol usage during adolescence has a multitude of psychiatric comorbidities, some of which gene therapy aims to treat, and the possibility of managing addictions with CRISPR could have enormous applications in the field of psychiatry.

For the first time in history, psychiatry and genetics, two specialties that have developed orthogonally for decades, are finally intersecting with promising results. Although there is no indication yet that CRISPR or other gene therapies will be applied in human psychiatric disorders any time soon, the idea is no longer out of the realm of possibility. Furthermore, it follows that CRISPR will most immediately be used for monogenic disorders, such as fragile X syndrome and Rett syndrome, due to their more easily identifiable gene loci. With technology advancing as rapidly as it is, and worldwide collaboration producing valuable research, gene therapy for complex psychiatric disorders is no longer a fictitious dream. CRISPR will never be an easy fix for psychiatry, and complete cures are unlikely. However, it does offer new treatments for wildly stigmatized disorders and their antiquated medications. The genesis of this field, molecular psychiatry, provides many applications for gene therapy moving forward.

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