

'SCHIZOPHRENIA' AND HEREDITY

Why the emperor (still) has no genes

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The consensus position in psychiatry during the past few decades has been that schizophrenia is caused by an inherited genetic predisposition in combination with environmental events or triggers. This is known as the 'predisposition-stress' or 'diathesis-stress' theory. The most frequently cited evidence in support of the genetic portion of this theory comes from family, twin, and adoption studies, and has compelled researchers to search for predisposing genes at the molecular level. However, the 40-year search for 'schizophrenia genes' has failed to bear fruit (Akil *et al.* 2010; Collins *et al.* 2012; Gilmore 2010; Turkheimer 2011). In this brief review we will see that the available evidence provides little if any support for a genetic basis or predisposition for schizophrenia, which suggests that the ongoing inability to identify genes is the result of psychiatry's failure to critically reexamine the research upon which genetic theories are based.

FAMILY STUDIES

Psychiatric genetic family studies identify people diagnosed with a given disorder, and then determine whether their biological relatives are diagnosed with the disorder more often than are members of the general population or a control group. If a disorder is found to cluster or 'run' in families, the disorder is familial. This is seen in schizophrenia family studies, where, in the more methodologically sound studies, the first-degree biological relatives of people diagnosed with schizophrenia are diagnosed with the same disorder roughly four times more often than the 1% rate in the general population (although some studies have found no significant elevation; Joseph 2006).

The key point here is, to the neutral observer, obvious: 'Familial' is not the same as 'genetic'. Although the familiarity of schizophrenia was once seen as

conclusive proof of its genetic basis, most investigators now realize that disorders and behavioral traits can run in families for non-genetic reasons such as exposure to common rearing patterns and other aspects of the physical and social environment. As behavioral geneticist Robert Plomin and his colleagues point out, 'Many behaviors "run in families," but family resemblance can be due to either nature or nurture' (Plomin *et al.* 2008: 70). They concluded, 'Family studies by themselves cannot disentangle genetic and environmental influences' (p. 151).

Therefore, although some authors continue to mistakenly interpret family data in support of genetic transmission (e.g. Gilmore 2010), psychiatric genetic and behavioral genetic researchers have turned to twin and adoption studies, which, they believe, are able to disentangle potential genetic and environmental factors.

TWIN STUDIES

The logic of schizophrenia twin studies, which use a technique called the 'twin method,' seems straightforward: If reared-together MZ (monozygotic, identical) twin pairs, who share 100% of the same genes, resemble each other more for schizophrenia than do reared-together same-sex DZ twin pairs (dizygotic, fraternal), who share on average only 50% of the same genes, the genetic position is confirmed. (When both members of a twin pair are diagnosed with schizophrenia, the pair is said to be *concordant* for the condition; when one twin is diagnosed but the other is not, they are *discordant* for schizophrenia.) However, we will see that genetic interpretations of twin method data are based on the acceptance of an implausible theoretical assumption.

As seen in Table 7.1, the pooled pairwise concordance rates for schizophrenia are MZ 39.9%, and DZ 7.5%. Reviewers sometimes divide these investigations into the 'classical' studies published before 1962, and the more methodologically sound 'contemporary' studies published after this date (Gottesman 1991). The older, more methodologically suspect classical studies, which used non-blinded, poorly defined diagnoses and potentially biased resident hospital samples (e.g., Kallmann 1946; Rosanoff *et al.* 1934; Slater 1953), reported higher rates than the more recent studies based on registers or consecutive hospital admissions. We see in Table 7.1 that the rounded pooled pairwise concordance rates in the contemporary studies are MZ = 23%, and DZ = 5%. Moreover, MZ concordance is 18% or less in three contemporary studies, which include two studies with large MZ samples. Thus in the more methodologically sound studies, when one member of an MZ pair is diagnosed with schizophrenia, nearly 80% of the time his or her genetically identical co-twin is *not* diagnosed.

