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Schizophrenia as a pseudogenetic disease: A call for more gene-environmental studies

E. Fuller Torrey[a,*], Robert H. Yolken[b]

[a] Stanley Medical Research Institute, 301-571-2078, 10605 Concord St, Suite 206, Kensington, MD20895, USA
[b] Stanley Laboratory of Developmental Neurovirology, Johns Hopkins Medical Center, Baltimore, MD, USA

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ABSTRACT

In recent years schizophrenia has been assumed to be largely a genetic disease with heritability estimates, derived primarily from family and twin studies, of 80%–85%. However, the results of genetic research on schizophrenia have not yielded results consistent with that estimate of heritability. In particular, extensive genetic studies have not led to new methods for diagnosis and treatment. An examination of the twin studies on which heritability is based shows why such studies exaggerate the genetic component of schizophrenia. In addition, the effects of infectious agents such as *Toxoplasma gondii* and the composition of the microbiome can produce a clinical picture that would also appear to be largely genetic due to familial aggregation and a role for a partial genetic contribution to the immune system. It is concluded that the genetic component of schizophrenia may have been overestimated and an increased focus on gene-environmental interactions is likely to accelerate research progress on this disease.

1. Introduction

Genetic theories of schizophrenia etiology have been proposed for more than a century. In 1919 Emil Kraepelin suggested that a "hereditary predisposition" should be considered based on the family clustering of cases: "I know a very great number of cases in which several brothers and sisters were attacked with dementia praecox." Kraepelin also suggested other possible etiologies, including "infections in the years of development" (Kraepelin, 1971).

By the 1960s genetic theories of schizophrenia were listed in textbooks alongside psychoanalytic and family interaction theories, and it was noted that "the relative importance of genetic factors still is far from clear" (Redlich and Freedman, 1966). However, by the end of the 20th century genetic theories had become predominant. It was said that schizophrenia "is an undoubtedly genetic disorder" with "heritability estimates of approximately 80%–85%" (Pearlson and Folley, 2008; Cardno and Gottesman, 2000). Some geneticists even suggested "a strong possibility that most or all of the remaining small proportion of variance can be explained by non-transmissible changes in gene structure or expression" (McGuffin et al., 1994). In other words, schizophrenia might be 100% genetic with environmental factors playing little or no role.

Given these assumptions, the expectations of researchers were very high when the Human Genome Project was declared complete in 2003. Those studying schizophrenia, like many other diseases, expected that major genes causing the disease would be identified, thereby leading to neurochemical pathways that could be targeted with new drugs. There was also hope that the genetic studies would allow for the identification of predisposed individuals prior to the onset of symptoms; provide an objective test for a definitive diagnosis; and provide treatment guidelines for those so diagnosed. To date the genetic studies have not accomplished any of these goals.

Researchers started by looking at nearly 800 candidate genes identified as possible genes of major effect. Despite the expense of approximately $250 million on this research (Sullivan 2017) and a large number of studies relating to supposedly plausible targets such as catechol 0 methyl transferase (COMT) and disrupted in schizophrenia-1 (Disc-1), the result has been that "few clear results have emerged from these studies, with many studies reporting contradictory results for the same candidate gene polymorphisms." When the most promising sets of 25 and 86 candidate genes were closely examined, the researchers "found little evidence that common SNPs within these genes are any more relevant to schizophrenia than SNPs within control sets of non-candidate genes" (Johnson et al., 2017). Geneticist Patrick Sullivan suggested that "we abandon candidate gene guesswork…as they have only provided false direction and wasted effort" (Sullivan, 2017).

Researchers turned next to genome-wide association studies (GWAS) to look for common variants of DNA that might contribute to

* Corresponding author.
E-mail address: torreyf@stanleyresearch.org (E.F. Torrey).

