The Naked Emperor Syndrome Revisited: An Evaluation of Schizophrenia Gene Studies Research Methods

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ABSTRACT

Aim: To assess current research method competence into studies about genetic cause of schizophrenia and appraise consequences.

Methods: Literature obtained through Google search, PubMed and PLoS search as well as references from recent publications.

Results: There are currently three approaches to investigating genetic cause of schizophrenia (twin and adoption studies, individual gene studies and genome wide association studies) and all approached were investigated. In all cases research integrity was compromised by irrational beliefs and incompetent research methodology. Researchers adhered to the fashionable prevailing opinion that genes are causative and distorted findings to concur in spite of no genuine evidence of genetic causation regardless of approach, albeit some more recent studies have begun to challenge this assumption. Research methods are badly taught. Much research money has been wasted. Psychiatry as a discipline needs to change paradigms and modernise. Studies about environmental cause are ignored. Studies by geneticists that demonstrate it is not possible for genes to be causative are ignored.

Clinical implications: Unfounded beliefs ensure genuine cause is not being addressed thereby preventing insight and understanding by practitioners, implementing prevention strategies or development of more effective treatment. Many sufferers do not receive appropriate treatment thereby preventing recovery.

Keywords
Research methods, Gene studies, Schizophrenia, Genome wide association studies.

Introduction
The cause of schizophrenia is still highly contested. Opinions are mostly divided into two groups: genes or environment. Saunders [1] published an article exposing research method inadequacies by medical researchers investigating genetic causes of schizophrenia. The aim of this paper is to further evaluate the research methods competence of medical researchers while investigating genetic causes of schizophrenia. That is, the emphasis is on investigating conformity to acceptable standards in methodology, including logic of arguments and consequences of findings.

Methods
Due to vast numbers, it is not possible to evaluate all studies, and hence only the most salient studies are cited and evaluated. Knowledge of these has been achieved through doing Google searches, investigating the PubMed website as well as the PLoS website and using lists of references from more recent studies.

Results
There are now three methods of investigating genetic causes of schizophrenia, the first being twin and adoption studies. There have been many such studies however, only one has been selected for in depth appraisal here as it clearly demonstrates the fallacy underlying all studies and it is that of Göttesman and Shields [2]. These authors investigated concordance rates in monozygotic twin...
pairs, one of each pair who had been hospitalised. MZ twins are chosen as respondents as they share close to 100% of their DNA, so if genes were responsible then both twins from each pair would necessarily have the disorder for all respondents. However, after initial interviews, only 4 out of 24 MZ pairs revealed concordance, that is, a mere 16%, which clearly and irrefutably demonstrated that it was not possible for genes to be responsible.

However, the researchers did not aim to investigate if genes were responsible; they aimed to prove that they were; there was no null hypothesis. This is hardly objective scientific research. They were so sure that genes were responsible that they changed their definition of schizophrenia half way through their study in order to increase the percentages to fit in with their preconceived ideas. They still were only able to produce data that demonstrated that a mere 42% of the monozygotic twin pairs in the study were concordant. The authors could not accept these findings and concluded that there was some genetic influence. In research methodology, this is called a type 1 or false positive error, that is, the null hypothesis is rejected when it should be accepted while the experimental hypothesis is accepted when it should have been rejected.

Reading the statistical evidence of this study should have caused any objective person to realise that it was not possible for genes to be responsible and searched for other explanations regardless of what Göttesman and Shields [2] concluded. There have been many subsequent twin and adoption studies that have further painfully tried to find this elusive gene or genes, rather like searching for the elusive new zoo gnu, the latter search being the more successful [3].

Kringlen [4] states that the pair-wise concordance rates in schizophrenia are 30-40% in MZ and 5-10% in DZ twins but are variable. In short, other studies confirm that there is less than a 50% concordance rate. That is, on replication of studies, similar low findings have been achieved thereby confirming that genes could not possibly be responsible. The fact that there is some concordance may well be explained by research method limitations, including presence of confounding and intervening variables that have not been controlled for. But it should have been realised fifty years ago after the results of these studies were published that genes were not responsible, and looked elsewhere for cause.