The equal environment assumption: the Achilles' heel of the twin method

There are several important methodological problems found in schizophrenia twin research. These include:

- the lack of an adequate and consistent definition of schizophrenia;
- the questionable reliability and validity of schizophrenia (Chapters 5 and 6);
- the use of non-blinded diagnoses, and diagnoses made on the basis of inadequate information;
- the use of unreliable methods of zygosity determination (whether a pair is MZ or DZ);
- the unnecessary, potentially biasing, use of age-correction formulas;
- the use of non-representative or small sample populations;
- the lack of an adequate description of the methods;
- investigator bias in favor of genetic conclusions.

These important problems, explained more fully elsewhere (Joseph 2004, 2006), have undoubtedly inflated concordance rates. Nevertheless, there is little doubt that MZ pairs resemble each other more than do DZ pairs for schizophrenia, and for most other psychiatric disorders and behavioral traits as well. The decisive question, however, is: 'Why?'

The twin method's critical theoretical assumption is that MZ and DZ pairs experience roughly the same childhood and adult environments. However, this 'equal environment assumption' (EEA) is not supported by the evidence, since MZs clearly experience much more similar environments than DZs (Joseph 2004; 2006; Kringlen 1967). Because it is widely understood that MZ pairs are treated more similarly, encounter more similar environments, and experience a greater level of 'identity confusion' (Jackson 1960) than DZ pairs, some critics have argued that MZ-DZ comparisons measure nothing more than the *environmental* differences distinguishing the two types of twin pairs.

Although most twin researchers now recognize that MZ pairs experience more similar environments than DZ pairs (e.g., Bouchard and McGue 2003; Kendler 1983), they continue to uphold the validity of the twin method and the equal environment assumption on the basis of two main arguments. The first is that, although MZ and DZ twin pair environments are different, these environments must differ on 'trait-relevant' factors that have been shown to have a causal influence on the disorder in question (e.g. Bouchard and McGue 2003). However, twin researchers do not make this 'trait relevant' argument when addressing potential environmental confounds in *family* studies. In this case they correctly recognize that, because family members share a common environment ('trait-relevant' or not), one cannot draw valid conclusions in

Table 7.1 Results of schizophrenia twin studies

Researcher(s)	Year	Country	Pairwise concordance rates					
			MZ pairs		Same-sex DZ pairs		C	
			N	%	N	%	N	%
Classical Studies								
Luxemburger ^a	1928	Germany	17	10.59	13	0	0	0
Rosanoff <i>et al.</i>	1934	USA	41	25.61	53	7.13	7	13
Essen-Möller ^b	1941,	Sweden	7	2.29	24	2	8	8
	1970							
Kallmann	1946	USA	174	120.69	296	34	11	11
Slater	1953	UK	41	28.68	61	11	18	18
Inouye	1961	Japan	55	20.36	17	1	6	6
Contemporary Studies								
Tienari	1963,	Finland	20	3.15	42	3	7	7
	1975							
Gottesman and Shields	1966b	UK	24	10.42	33	3	9	9
Kringlen ^c	1967	Norway	45	12.27	69	3	4	4
NAS-NRC ^d	1970,	USA	164	30.18	268	9	3	3
	1983							
Fischer	1973	Denmark	25	9.36	45	8	18	18
Koskenvuo <i>et al.</i> ^e	1984	Finland	73	8.11	225	4	2	2
Onstad <i>et al.</i>	1991	Norway	24	8.33	28	1	4	4
Franzek and Beckmann	1998	Germany	9	6.67	12	2	17	17
Cannon <i>et al.</i> ^f	1998	Finland	—	—	—	—	—	—
Cardno <i>et al.</i> ^g	1999	UK	42	13.31	56	5	4	4
Pooled rates			761	304.39.9	1,242	93	7.5	7.5
'Classical'			335	205.61.2	464	55	11.9	11.9
'Contemporary'			426	99.23.2	778	38	4.9	4.9

Notes
 N = Number of twin pairs; C = Number of concordant twin pairs. Concordance rates based on the researchers' 'strict' definition of schizophrenia; age correction factors not included. Unless otherwise noted, when two dates are stated, the first indicates the year results were first published, the second indicates the final publication, whose figures are reported in the table.

^a Reported by Gottesman and Shields 1966a.