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the risk for schizophrenia. Despite having samples from over 170,000 subjects in the Psychiatric Genomics Consortium and research support from NIMH of over $100 million per year, the results have been very modest. Common variants that may represent risk genes have been found everywhere; one recent study estimated their number at 1551 (Nguyen et al., 2017) and another study concluded that the common variants are so common "that increasingly powered complex trait GWAS will ultimately implicate the entire genome, becoming uninformative" (Loh et al., 2015). Similarly Weinberger recently noted that "the significant SNPs in the PGC2 [second Psychiatric Genomics Consortium] study explain only a few percent of heritability…The reasons for this apparent 'missing heritability' are unclear and the subject of considerable debate" (Weinberger, 2019). When the most important SNPs are combined to form a polygenetic risk score, the score does not correlate with individual genes or sets of genes any more than by chance (Curtis, 2018a). In addition, variation in the genetic findings geographically and ethnically make it difficult to use such findings diagnostically, and most of the genetic findings have no known biological relevance. The situation has been made even more complex by the finding that many of the schizophrenia-risk genes have also been found in bipolar disorder, major depressive disorder, and attention deficit hyperactivity disorder (ADHD), suggesting that they are not specific for schizophrenia but are shared among disorders with different phenotypes (Anttila et al., 2018). While it is likely that still larger sample sizes will increase the number of significant associations, methods of analysis linking a large number of genes to an increased understanding of schizophrenia or the development of new interventions remain elusive.

So what is the current state of genetic research on schizophrenia? According to one recent analysis, "the current trend in psychiatric genetics is to use enormous samples to find genes of minuscule effects" (Leo, 2016). A schizophrenia geneticist, noting the "relatively sparse findings of GWAS-based associations," noted that "among scientists in the field, there is a sense of disappointment in the air" (Gershon et al., 2011). And a science journalist, under the heading "Hoopla, and Disappointment, in Schizophrenia Research," likened the genetic results to a "Pearl Harbor of schizophrenia research" (Wade, 2009). The large number of targets and the small effect sizes has made culling biological insights from GWAS studies difficult. While it is comforting that the GWAS identified polymorphisms in the region of the dopamine D2 receptor as one of the many genomic regions associated with increased risk, detailed analysis indicated that genetic variation within dopamine genes makes only a small contribution to the role of dopamine in schizophrenia (Edwards et al., 2016). Similarly, while the finding of genes encoding components of the complement system has received a great deal of attention, this finding also builds on previous studies which identified the complement system as an important source of gene-environmental interactions affecting brain development (Nimgaonkar et al., 2017). Also, the polygene score, representing a summation of multiple polymorphisms of small effect, has been used for a number of studies relating to the genetic schizophrenia risk. However recent studies have indicated a substantial variation in the schizophrenia polygene score across populations leading to questions concerning its interpretation (Curtis, 2018b).

Given the disconnect between our assumptions and the results of the research, it would seem a propitious time to step back and review how we got to this point.

2. Twin studies and heritability

Genetic theories of schizophrenia rest on family studies, adoption studies, and especially on twin studies. Most calculations of heritability for schizophrenia have been derived from the difference in concordance rates between dizygotic (DZ) and monozygotic (MZ) twins (Gejman et al., 2010). It is therefore important to understand the twin studies in order to understand the origin of the high heritability estimates and consequent widespread assumptions that schizophrenia is primarily a genetic disease.

As early as 1961 David Rosenthal published a classic paper pointing out the limitations of using twin studies to estimate the heritability of schizophrenia (Rosenthal, 1961). Researchers have subsequently confirmed his observations that if the twin pairs are not ascertained from a population-based register; if zygosity is not carefully done; or if the diagnostic criteria are too broad, then the MZ concordance rate will be artificially elevated (Walker et al., 1991). Others have pointed out that twins in general are not representative of the general population since they have more birth injuries, a higher mortality rate and lower birth weights (Eagles, 1994). As twin researchers themselves have noted, twin concordance for schizophrenia "could be concordant equally on the basis of birth injury as on the basis of genetic predisposition" (Reveley and Reveley, 1987).

Another major problem in using twins to estimate heritability is the fact that "the twin method relies on the crucial assumption that common environmental factors in MZ and DZ twins are equal in magnitude" (Tenesa and Haley, 2013). However this is often not the case. In approximately 15% of MZ twins one twin gets more blood than the other (the twin transfusion syndrome) producing an unequal exposure to hormones, drugs, and infectious agents coming from the maternal circulation (Torrey et al., 1994). The twin method also assumes that MZ and DZ twins "share common social environments" when in fact it has been shown that MZ twins spend more time together and also have more similar social networks than DZ twins (Horwitz et al., 2003).

Yet another problem in using twins to estimate heritability is that the twin method assumes the effects of genes and environment are independent and do not interact (Tenesa and Haley, 2013). For many diseases, however, including schizophrenia, it is assumed that such interactions do occur. For example, it is believed that peptic ulcers and stomach cancers are caused by an interaction between gene polymorphisms and *Helicobacter pylori* bacteria.

