Episode 060: Genetics and Environmental Factors in Suicide

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There are no conflicts of interest for this episode.

In the previous episode on Suicide, we discussed epidemiology, general risk factors, and associations of suicide with various mental health disorders. Now, in this second part of this series, we will focus on genetic and environmental factors associated with suicide. The data here might be cold and distant, and so is the nature of suicide. It cuts at the core of families that have struggled with it. I have had many patients who have had family members commit suicide, and it devastates them forever.

Struggling with suicidal thoughts is a burden and carries weight in those that live with it on a daily basis. Our hope would be that those who struggle with suicidal thoughts would look for effective, evidence-based treatment. Our hope for providers is to know more about suicide, be more comfortable in having discussions with patients, and feel more like an expert in both knowledge and the ability to empathize with patients' distress.

Genetic Links to Suicidal Behavior

For families that have seen multiple suicides, the burden and angst that comes with continuing to live without their loved ones runs deep. With regards to genetics, suicidality has been noted to cluster in certain families, particularly families filled with mood disorders (Brent, Oquendo et al. 2002, Brent and Mann 2005). Further evidence for a genetic component comes from various twin and adoption studies that have been conducted over the years.

- The Swedish National Registry, a study with nearly 84,000 probands, suggests a heritability pattern of between **30-50%** (Tidemalm, Runeson et al. 2011).
- When corrected for transmission of psychiatric disorders that could be confounding factors, this heritability for suicidal behavior remains between **17-36%** (Fu, Heath et al. 2002).

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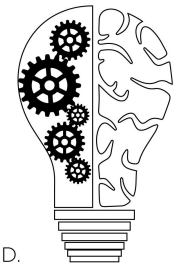

- To put this into a more concrete number, children of a parent who attempted suicide are nearly five times more likely to attempt suicide themselves than the average person (Brent, Melhem et al. 2015).

Just to give you a frame of reference to things that are highly heritable include things like height, whereas things more complex like IQ have a lot more variation. The heritability of height is approximately **80%** (Yang et al 2010). The literature generally estimates IQ heritability to be between 40% and 80% (and generally less for children). However, it must be stated that heritability of IQ varies significantly by social class. Additionally, almost no genetic polymorphisms have been discovered that are consistently associated with variation in IQ in the normal range (Nisbett et al, 2012). So in summary, the heritability of suicidal behavior is present but not very strong compared to things like height.

Lessons from Monozygotic Twins

A unique way of looking at just how significant genetics are for variance in suicidal thoughts and behaviors is through the use of a **monozygotic versus dizygotic twin study**. Monozygotic twins share all of the same genetic information because they come from the same sperm and egg, whereas dizygotic twins just share the same in utero environment. Data from the Swedish Twin Registry showed that if one monozygotic twin committed suicide, than the rate for the other twin committing suicide was 6%, as compared to 2% for dizygotic twins. A similar, but smaller study from the Danish Twin Registry showed an even greater disparity, with rates of 35% for monozygotic and 0% for dizygotic twins (Juel-Nielsen and Videbech 1970, Pedersen and Fiske 2010).

Does Adoption Change these Results?

Another factor that needs to be addressed is the difference between pure genetics and the influence of siblings or twins sharing the same home environment, with regard to influence on suicidal behavior. Here, we look to adoption studies that reveal that suicide in biological parents had similar effects on offspring suicide in the non-adopted and

adopted, suggesting the primary effect of parental suicide is hereditary rather than mediated by the post-natal environment (von Borczyskowski, Lindblad et al. 2011).

What Genes Increase Suicide?

With the evidence for a genetic component in mind, it is little wonder that much research has been done to try to elicit more specifically what genes might be related to suicidality. **Over 200 genes have been reported as being associated with suicidal attempts**, and there has been exponential growth of discovery of candidate genes in the past decade. Most of the individual genes that have been studied have been driven by biological hypotheses regarding rates of serotonin synthesis, serotonergic neurotransmission, and neurotrophic factors. These studies have produced inconsistent results (Anguelova, Benkelfat et al. 2003, Brezo, Klempan et al. 2008, Dwivedi 2010). More recently, there has been a shift towards looking at genome-wide association studies (GWAS) or familial linkage studies to try to find a genetic link. Some evidence, though not conclusive, points to a genetic tendency linked to a particular area on the genome of chromosome 2. Data gathered from 162 families diagnosed with schizoaffective disorder or bipolar disorder showed that family members within this cohort who had attempted suicide had a higher degree of genetic similarity at a specific are of chromosome 2, 2p12 (Willour, Zandi et al. 2007). This replicated similar findings from two previous studies of attempted suicide in pedigrees with alcohol dependence and in pedigrees with recurrent early-onset depression.

What Role Does BDNF Have?