Nonetheless Hilker et al. [5] undertook analysis of the Danish twin register and made an estimate that 79% of schizophrenia is heritable. That is not the same as data demonstrating concordance. They did not control for environmental (intervening) variables such as the fact that parents often treat twins the same, and that there can be physiological and developmental differences in twins [6].

In 1962 Watson and Crick won the Nobel Prize for revealing the structure of our DNA. This knowledge of DNA structure paved the way for an analysis of the genes of individuals through the genome project. Since then research into the cause of schizophrenia has continued through an analysis of the genes of those who have been diagnosed with schizophrenia, and genome wide association studies (GWAS) as well as twin studies.

The second method therefore, is investigation of individual families and therefore individual genes. Edinburgh University researchers published several articles hypothesising to have found the genes responsible [7-11]. Millar et al. [12] investigated a Scottish family whose six members had a variety of mental health problems including schizophrenia. Throughout the article yet again is the assumption that genes are somehow responsible due to unquestioning espousal of the opinions of McGuffin et al. [13], also a flawed study as its comments about environment are naïve. Millar et al. undertook a translocation co-segregation investigation, and discovered two unusual features on alleles which they named DISC1 and DISC2. They stated:

‘We propose that alteration of DISC1 and/or DISC2 activity, by truncation and/or by abnormal regulation of expression, is causally linked to the psychiatric illness…’ [12].

There are multiple problems with the structure, arguments and evidence of these researchers. There was no introduction justifying and explaining rationale for the research as well as what the experimental hypothesis was. Why they thought that DISC1 and DISC2 might be causative as distinct from intervening or confounding is equally not addressed. They have not explained what caused the translocation in the first place. Why gene density on chromosomes might be a consideration for contributing to cause of psychosis is also not explained. They admitted that their findings were hypothetical only. They provided no genuine evidence of cause and effect; there was no control group; they did not control for environmental influence within the family; no subsequent studies have been able to replicate their findings. There is no data providing a recognisable link between DISC1 and DISC2 and any form of psychosis. In short, research methods were amateurish and findings purely speculative.

Strangely enough, years previously, DISC1 had apparently been found in a study by Jacobs et al. [14] on an 18-year-old male. They also found that the same translocation occurred in his father, paternal grandfather, and four generations of descendants of his paternal grandfather, yet apparently none had been diagnosed with schizophrenia. Even Sullivan [15] has stated: ‘my group has found non-significant but “intriguing” results about DISC1 twice, and both times its salience faded with more data.’

Sullivan [15] further disputed the Millar et al. [12] findings, but his criticisms were not well received. In reply, Porteous et al. [16] stated among other: ‘denying a role for variants makes no sense and contradicts theoretical considerations.’ In other words, theory equals fact, while evidence or lack thereof, does not. They seem to forget that theories are sometimes wrong; that is why they are called ‘theories’ and data are collected to assess how accurate they are. Claiming that something ‘makes no sense’ does not refute the logic of Sullivan’s arguments.
This was stated after having listed other mental health problems where there have been investigations into genetic cause where researchers made the same mistake: finding evidence of abnormality or difference was equated with cause and effect. This included autism which has recently been proven to be caused by inadequate parent-child interaction and communication problems in neonates [17] not genes. Their arguments demonstrate subjectivity. The findings by Saunders [17] regarding cause of autism suggest that it may well be that all such mental health issues are caused by environment and not genes.

Also, in 2000 Hyman [18] stated:

‘It is well established that the risk of mental illness runs in families. Family, twin and adoption studies have shown that, for schizophrenia, autism, manic depressive illness, major depression, attention deficit hyperactivity disorder, panic disorder and other mental illnesses, the transmission of risk is due to heredity.’

Although Hyman [18] did also state that environment played a part he concluded that: ‘Breakthroughs in preventive and treatment interventions should come from progress in genetics research and neuroscience.’ In short, he is summarising the fundamentally flawed assumption in so much psychiatric research, when cause is attributed to heredity, while ignoring the impact of learned dysfunctional intergenerational behaviour. Parents’ behaviour is dysfunctional and this has an impact on the socialisation of children who react negatively to the dysfunction [19]. This is not controlled for in so many studies, leading to researchers’ falsely concluding cause and effect between onset of disorder and genetic makeup without investigating psychosocial issues.