^b MZ figures from Essen-Möller 1970. DZ concordance rate based on (1941) definite cases among co-twins, as reported by Gottesman and Shields 1966a: 28.

^c Based on a strict diagnosis of schizophrenia; hospitalized and registered cases.

^d National Academy of Sciences-National Research Council. Original report by Hoffer and Pollin 1970; final report by Kendler and Robinette 1983.

^e The Koskenvuo *et al.* study is rarely mentioned in textbooks or reviews.

^f Cannon *et al.* 1998 reported probandwise concordance rates of MZ = 46% and DZ = 9%. The pairwise equivalents are not listed because Cannon *et al.* did not give the number of pairs in each group.

^g Pairwise data supplied by A. Cardno (personal communication, 19 March 2010).

favor of genetics on the basis of finding a family resemblance for behavioral traits. Many critics have argued that a similar evaluation holds true for the twin method as well.

The second argument contemporary twin researchers make in defense of the EEA is that, although it is true that MZ environments are more similar than DZ environments, MZ pairs 'create' or 'elicit' more similar environments for themselves by virtue of their greater genetically caused similarity of behavior (e.g. Kendler 1983; see also Joseph 2012). Twin researchers fail, however, to understand that the *reason* MZ pairs experience more similar environments than DZ pairs is irrelevant in assessing the validity of the EEA. The only relevant question is whether – not why – MZ environments are more similar (Joseph 2004, 2010a).

Moreover, this 'twins create their own environment' argument rests on the logical fallacy of circular reasoning, as twin researchers simultaneously and circularly *assume and conclude* that MZ pairs' greater behavioral resemblance is caused by their greater genetic similarity. In the process, modern twin researchers must assume the validity of genetic interpretations of previous twin studies in order to validate subsequent twin studies (Joseph 2010a, 2012).

Finally, the circular 'twins create their own environment' argument renders the 'trait-relevant' argument irrelevant because, even if critics demonstrate that MZs experience more similar trait-relevant environments than DZs, twin researchers could still argue in favor of the twin method's validity on the basis of MZ pairs having 'created' more similar 'trait-relevant' environments for themselves. (For an example of psychiatric genetic twin researchers making this argument, see True *et al.* 1993.)

Thus, there are two main conclusions that one can reach on the basis of schizophrenia twin method data (Joseph 2010b):

- 1 *Twin researchers' and contemporary psychiatry's conclusion, based on the acceptance of the equal environment assumption:* The greater resemblance of MZ vs. same-sex DZ twin pairs provides solid evidence that a sizable portion of the schizophrenia population variance can be explained by genetic factors, or
- 2 *Twin method critics' conclusion, based on the rejection of the equal environment assumption:* The twin method is a faulty instrument for assessing the role of genetics, given the likelihood that MZ vs. same-sex DZ comparisons measure environmental rather than genetic influences. Therefore, it is likely that previous interpretations of the twin method's results in support of genetics are wrong.

I argue here, and in detail elsewhere (Joseph 2004, 2006, 2010a), that the evidence supports the acceptance of Conclusion #2. Therefore, we can assume that the equal environment assumption (EEA) is false, and that the results of

schizophrenia twin studies can be completely explained on the basis of methodological problems and the more similar treatment, socialization resemblance, environment, and emotional bond experienced by MZ vs. DZ twin pairs. Like schizophrenia family studies, schizophrenia twin studies cannot disentangle the potential impact of genetic and environmental influences, and all previous interpretations of these studies in favor of genetics should be rejected outright.

Thus, it is likely that twin studies of psychosis have revealed little more than MZ pairs' more similar environments, and their greater propensity to experience *folie à deux* (shared psychotic disorder) than DZ pairs (Jackson 1960). As schizophrenia genetic researcher David Rosenthal (1970: 247) concluded, due to MZ pairs' greater 'identificatory bond', the 'difference in concordance rates between the two types of twins could have a psychological explanation.'