Most of the twin studies from which schizophrenia heritability estimates have been derived have included some twin pairs from selected samples. There are only six twin studies that have used the most reliable, population-based samples, all based on national twin registers in Scandinavian countries, as shown in Table 1. When combined, they show that the pairwise concordance rate for MZ twins with schizophrenia is 28% (74/268) and for DZ twins is 6% (41/654). In other words, among 268 twin pairs with identical genes, both twins developed schizophrenia only 28% of the time, whereas one twin become affected 72% of the time. The schizophrenia twin studies have also all

Table 1
Twin Studies of schizophrenia using population-based samples.

Author, year, country, years of twin births	Pairwise monozygotic concordance	Pairwise dizygotic concordance
Kringlen, 1967, Norway, 1901–1930	21/55 (38%)	8/90 (9%)
Fischer et al., 1973, Denmark, 1870–1920	10/21 (48%)	8/41 (20%)
Tienari, 1975, Finland, 1870–1928	3/20 (15%)	3/42 (7%)
Onstad et al., 1991, Norway, 1936–1960	8/24 (33%)	1/28 (4%)
Cannon et al., 1998, Finland, 1940–1957	20/67 (30%)	9/86 (5%)
Hilker et al., 2017, Denmark, 1951–2000	12/81 (15%)	12/367 (3%)
Totals	**74/268 (28%)**	**41/654 (6%)**

used the probandwise, rather than pairwise, method of counting concordant twins. The former has been criticized because it involves the double counting of concordant twin pairs if both members of the pair have been ascertained independently (Torrey, 1992) but it has been defended by genetics researchers (McGue, 1992). The probandwise method increases the concordance rate on which the calculation of heritability is based.

To illustrate the problem of using twin studies to estimate the heritability of schizophrenia, consider the most recent study by Hilker et al. (Hilker et al., 2018). Among the MZ twins only 12 out of 81 pairs (15%) became concordant. However, because some of the twin pairs were each ascertained independently, the probandwise concordance rate was reported to be 33% and this figure was used as the starting point for their use of structural equation and liability threshold modeling, as has been used in other schizophrenia twin studies of heritability. The authors acknowledged that such modeling assumes that "twins are comparable to the general population"; that "MZ and DZ pairs share common environmental effects to the same extent"; and that "gene-environmental interactions are minimal," assumptions that are known to be incorrect, as discussed above. The authors then report a schizophrenia heritability figure of 79% from their study. The derivation of 79% heritability from a study in which only 15% of the MZ twins became concordant suggests that something is fundamentally wrong with this modeling. And yet these are the calculations on which the genetic hypotheses of schizophrenia's etiology are primarily based.

Although most calculations of heritability for schizophrenia have been derived from twin studies, a few have been based on family studies. Studies in Sweden and Denmark used national registers to ascertain how often the offspring of individuals with schizophrenia were similarly diagnosed (Lichtenstein et al., 2009; Wray and Gottesman, 2012). These studies then used those data to calculate heritability, reporting it to be 64% in Sweden and 67% in Denmark. Similarly, researchers in Taiwan also used family data obtained from the Taiwan National Health Insurance Database and reported the heritability of schizophrenia to be 47% for genetic factors and 53% for shared and nonshared environmental factors (Chou et al., 2017).

We assume schizophrenia, like almost all human diseases, has some genetic antecedents. What we are questioning is whether it is primarily a genetic disease. One possible explanation for the missing heritability problem is that some environmental factors that may be involved in the etiology of schizophrenia have characteristics that appear to be, but are not truly, genetic in origin thus giving schizophrenia a pseudo-genetic appearance. We will illustrate this using two examples, an infectious agent and the microbiome.

2.1. An infectious agent

Toxoplasma gondii is one example of how this might work and is also an infectious agent that has been linked to schizophrenia (Yolken and Torrey, 2015) *T. gondii*, which causes toxoplasmosis, is a widespread parasite for which cats and other feline species are definitive hosts. When a cat initially becomes infected it excretes in its feces up to 50 million *T. gondii* oocysts per day for an average of eight days. The oocysts are remarkably hearty, remaining infective in loose soil for more than a year and in fresh water for more than four years. It is not known how many oocysts are required to infect a human but for pigs, which weigh about the same as humans, a single oocyst is sufficient (Torrey and Yolken, 2013).