In 2014 Escudero and Johnstone [20] also stated that ‘….recent studies, especially in the past year, have confirmed genetics as the major cause of this complex condition’.

In 2015, Farrell et al. [21] stated:

‘On the basis of current empirical evidence and mostly consensual assessments of informed opinion, it appears that the historical candidate gene literature did not yield clear insights into the genetic basis of schizophrenia. A likely reason why historical candidate gene studies did not achieve their primary aims is inadequate statistical power. However, the considerable efforts embodied in these early studies unquestionably set the stage for current successes in genomic approaches to schizophrenia.

And in their conclusion:

‘In summary, the current empirical evidence strongly supports the idea that the historical candidate gene literature yielded no robust and replicable insights into the etiology of schizophrenia’.

That is, they admitted that they did not have evidence of genes as cause, but suggested that inadequate statistics were responsible rather than absent evidence. They finally suggested that genomic approaches are being ‘successful’, whatever ‘successful’ means.

Blaming statistics for not being able to find cause is like a tradesman blaming his tools for not being able to do his job properly; it is an excuse for incompetence. They accept that research findings have not been replicable.

Yet Huang et al. [22] also wrote on the assumption that genes were causative. They claimed that they had identified 87 genes that showed higher gene expression which they seemed to think was somehow relevant to revealing cause of mental illness. They concluded in the abstract that: ‘Taken together, our results suggest that SCZ brains are characterized by over dispersed gene expression—overall gene expression variability among SCZ samples is significantly higher than that among CTL samples. Our study showcases the application of variability-centric analyses in SCZ research’.

Although they used a control group, the assumptions concerning the experimental group, that is, those who had been diagnosed with schizophrenia, were multiple. They state that the study showcases the application of variability-centric research analyses, but they have not explained the relevance of such a finding, that is, its significance or consequences for future studies or greater understanding of the disorder. It is like stating that a swan is black. This does not tell us anything other than the colour of the swan.

They have also considered so many physiological variables such as VEGFA (vascular endothelial growth factor) and BDNF (brain-derived neurotrophic factor), cerebellar cortex morphogenesis, neuromuscular junction development, and cerebellar Purkinje cell layer development that on the surface seem totally irrelevant to determining cause. It is difficult to comprehend how neuromuscular junction, for example, could be of relevance to determining cause of a mental illness; there are no muscles in the brain. Moreover, there is no explained link between acknowledged behaviour of schizophrenics and these variables.

But Duncan et al. [23] argued that gene studies have now been made obsolete by genome wide association studies (GWAS). In their conclusion they state:

‘Candidate gene studies nearly always hypothesized the wrong portions of the genome (and they may have always hypothesized the wrong variants), they hypothesized effect sizes larger than those that exist in nature. Further, candidate gene studies are methodologically inadequate in their ability to account for subtle differences in ancestry and relatedness, which can confound results. In sum, it is time to abandon candidate gene studies, and the results that they produced, in favour of the numerous highly reliable results that have emerged from GWAS.’

And:

‘At this juncture it is arguably time to declare that the candidate gene era has ended. Approximately $250 million was spent. Graduate students, postdocs, and professors devoted portions of their lives to these investigations. Yet, a more comprehensive and more statistically robust approach has emerged, and the results
from GWAS have rendered old ideas and technology obsolete.’

Hence, at least some sense has prevailed, due to more people recognising that individual gene studies lack reliability, prove little and that huge sums of money have been wasted on such studies. However, the idea that huge databases are going to be more successful is also dubious given what geneticists say. If schizophrenia is caused by environment then greater genome database size will not provide answers.

His opinions that individual gene studies are obsolete have been supported by Colhoun et al. [24], Johnson et al. [25], and Border et al. [26].