Other twin studies

Two other types of schizophrenia twin studies should be mentioned. The first (Fischer 1973; Gottesman and Bertelsen 1989) studied schizophrenia rates among the biological offspring of discordant MZ pairs. Genetic theories predict that we would find comparable schizophrenia rates among the offspring of the diagnosed twins, versus the offspring of their non-diagnosed co-twins. However, these studies are greatly flawed, and no valid conclusions about genetic factors can be drawn from them (Joseph 2004; Torrey 1990). Although no systematic reared-apart twin study of schizophrenia has ever been published, there have been a handful of single-case reports of purportedly 'reared-apart' MZ pairs concordant or discordant for schizophrenia. In Farber's (1981) review of these cases, she concluded that only nine MZ pairs qualified as having been truly reared apart. However, even in these cases the twins were aware of each other's existence and had periodic contact. Regardless of how many individual reared-apart MZ pairs are reported as being concordant for schizophrenia, however, they do not constitute scientific evidence in favor of genetics because, among other reasons, they were not ascertained in a systematic study.

ADOPTION STUDIES

Most schizophrenia researchers believe that adoption studies are able to make a clean separation between genetic and environmental influences, since adoptees inherit the genes of their biological (birth) parents but are reared in the environment of another (adoptive) family with whom they share no genetic relationship. Although adoption studies appear at first glance to be free from the environmental confounds plaguing family and twin studies and have

therefore played a crucial role in creating the perception that schizophrenia is a genetic disorder, a closer look at these studies reveals several invalidating flaws and biases.

In all six adoption studies of schizophrenia, the researchers compared the diagnostic rate of their index (experimental) group relatives or adoptees, versus the diagnostic rate of control group relatives or adoptees.

- 1 Heston (1966) assessed the rate of schizophrenia among 47 adopted-away biological offspring of women diagnosed with schizophrenia who were confined to Oregon state mental hospitals.
- 2 Rosenthal and colleagues (1968, 1971) studied the adopted-away biological offspring of Danish parents diagnosed with schizophrenia, 'schizophrenia spectrum disorders', or manic depression.
- 3 Kety and colleagues (1968) began with the records of Danish adoptees from the greater Copenhagen area, identified those diagnosed with a 'schizophrenia spectrum disorder,' and recorded diagnoses among their adoptive and biological relatives. In a follow-up (Kety *et al.* 1975), the investigators interviewed and re-diagnosed many of the 1968 relatives. The study was then extended to the rest of Denmark, and the final results were published in 1994 (Kety *et al.* 1994).
- 4 The 'crossfostering' investigation by Wender and colleagues (1974) studied the adopted-away biological offspring of Danish parents not diagnosed with schizophrenia, but who were raised by an adoptive parent eventually diagnosed with schizophrenia.
- 5 In contrast to the earlier investigations, Tienari and colleagues' Finnish study (1987, 2003) took the important (but previously ignored) step of looking at adoptive family environments as well as adoptees' genetic background. Their index group consisted of the adopted-away biological offspring of mothers diagnosed with schizophrenia and 'schizophrenia spectrum disorders.' Tienari and associates concluded that both genetic background *and* adoptive family rearing environment are 'predictor variables' for schizophrenia.
- 6 Lichtenstein and colleagues (2009) used hospital and population records of Swedish parents and children (including some adoptees) to assess whether schizophrenia and bipolar disorder are genetically distinct disorders. Based on these records, they found an elevated schizophrenia risk among the adopted-away biological offspring of parents diagnosed with schizophrenia. However, they did not state how many adoptees were studied.

Methodological problems

In all schizophrenia adoption studies, the investigators concluded that genetic factors play a major role, while Tienari added the important finding that disturbed family environments also play a role. However, these studies have

been the subject of several critical analyses (e.g., Benjamin 1976; Boyle 2002; Jackson 2003; Joseph 2004, 2006; Lidz and Blatt 1983; Lidz *et al.* 1981; Rose *et al.* 1984).

The Danish-American investigations by Kety *et al.* (1968, 1975, 1994), and Rosenthal *et al.* (1968, 1971) are the most frequently cited studies. The most important methodological problems in these studies, elaborated upon by the previously listed critics and others, are outlined below.

