Gene Editing Anxiety: The Uncertain Cost of Engineering Peace of Mind

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Introduction

Many parents diagnosed with debilitating anxiety disorders fear their children will suffer from the same psychiatric illness that has plagued their entire lives. While Preimplantation Genetic Diagnosis has long allowed parents to screen out embryos with a predisposition to certain disorders, the practice collides with many religious or personal beliefs. With the advancement of genetic-engineering technologies, such as CRISPR-Cas9, scientists have speculated about using such techniques to alter genetic material to reduce the risk of acquiring – or passing along – complex psychiatric disorders. Although somatic cell engineering could theoretically correct genetic variants associated with anxiety in any one individual, the prospect of editing the germline to permanently induce genetic changes for multiple generations proves enticing. However, the unforeseen consequences of applying germline engineering for complex anxiety disorders raise important moral considerations. The unpredictable health risks to future generations incurred by germline genetic engineering for anxiety disorders outweigh the potential probabilistic benefits through a consequentialist lens.

Health and Genetic Risks of Germline Editing

Editing the human germline to prevent psychiatric disorders poses serious health risks to individuals. Currently, scientists warn that genetically altering the human genome can result in off-target mutations that increase the risk of disease. For instance, gene-editing technologies like CRISPR-Cas9 can make unintended cuts in the genome, possibly preventing important genes from functioning properly. Additionally, cells may divide before gene-editing has completed, or the editing technology may inadvertently modify only one copy of the target alleles. Such mistakes produce a mixture of distinct genotypes within a single individual—a phenomenon known as genetic mosaicism.[1]

[1] Edward Lanphier and Fyodor Urnov, "Don't Edit the Human Germ Line," *Nature; London* 519, no. 7544 (March 26, 2015): 410–11, http://dx.doi.org.ezp-prod1.hul.harvard.edu/10.1038/519410a.

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However, even assuming germline editing has advanced enough for these off-target effects to prove negligible, serious consequences still may arise from the intended genetic alterations due to pleiotropy. Many individual genes impact various aspects of physiology or behavior. For example, the CCR5 gene encodes a macrophage receptor targeted by certain HIV strains. Interestingly, a naturally-occurring 32 base-pair deletion within the CCR5 gene confers greater resistance to these strains of HIV.[2] While inducing this deletion in the germline via genetic editing would seemingly reduce HIV transmission – a clear benefit to humanity – such a mutation may increase a person's susceptibility to infection due to CCR5's role in staging an immune response.[3] These pleiotropic effects extend to psychiatric disorders influenced by multiple genes, in which alleles associated with OCD risk, for example, positively contribute to educational attainment and performance.[4] Therefore, even if off-target effects are mitigated, editing anxiety risk genes can lead to unforeseen consequences due to their non-specific nature.

There is a risk that genetic germline engineering would affect all of society due to its generational implications. While somatic engineering ensures any effects are contained to a single individual, altering the genetic material of germline cells may create pleiotropic consequences or genetic mosaicism that will persist for generations. Importantly, without sufficient quality control measures, researchers cannot know the precise effects of germline editing until after birth—and some problems may only emerge years later.[5] As a result, large portions of society may endure the unintended ramifications or elevated risks of editing anxiety-related genes for generations.

In contrast, the British bioethicist John Harris equates the potential harms inflicted by germline editing as no more risky than natural sex: "Human reproduction involves genes being recklessly combined in the dark, with unforeseeable consequences for the resulting children, parents, and the generations to come."[6] However, the risks associated with conception through "natural sex" do not justify conducting an expensive procedure with unknown effects given the mere probabilistic nature of anxiety-related genes. Proposing such a comparison assumes a cavalier attitude towards the real risk of pleiotropic effects and increasing the prevalence of ill-suited alleles. In essence, if germline editing is no different from conventional reproduction, why bother using the technique at all for anxiety disorders? At least with natural reproduction, parents avoid unnecessary costs and the potential guilt of unintentionally harming their child's cognitive development or increasing their risk for other disorders.