Like schizophrenia, toxoplasmosis often clusters in families. Family outbreaks have been documented because of shared food, such as undercooked lamb (Masur et al., 1978) or raw goat's milk (Sacks et al., 1982), contaminated with *T. gondii*. Families may also become infected by sharing a common oocysts-infected water supply (Bowie et al., 1997). Multiple children in a family may become infected by playing in a sandbox or yard contaminated with oocysts from cat feces (Stagno et al., 1980).

Like schizophrenia, toxoplasmosis can also appear to be passed from mothers and fathers to their children. The vertical transmission of *T. gondii* from an infected mother to her fetus is well established, including cases in which the mother became infected up to five months prior to conception (Vogel et al., 1996). Multiple episodes of transmission during successive pregnancies have also been documented in humans (Garcia, 1968) and other animals (Morley et al., 2008). In mice it has been shown that vertical transmission from an infected female can occur continuously for up to ten generations, giving the strong appearance of being a genetic disease (Beverley, 1959; Dubey 2009). Transmission of *T. gondii* from males to pregnant females and then to the fetus has been shown to occur in dogs (Arantes et al., 2009) and sheep (Lopes et al., 2013), since *T. gondii* oocysts have occasionally been found in the seminal fluid of men, it seems likely that such transmission also occurs in humans (Disko et al., 1971).

Regarding toxoplasmosis in twins, when the transmission of *T. gondii* takes place *in utero* it has been shown to affect both twins in a MZ pair most, but not all, of the time (19/20) (Peyron et al., 2003). This is consistent with what is known about the transmission of other infectious agents to MZ twins *in utero*; it has been reported that the bacteria that causes syphilis and the HIV-1 virus that causes AIDS can occasionally infect only one twin in an MZ pair (Torrey et al., 1994). When the transmission of the infectious agent takes place in childhood, by contrast, the concordance rates are much lower. No information is available on the twin concordance rates for *T. gondii* in childhood, but the concordance rates for polio (Bracha, 1986) and tuberculosis (Torrey, 1992), both of which are thought to have predisposing genes and thus be products of genes and environment, are remarkably similar to the rates for schizophrenia when taken from population-based studies, as shown in Table 2.

An association between schizophrenia and *Toxoplasma* exposure is supported by several meta-analyses indicating odds ratios ranging from 1.8- 2.7 (Sutterland et al., 2015; Torrey et al., 2012), levels which are substantially higher than that of any common variant from GWAS studies. In the United States, increased rates of *Toxoplasma* exposure was particularly associated with recent onset psychosis rather than established schizophrenia (Yolken et al., 2017), a fact probably related to anti-protozoan effects of some of the medications used to treat schizophrenia (Jones Brando et al., 2003). Furthermore, a prospective cohort study from Denmark documented that an increased rate of *Toxoplasma* seropositivity can be detected prior to the onset of psychiatric symptoms, indicating that the increased rate of *Toxoplasma* exposure cannot be ascribed to hospitalization of other artefactual associations (Burgdorfer et al., 2019).

Thus if an infectious agent such as *T. gondii* causes some cases of schizophrenia, the clinical picture could appear to be similar to a largely genetic disease. This would not mean that genes play no role in schizophrenia's etiology. In fact, it has been known for many years that genes within the major histocompatibility complex (MHC) influence resistance and susceptibility to *T. gondii* (Blackwell et al., 1993). For example, the HLA-DQ3 gene is a susceptibility gene for the development of *T. gondii* infection in the brain; similarly, the HLA-DQ1 gene is known to be a resistance gene for such infections (Suzuki, 2002). The HLA genes are part of the MHC that has been the strongest genetic finding in schizophrenia GWAS research (Corvin and Morris, 2014). Other genes such as NALP1 and ALOX12 have also been shown to play roles in congenital *T. gondii* infection (Witola et al., 2011; 2014).

Table 2
Pairwise concordance rates.

	MZ	DZ
Poliomyelitis	36%	6%
Tuberculosis	31%	15%
Schizophrenia	28%	6%

Furthermore, a recent study documented a substantial overlap in genetic polymorphisms associated with *Toxoplasma* seropositivity and those associated with risk of schizophrenia (Wang et al., 2019). In the final picture, therefore, schizophrenia could be a disease in which environmental factors, infectious or otherwise, play the major etiological role but with genes determining susceptibility to the environmental factors. Heritability could thus be in the range of 30 percent rather than 80 percent.