- The Danish-American investigators decided to expand the definition of schizophrenia to include non-psychotic 'schizophrenia spectrum disorders,' and they would not have found statistically significant results without such an expansion. The 1968 Kety study found *zero* cases of chronic schizophrenia among the 65 identified first-degree biological relatives of adoptees diagnosed with a schizophrenia spectrum disorder, and Rosenthal *et al.* (1971) found that only one of the 76 adopted-away biological offspring of a parent diagnosed with a schizophrenia spectrum disorder had received a hospital diagnosis of schizophrenia.
- In the Kety *et al.* (1968) study there is evidence suggesting that the researchers decided to change the study's design after the initial relative group comparisons failed to obtain statistically significant results in the genetic direction (Joseph 2004: 220–22).
- The researchers failed to adequately define schizophrenia and 'schizophrenia spectrum disorders.'
- In the Rosenthal *et al.* (1971) study, the researchers counted 'manic-depression' as a 'schizophrenia spectrum disorder' despite their insistence elsewhere that this diagnosis is genetically *un*related to schizophrenia. Without these manic-depressive subjects, Rosenthal would not have been able to claim statistically significant results in the genetic direction (Joseph 2004; Lidz *et al.* 1981).
- In the Kety *et al.* (1968, 1975) studies, there were inconsistencies in the way that the researchers decided to count and diagnose dead or unavailable relatives (Joseph 2004; Rose *et al.* 1984).
- The researchers failed to provide case history information on adoptees or relatives and failed to study important environmental variables.
- In the Kety *et al.* Adoptees' Family study (1975), the 'procedure of counting up all the possible relatives of each index case and pooling them as if they were independent samples . . . would allow some families to disproportionately affect the results' (Benjamin 1976: 1130). Thus, the investigators' decision to emphasize the diagnostic rate among individual *relatives*, as opposed to individual *families*, violated the assumptions of independent observations underlying the statistical comparisons they used.
- In the Kety *et al.* studies (1968, 1975, 1994), the researchers counted first-degree biological relatives (e.g. siblings) and second-degree biological relatives (e.g. half-siblings) with equal weighting.

- The researchers decided to include many late-separated and late-placed adoptees in their samples. Therefore, during sensitive developmental periods, these adoptees (a) were reared for a certain period of time by their biological parent(s), (b) suffered a disruption of attachment bonds with their biological parent(s), and/or (c) were placed in unstable environments between separation and adoption.
- The investigators used standard interviews to make diagnoses. In the Kety *et al.* (1975) study, many of these 'interviews' never took place, but instead were fabricated by the investigators on the basis of hospital records (Kendler and Gruenberg 1984; Rose *et al.* 1984). In the raw data Kety called them 'pseudointerviews,' but no mention of their existence appeared in any Danish-American publication.

Table 7.2 summarizes the presence or absence of important methodological problems in all schizophrenia adoption studies published to date.

Selective placement: the Achilles' heel of adoption studies

A critical component of psychiatric adoption research is the 'no selective placement assumption,' which requires investigators to assume that factors relating to the adoption process (including the policies of adoption agencies) did not lead certain groups of adoptees to be placed into environments contributing to a higher rate of the disorder in question. The investigators must assume that children were not systematically placed into adoptive homes correlated with the socioeconomic status – or presumed genetic status – of their biological family. In many psychiatric adoption studies, however, the evidence suggests that index adoptees did experience more psychologically harmful rearing environments than those experienced by control adoptees (Joseph 2004, 2006; Rose *et al.* 1984). This suggests that adoptees with a biological family history of mental disorders were seen as inferior potential adoptees and therefore were placed into more chaotic and harmful (and potentially 'schizophrenogenic') adoptive families.

Most adoptees were placed in the early- to middle part of the twentieth century in Denmark, the United States (Oregon), and Finland. The Swedish study index relatives were born between 1932 and 2002. All four regions had laws permitting the compulsory eugenic sterilization of people labeled 'schizophrenic,' 'insane,' 'feeble-minded,' and so on. Society and scientists alike viewed as axiomatic that the offspring of 'insane' people were the undesirable carriers of 'hereditary taint.'