The Complex Heritability of Anxiety Disorders

Because genetic germline engineering does not guarantee desired outcomes for anxiety-related disorders, its potential harms outweigh the anticipated benefits. The germline is not a sacrosanct entity considering its fluidity in

[2] Alison P. Galvani and John Novembre, "The Evolutionary History of the *CCR5-Δ32* HIV-Resistance Mutation," *Microbes and Infection* 7, no. 2 (February 1, 2005): 302–9, https://doi.org/10.1016/j.micinf.2004.12.006.

[3] Jean K. Lim et al., "Genetic Deficiency of Chemokine Receptor CCR5 Is a Strong Risk Factor for Symptomatic West Nile Virus Infection: A Meta-Analysis of 4 Cohorts in the US Epidemic," *The Journal of Infectious Diseases* 197, no. 2 (January 15, 2008): 262–65, https://doi.org/10.1086/524691; Maximiliano Ruben Ferrero, Luciana Pádua Tavares, and Cristiana Couto Garcia, "The Dual Role of CCR5 in the Course of Influenza Infection: Exploring Treatment Opportunities," *Frontiers in Immunology* 12 (January 20, 2022), https://doi.org/10.3389/fimmu.2021.826621.

[4] The Brainstorm Consortium et al., "Analysis of Shared Heritability in Common Disorders of the Brain," *Science* 360, no. 6395 (June 22, 2018): eaap8757, https://doi.org/10.1126/science.aap8757.

[5] Lanphier and Urnov, "Don't Edit the Human Germ Line."

[6] John Harris, "Germline Modification and the Burden of Human Existence" 25, no. 1 (2016): 6–18, https://doi.org/10.1017/S0963180115000237.

everyday life: the genetic material of sperm modulates with age while sexual selection determines the combination of genes for potential offspring.[7] Researchers and clinicians should approach germline editing like any other medical procedure, weighing the benefits against potential harms. Of course, anxiety-related disorders lead to serious manifestations in patients, often requiring decades of psychopharmacology and psychotherapy.[8] However, genetic germline engineering does not provide a definitive and permanent solution to the underlying causes given the very nature of anxiety-related disorders. While anxiety disorders exhibit a heritability of 30-60 percent depending on the specific disorder, genes associated with such disorders behave probabilistically – not deterministically.[9] Whether a person develops a disorder and the severity of a disorder depend significantly on environmental factors.[10] As such, the variants associated with anxiety do not invariably lead to disorders.

As a result, parents may be opting in to preemptively treat a disorder their child may not develop in the first place. Despite this, even if their offspring do develop an anxiety disorder, the magnitude of the condition may not warrant a treatment as drastic as germline engineering—one that risks unforeseen pleiotropic effects that last generations. Even if genes for anxiety could be edited with great predictive success, the line separating non-genetic anxiety from pathological versions is unclear. Emotions like fear and anxiety have evolved as important survival mechanisms for dangerous situations.[11] Gene editing could inadvertently weaken their protective functions.

Safer and Less Intrusive Alternatives

Genetic germline engineering offers a drastic option for individuals concerned about their high genetic risk for anxiety disorders, especially when safer and less extreme alternatives are available. Currently, multiple treatment options exist to improve the quality of life of patients living with mild anxiety disorders. For instance, medication and cognitive-behavioral therapy commonly manage many disorders, such as mild to moderate forms of social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD).[12] Unfortunately, many individuals living with severe anxiety disorders do not respond to mainstream interventions. In these patients, overwhelming thoughts and compulsive tendencies that prevent basic facets of daily life may warrant treatments more aggressive than standard medication or therapy. Nonetheless, these patients could still explore the possibilities of genetic engineering technology without altering their germline and potentially endangering future generations. Somatic cell engineering more closely resembles standard medical treatments in that an individual weighs the benefits and harms to *his or her own person*. In the case of somatic cell editing, any unforeseen complications will die with the patient, preventing multiple generations from inheriting elevated health risks. Therefore, editing somatic cells to alter anxiety-correlated genes can yield similar results as genetic germline engineering without the added unknown ramifications. Although germline engineering may appear more cost-effective due to its long-lasting, multi-generational impact, the potential savings do not justify

[7] Harris.