One set of genes to highlight as potentially interesting are Brain Derived Neurotrophic Factor (BDNF) and its receptor, NTRK2. BDNF is one of the neurotrophins that regulates neuronal survival, plasticity, and synaptic function (Morse, Wiegand et al. 1993, McAllister 2001, Tsankova, Berton et al. 2006). We have talked about how BDNF can be increased by certain medications, exercise and diet in prior episodes. BDNF has been shown to be modulated by stress through epigenetic regulation (Roceri, Cirulli et al. 2004). This is one example of many where early life adversity or other stressors can take the preexisting raw genetic data in our bodies and modify it to be more or less

expressed through DNA methylation or histone modifications (Turecki, Ota et al. 2014). Beyond BDNF, there have been widespread changes in methylation patterns of neurotrophic and neuroprotective factors in the hippocampus and prefrontal cortex associated with suicide (Labonte, Suderman et al. 2013, Schneider, El Hajj et al. 2015). Specifically with BDNF, studies have looked at mutations in the gene, as well as expression of the protein levels in the brain, in association with depression and suicide (Youssef, Underwood et al. 2018). A polymorphism in the gene, Val66Met, is associated with an increased risk for depression. Suicide itself was not associated with this genotype, but lower levels of BDNF were found in the anterior cingulate cortex of the brains of individuals who had committed suicide. Further meta-analysis and systematic review of 23 small sample size studies shows no significant association of the Val66Met polymorphism and suicidal behavior, except when broken down by ethnicity. In that case, Caucasians and Asians are found to have an increased odds ratio for suicidal behavior of 1.96 and 1.36 respectively (Gonzalez-Castro, Salas-Magana et al. 2017). Overall we know BDNF is one thing that we can influence which provides some hope as we struggle to help those who struggle with suicidal thoughts.

Environmental Influences on Suicide

Beyond genetics, environmental factors and traumatic events are also associated with higher rates of suicide and suicidal thoughts. While not exhaustive, this list includes adverse childhood events such as physical or sexual abuse, witnessing domestic violence in the home, or being in the foster care system. Traumas throughout adulthood including divorce, rape or physical assault, serious accidents, and loss of pregnancy also contribute to higher rates of suicide. A large epidemiological study in Australia showed that a history of childhood sexual abuse was associated with a 3.79x greater suicide rate, while female rape or physical assault was associated with a 3.63x and 3.69x greater incidence of suicide, respectively. Other factors identified included being currently separated or divorced (2.38x), experiencing a serious accident (2.04x), and loss of a pregnancy (1.54x) (Statham, Heath et al. 1998).

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The Third Factor: Choice

While genetics and environmental influences certainly are external factors associated with suicide risk, we want to emphasize that these are not the only factors.

- The average rate of suicide is around 10 per 100,000 people years (1% of the population dies by suicide).
- If a monozygotic twin commited suicide, in the largest study, there was only an absolute increase in 4% compared to dizygotic twins.
- If you had 4x the risk of commiting suicide due to environmental factors, it would still be 40 per 100,000 people years.

So there are factors outside of genetics and environment that influence suicide, and I would argue one of those is choice. It is important to recognize the role of choice (we are not just a bag of genetics and things that happen to us, and actually thinking that way is harmful).

Thinking You Have No Choice is Harmful!

In studies where they try to convince one group that they don't have a choice (by having them read that they are just doing things predetermined by their biology, genetics or environment), it leads to them:

1. Being more likely to cheat (Vohs, 2008)
2. More likely to conform to social norms (Alquist, 2013)
3. Reduced helping behavior and increased aggression (Baumeister, 2009)
4. Not slow down after making an error to re-evaluate. (Rigoni, 2013)

Essentially, thinking you have no choice makes you more likely to do things that are not as thoughtful and decrease your frontal lobe function.

Furthermore, a recently-published Israeli study sought to elucidate the origins of suicidal tendencies by comparing patients of open wards in a psychiatric hospital (n = 59) to a control population (n = 65; N = 124). Notably, the study's results clearly demonstrated in

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both groups a decreased sense of meaning in life (—0.82, $p < 0.001$) and lower amount of an internal locus of control (—0.49, $p < 0.001$) each were significantly correlated with risk of suicide. Simply defined, a life with meaning is one the individual feels is worth living (Frankl, 1984). The presence of meaning in one's life is essential to enduring adversity. Meaning in life is especially relevant to providing individuals with the ability to avoid harmful behaviors adopted in response to difficult circumstances. This underscores the notion that genetics alone do not determine the course of our lives. As indicated by the study, the interactions we have with our surroundings and the people in our lives are significant factors. From those interactions, we interpret and construct a meaning — a purpose (Aviad-Wilchek, 2019).

With this in mind, we encourage our listeners and readers to check out our final episode in the series on treatments and therapies that can be helpful. In the final episode we will discuss how important it is to make choices to change your environment (like enrolling in a day treatment program) and get treatment, and how no case is hopeless. Treatments we will discuss in the next episode that help people struggling with suicidal thoughts include:

- Psychotherapy (especially with a strong therapeutic alliance)
- Medication Management (treat underlying psychiatric issue)
- TMS, ECT, Ketamine
- Partial and Day-Treatment Programs (Mentalization, DBT)
- Exercise
- Diet
- Optimizing Sensorium
- Treating Anxiety
- Treating Akathisia if present
- Optimizing Sleep
- Recognizing and Treating Substance Disorder
- Taking Away Guns