Denmark

In 1929 Denmark became the first European nation to pass a eugenics-inspired sterilization law (Hansen 1996). This law was in force until well after the last

Table 7.2 Important methodological problems in schizophrenia adoption research

Researchers	Year	Country	Significant chronic Schiz first-degree Bio relative rate family rate vs. controls? vs. controls?	Significant chronic Schiz first-degree Bio relative rate family rate vs. controls? vs. controls?	Used late separated adoptees?	Probable selective placement blindly?	Adequate definition of Schiz?	Controlled Schiz as adoptive environments?	Adequate case history information to make diagnoses? relatives equally?	Used fabricated first- and second-interviews?	Counted
Heston	1966	USA (Oregon)	Yes	Yes	No	Yes	No ^b	No	No	No	N/A
Kety <i>et al.</i>	1968	Denmark	No	N/A	Yes	Yes	No	Yes	No	N/A	Yes
Kety <i>et al.</i>	1975	Denmark	No	N/A	Yes	Yes	No	Yes	No	Yes ^d	Yes
Kety <i>et al.</i>	1994	Denmark	Yes	No	N/A	Yes	No	Yes	No	?	Yes
Rosenthal <i>et al.</i>	1968	Denmark	No	N/A	Yes	Yes	No	Yes	No	N/A	Yes
Rosenthal <i>et al.</i>	1971	Denmark	No	N/A	Yes	Yes	No	Yes	No	N/A	Yes
Wender <i>et al.</i>	1974	Denmark	No	N/A	Yes	Yes	No	Yes	No	N/A	N/A
Tienari <i>et al.</i>	1987	Finland	No	N/A	Yes	Yes	No	Yes	No	N/A	N/A
Lichtenstein <i>et al.</i>	2003	Sweden	Not stated	Not stated	N/A	Not stated	Yes	No	No	No	No

Notes: Schiz = Schizophrenia; Bio = Biological; SSD = Schizophrenia spectrum disorders (as the researchers defined them); N/A = Not applicable.
^a Using the traditional one-tailed .05 level of statistical significance. Based on a comparison between either (a) the first-degree biological relatives of chronic schizophrenia index adoptees vs. the first-degree biological relatives of control adoptees (Kety); (b) the chronic schizophrenia rate among the adopted-away biological offspring of people diagnosed with chronic schizophrenia vs. the biological offspring of controls (Heston, Rosenthal, Tienari, Lichtenstein); or (c) the chronic schizophrenia rate of cross-fostered adoptees vs. controls (Wender).
^b Although two of the three raters made diagnoses while unaware of the adoptees' group status, the third rater, Heston, was not blind to their status.
^c Used DSM-III-R criteria (APA 1987).
^d See Rose *et al.* 1984, and Kendler and Gruenberg 1984.
 *Lichtenstein *et al.* 2009 obtained diagnoses from hospital records. As they acknowledged (p. 238), 'diagnostic bias could have happened if diagnostic assessments by physicians were influenced by knowledge of family psychiatric history.'
 *Used *International Classification of Diseases* (ICD 8, 9, 10) criteria (WHO 1967, 1978, 1992).

studied Danish adoptees were placed (placements were made between 1924 and 1947). The Danish adoption agencies checked potential adoptees' perceived genetic family backgrounds to determine their suitability (or desirability) for adoption (Mednick and Hurchings 1977). Clearly, the most qualified potential adoptive parents, who were usually informed of 'deviance' in the adoptee's family background, would not have selected children with a biological family history of mental disorders.

Oregon

Similar conditions existed in Oregon (Joseph 2004), where adoptees were placed between 1915 and 1945. Although Heston failed to mention it, Oregon passed a law in 1917 creating a 'State Board of Eugenics,' whose duty was to authorize the compulsory sterilization of 'all feeble-minded, insane, epileptic, habitual criminals, moral degenerates and sexual perverts,' because they might produce 'inferior' offspring (Olson 1920: 1487).

An additional Oregon law passed in 1919 stipulated that, if a person had been admitted to a mental hospital, this constituted 'prima facie evidence that procreation by any such person would produce children with an inherited tendency to feeble-mindedness, insanity, epilepsy, criminality or degeneracy' (Olson 1920: 3176). Because Heston's index adoptees were born to women hospitalized with schizophrenia, it is unlikely that these 'inferior' children were placed into the same types of adoptive homes as the control adoptees.