[8] Borwin Bandelow, Sophie Michaelis, and Dirk Wedekind, "Treatment of Anxiety Disorders," *Dialogues in Clinical Neuroscience* 19, no. 2 (June 2017): 93–107.

[9] In addition, many DNA variants linked to anxiety disorders are not exclusive to a single syndrome, further complicating the ability to predict risk scores for polygenic anxiety conditions.

[10] The Brainstorm Consortium et al., "Analysis of Shared Heritability in Common Disorders of the Brain."

[11] Joseph E. LeDoux, "Chapter 21 - Evolution of Human Emotion: A View through Fear," in *Progress in Brain Research*, ed. Michel A. Hofman and Dean Falk, vol. 195, Evolution of the Primate Brain (Elsevier, 2012), 431–42, https://doi.org/10.1016/B978-0-444-53860-4.00021-0.

[12] Bandelow, Michaelis, and Wedekind, "Treatment of Anxiety Disorders."

the risks of a therapy that could have severe consequences for many individuals. In addition, while the current costs of somatic engineering could be prohibitive, ongoing innovation may reduce its price over time. Considering individuals can benefit from less severe treatment plans if and only if they develop an anxiety disorder in the first place, germline engineering should not be offered for anxiety-correlated genes.

Autonomy Concerns

Genetic germline engineering violates the autonomy of potential offspring by imposing a procedure without their informed consent. Medical professionals and researchers must disclose enough information for individuals to weigh the benefits and risks of participation, enabling fully informed consent. However, germline editing causes repercussions that extend many generations into the future. It is clearly impossible to obtain consent of future individuals.[13] Proponents of genetic germline engineering refute this, citing the immense influence society generally allows parents to hold over their children's education, medical issues, and more.[14] Although true, this argument assumes an absolute totalitarian view of parenthood in which parents never discuss medical risks with their child before making a final decision. Moreover, there is a huge ethical difference between genetically correcting a fatal disease caused by a single gene and altering anxiety-related genes in terms of autonomy. For instance, suppose a couple decides to genetically correct the gene that causes cystic fibrosis in their germline, obviously without clear consent from their potential offspring. This decision arguably promotes the overall autonomy of their children by removing the physical limitations imposed by the disease, thus outweighing any previous infringements on autonomy. In contrast, variants influencing anxiety-related disorders are not as concrete, given their complex genetic nature and susceptibility to environmental factors. Therefore, children would be subject to the risks and unknowns of germline editing all to preemptively treat a disorder they may or may not have developed. Rather, parents should allow future generations to dictate their own treatment – if any treatment is indicated at all – whether that entails medication, therapy, or (one day) somatic cell engineering.

Conclusion

While genetically engineering the germline to permanently reduce transmission of anxiety-related genes may seem like an ideal solution to prevent anxiety disorders, the practice presents substantial risks and unclear benefits. There is a risk of pleiotropic effects that could trigger health problems as serious or more severe than the targeted anxiety disorder itself.

The potential complications not only endanger the recipient but jeopardize the health of future generations by altering the germline. These ramifications trump the prospective benefits of germline engineering for anxiety disorders considering anxiety-correlated genes act probabilistically – not deterministically — and are subject to a host of environmental influences. Based on a typical risk-benefit analysis, genetic germline engineering of anxiety-related genes crumbles in comparison to therapy, medication, and somatic cell engineering – all safer treatments that can be applied after birth, if necessary.

[13] Lanphier and Urnov, "Don't Edit the Human Germ Line."

[14] Harris, "Germline Modification and the Burden of Human Existence."