2.2. The microbiome

Another microbial source of a pseudogenetic association in schizophrenia involves the microbial composition of mucosal sites, generally characterized as the microbiome. The microbiome is largely inherited from the mother during and after the birth process although fathers and other members of the family also contribute to its overall composition (Korpela et al., 2018) during the first years of life. Diet and other family based environmental exposures also contribute to the composition of the microbiome during childhood and later life. Twin studies suggest some genetic component to the microbiome based, presumably, on genetic determinants of the immune system and microbial receptors (Goodrich et al., 2016). However the strong household-based environmental contributors to the composition of the microbiome indicate that most apparent familial association are environmental rather than genetic in nature (Rothschild et al., 2018).

The composition of the microbiome has been shown to affect behavior and cognition in both humans and experimental animals through a series of interactions characterized as the gut-brain-immune axis (Severance et al., 2018; Dickerson et al., 2017). In the case of schizophrenia, studies have found substantial alterations in the composition of the gastrointestinal (Nguyen et al., 2018) and oropharyngeal (Yolken et al., 2015) microbiomes in individuals with schizophrenia as compared to controls. Furthermore, exposure to antibiotics early in life has been shown to be associated with increased risk of schizophrenia and other psychiatric disorders in later life, presumably through alterations in the composition of the microbiome (Kohler-Forsberg et al., 2018). It is also of interest that many antipsychotics and other medications which are used to treat schizophrenia can alter the composition of the microbiome (Maier et al., 2018) suggesting that the alteration in the microbiome might contribute to their mode of action, perhaps through alterations in serotonin and other neuroactive molecules present in the gastrointestinal tract (Dinan and Cryan, 2017). However the fact that the microbiome is altered in recent onset psychosis in individuals who had received minimal treatment (Schwartz et al., 2018) suggests that an altered microbiome may be an contributing factor to the development of schizophrenia in some individuals. The possibility of preventing and treating schizophrenia through alterations of the microbiome and the gut-brain-immune axis remains an exciting possibility for future development (Severance and Yolken, 2018; Severance et al., 2018).

3. Discussion

If in fact we have overestimated the genetic etiology of schizophrenia, that would explain the consistent failure by geneticists to find any common genes of large effect. It would also explain the genetic paradox of the persistence of schizophrenia despite the very low fertility rate of those affected. From the early nineteenth until the mid-twentieth century we confined most individuals with schizophrenia in hospitals with a consequent very low rate of reproduction. Even since then the fertility rate of people with the disease is one-quarter to one-third that of the general population (Kendler et al., 1993; Hauka et al., 2003). Furthermore, studies have disproven the alternate explanation that individuals who carry risk alleles but are unaffected have some reproductive advantage (Escott-Price et al., 2019). If schizophrenia is truly a genetic disease one might have expected its prevalence to have decreased significantly. Instead, there are suggestions that its prevalence might have increased during that period (Torrey and Miller, 2002).

The issue of schizophrenia's genetic antecedents also has social implications. As noted by Jonathan Leo in his thoughtful essay on “The Search for Schizophrenia Genes,” genetic studies are very costly. “In the debate about how to spend our health care dollars, the general public should be very skeptical about the economics of this research” (Leo, 2016). The funds for research are finite and when NIMH decides to spend $100 million a year on genetics research, other promising research areas, such as inflammation, infectious agents, and the microbiome, do not get adequately funded. Especially important to pursue are more studies of gene-environment interaction since such studies are more likely to be productive than studies of genes or environmental factors individually. It is interesting to speculate how today's schizophrenia genetic research will be regarded in historical retrospect and its role in delaying true advances in finding better treatments for this disease.

Most diseases that are largely genetic are proving to be difficult to treat. For example, the gene for Huntington's disease gene was discovered in 1993 but has not yet led to a definitive treatment. The progress of gene therapy for other genetic disorders such as hemophilia, sickle cell disease, fragile x syndrome, lysosomal storage diseases, and the most common forms of cystic fibrosis has also been slow despite substantial knowledge relating to the underlying disease processes (Hanna et al., 2016).

A major purpose of all such research, of course, is to develop better treatments for schizophrenia. Insofar as environmental factors are dominant, the development of treatment or even prevention would appear to be more promising but that remains to be proven. Environmental factors may be extremely complex and heterogeneous. For example, in the examples cited the results of infection with *Toxoplasma gondii* vary widely depending on the strain of the parasite and timing of the infection. Similarly, complexities of the human microbiome are just beginning to be understood and reliable methods for microbiome manipulation are in early stages. Nevertheless, the promise of progress from funding more gene-environmental studies is real and deserves a trial.

Competing interests

None

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