Finland and Sweden

In 1935 the Finnish parliament passed the Sterilization Act, which allowed the compulsory eugenic sterilization and castration of 'idiots,' 'imbeciles,' and the 'insane,' which included people diagnosed with schizophrenia and manic depression (Hietala 1996). In 1950, Finland passed the Castration Act, which permitted the compulsory castration of criminals, the mentally retarded, and the 'permanently mentally ill.' Compulsory eugenic sterilization was not legally abolished in Finland until 1970. Sweden also had a long history of eugenics and compulsory eugenic sterilization (Broberg and Tydén 1996).

Kety argued (Kety *et al.* 1994) that because his studies began with diagnosed adoptees, as opposed to diagnosed biological parents, they were less vulnerable to selective placement bias. However, in 8 of 33 index *adoptive* (rearing) families, a parent had been admitted to a Danish psychiatric facility, which was not true for any of the 34 control adoptive families (Rose *et al.* 1984). This finding suggests that index adoptees were placed into more psychologically harmful adoptive homes than the control adoptees. Thus, the higher rate of schizophrenia spectrum diagnoses among index versus control biological relatives

might reflect little more than the agencies' placement of children with 'hereditarily tainted' biological relatives into these types of adoptive homes.

It appears that a violation of the crucial 'no selective placement assumption' has introduced a major environmental confound into all schizophrenia adoption studies. Thus, like family and twin studies, the results of these studies are explainable on nongenetic grounds. When we consider these studies' other glaring methodological problems (Table 7.2), they clearly fail to provide scientifically acceptable evidence in favor of genetics.

THE FRUITLESS SEARCH FOR SCHIZOPHRENIA GENES

Based on the widespread yet mistaken belief that family, twin, and adoption studies have established schizophrenia as a genetically based disorder, psychiatric molecular genetic researchers have attempted to identify genes for schizophrenia. However, although gene-finding attempts go back to the 1970s (Elston *et al.* 1973) and earlier, to date they have been unable to do so (Collins *et al.* 2012; Gilmore 2010; Joseph and Ratner 2013; Plomin 2013; Turkheimer 2011). As the Nobel-Prize-winning coauthors of a 'Policy Forum' article published in *Science* recognized, there has been a 'frustrating lack of progress' in understanding the genetics of mental disorders (Akil *et al.* 2010: 1580).

Still, despite the publication of over 1,700 schizophrenia molecular genetic studies (www.szgene.org/), the search continues on the basis of researchers' belief that it is beyond question that schizophrenia is a 'highly heritable' disorder. Researchers long ago abandoned the search for a major causative single gene and now view schizophrenia and other psychiatric conditions as 'multifactorial complex disorders,' which refers to a condition being caused by a complex interaction of multiple genes and multiple environmental risk factors. It is important to note, however, that the failure to discover genes is currently a *defining feature* of 'multifactorial complex disorders' in psychiatry (Joseph 2006, 2012).

Until the mid-2000s, the most common methods in molecular genetic research were linkage studies and association studies. These methods did not yield any genetic variants that were shown by replication studies to cause schizophrenia. Since 2005, researchers have pinned their hopes on genome-wide associations studies (GWAS), which Plomin and colleagues (2009: 873) defined as 'A hypothesis-free genetic method that uses hundreds of thousands of DNA markers distributed throughout the chromosomes to identify alleles that are correlated with a trait.' We must keep in mind, however, that *association* (correlation) is not the same thing as *cause*.

Although genome-wide association studies remain the current focus of attention, a seemingly more potentially fruitful research avenue concerns *epigenetics*, which refers to the effect of environmental factors on gene expression (Petronis 2004; Read *et al.* 2009).

Many authors of the 1,700+ studies published over the past 40 years claimed to have found a marker for a schizophrenia gene, with the various claims encompassing most of the 23 pairs of chromosomes. However, subsequent attempts failed to replicate the original findings. In a highly publicized case, Sherrington and colleagues believed they had identified a genetic marker for schizophrenia in their (1988) *Nature* publication, but this result was not replicated. Clearly, psychiatric molecular genetic research is massively plagued by false positive results, and systematic error appears to have been repeated year after year and decade after decade (Ioannidis 2005). In this context, leading psychiatric genetic researchers have publically asked funding sources not to 'give up' on schizophrenia GWAS research (Sullivan *et al.* 2012).

Nevertheless, because some researchers claim that schizophrenia genes have already been found (e.g., Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Kim *et al.* 2011), accompanied by sensationalized media accounts, it is still widely believed that gene variants or genetic markers for schizophrenia and other psychiatric disorders have been found. In fact, the past 40 years has been characterized by the stunning and unexpected *failure* to discover genes for these disorders (Joseph 2012). Attempts to identify genes presumed to underlie personality traits and IQ (general intelligence) have also failed (Joseph 2011; Plomin 2012; Wahlsten 2012).

In 2008, leading genetic researchers developed the 'missing heritability' position to explain the lack of gene findings for psychiatric disorders and common medical conditions (Gershon *et al.* 2011; Manolio *et al.* 2009; Plomin 2013; Turkheimer 2011). Regarding schizophrenia, proponents of this position argue that schizophrenia genes are 'missing' because researchers must find better ways to uncover them, as opposed to the critics' contention that these genes probably do not exist (see Joseph 2006, 2012; Larham and Wilson 2010).

A 2012 study (Collins *et al.* 2012) co-authored by many of the world's leading schizophrenia molecular genetic researchers taking part in the International Schizophrenia Consortium (ISC; <http://pngu.mgh.harvard.edu/isc>) compared the results of 732 previously identified 'hypothesis-driven candidate genes' for schizophrenia with genome-wide association study results from the ISC. The investigators found 'no notable ISC results' for the most studied candidate genes (Collins *et al.* 2012: 607). They concluded that these results 'suggest, but do not prove, that many traditional ideas about the genetic basis of SCZ [schizophrenia] may be incorrect,' and that 'it is possible that the next few years will lead to marked changes in major hypotheses about the genetic basis of SCZ' (p. 614).

In an earlier review of the 'genetics of schizophrenia' question, I concluded: 'Based on the weight of the evidence, it is predicted here that a gene for schizophrenia will not be found, because it does not exist' (Joseph 1999: 137). Some 14 years later, I see no reason to modify this prediction.

Thus, the time has come to institute a moratorium on schizophrenia molecular genetic research and to undertake a thorough reassessment of the original

family, twin, and adoption studies that inspired the fruitless search for genes in the first place. As the authors of an article on the 'facts' of schizophrenia concluded: 'A reconsideration of our basic strategies and fundamental assumptions may be in order' (Tandon *et al.* 2008: 12). Indeed, such a reconsideration is long overdue.

CONCLUSION

The fact that mainstream psychiatry regards the genetic basis of schizophrenia as a proven fact speaks volumes about the discipline's failure to critically analyze the methods and assumptions of its own research. In countless textbooks in psychiatry, psychology, and other behavior sciences, we find the same uncritical acceptance of the conclusions of twin and adoption researchers. Too often, these textbooks provide an inaccurate presentation of the evidence supporting the genetic position, and only a handful attempt some kind of critical analysis (Joseph 2006).

Psychiatry's uncritical acceptance of the conclusions of schizophrenia twin and adoption researchers is an appalling development in the history of scientific research. It can be understood much more by psychiatry's interest in maintaining itself as a viable profession than on the basis of a careful analysis of the original studies. Moreover, genetic theories aid the interests of the social and political elites, and the interests of the psychopharmaceutical industry, to locate the causes of psychological distress within people's bodies and brains, as opposed to their familial, social, and political environments (Read *et al.* 2009, and see Part II of this book). It is not surprising, therefore, that these groups continue to channel research funding in the genetic and biological direction. Focusing attention on genetic research, regardless of the massive flaws, biases, and untenable assumptions contained therein, successfully diverts attention from the social factors that contribute to people exhibiting behaviors given the schizophrenia label.

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