There are several further criticisms of many of these individual gene studies in general. Firstly, investigation occurred after a medical diagnosis of schizophrenia had been made and there was therefore no comparison evidence of state of patient’s genetic makeup before onset. Where I to assert that fire engines cause house fires because the two co-occur, I would be immediately discredited as being mad or stupid or both - we all know that engines arrive after fires have started. But such logic is the same as that of many researchers. They have said these genes co-occur with a diagnosis; therefore they are causative without being able to prove that the same epigenetic structures were in place before onset of disorder due to no evidence being collected.

Secondly, research findings of geneticists themselves do not concur with research findings of medical researchers. Work by researchers such as Idaghdour and Gibson [27] demonstrated that alleles change in response to environment, not the reverse, and so epigenetic change happens on a daily basis.

A second study, by Slatkin [28], explains how epigenetics and gene mutations contribute to disease risk in a population at a given time and in subsequent generations. The model described in the report represents a first step in quantifying the effect of epigenetic change on disease risk and recurrence risk.

Ridley [29] has concluded that there is insufficient variation in gene structure for genes to be responsible, so it is impossible for genes to cause schizophrenia. He has further stated:

‘[Genes] are devices for extracting information from the environment. Every minute, every second, the pattern of genes being expressed in your brain changes, often in direct or indirect response to events outside the body. Genes are the mechanisms of experience.’

Such studies are consistently ignored by medical researchers who are not specialists in genetics and clearly have not read such literature.

Several other studies have commented about the possibility of making a type 1 error in epigenetic studies. Czyz et al. [30] have stated that:

‘Studies investigating epigenetic changes are potentially prone to false conclusions as a result of reverse causation or confounding. Because the nature of the epigenome is dynamic and most epimutations arise throughout a person's lifetime, the key to addressing causality might be in their timing.’

Their comments are supported by Bell et al. [31] and by Rakyan et al. [32]. However, nine years later, type 1 errors are still being made in studies that set out to prove an assertion, rather than asking if a hypothesis is true or false.

The third type of research, the genome wide association study, investigates genetic cause of many medical diseases as well as psychiatric disorders including schizophrenia and therefore data are not specific to schizophrenia. Henriksen et al. [33] have summarised their importance as well as warning against making type 1 errors but in spite of this, they too state the opinion that genes are a risk factor for schizophrenia. They do caution:

‘However, we should not fail to also notice: (i) that associations between common (SNPs) or uncommon (CNVs, SNVs) genetic variants and schizophrenia, though statistical facts, are not necessarily indexes of causal pathways; and (ii) that many of the discovered associations are, in fact, non-specific to schizophrenia but indicative of a genetic vulnerability to several mental disorders. Overall, the details of the etiopathogenesis of schizophrenia and the genotypic environment interactions remain to large extent unknown, and therefore caution is still warranted when drawing conclusions about the size of the genetic contribution in the etiology of the disorder.’ (ibid).

In short, the conclusion is that genetic cause remains unproven in spite of the database size, due to data being collected after a diagnosis has been made or evidence being applicable to more than one disorder and therefore it is not possible to assert a connection with schizophrenia with confidence.

Discussion

Let us further this article’s assertions by reviewing the meaning of ‘scientific method’. The accepted scientific process now used in all science, whether natural, medical or social, is based on the hypothetico-deductive model, and was proposed by Popper [34,35]. Popper suggested that theories/laws about the world should come first and these should be used to generate expectations/hypotheses which can be falsified by observations and experiment. He believed that falsification of the experimental hypothesis is the only way to be completely certain about the world as we can never know all conditions or variables that are relevant to any study with total certainty.

For example, if I hypothesise that all swans are white, I must do much research to prove or refute this which may well include travelling around the world to find evidence. Unless I fortuitously travel to Australia, the home of black swans, I might not be aware of the existence of other coloured swans and falsely reject the null
hypothesis, a type 1 error, through lack of contradictory evidence. Although such a conclusion was made in good faith, that is, it is a genuine belief; it is still incorrect due to inadequate data collection. Beliefs do not equate to facts or truth.

Therefore, it has come to be accepted that the key features of the scientific method are objectivity, use of empirical evidence, use of control, the ability to replicate research and provide the same results (reliability), a generally accepted theoretical orientation called a paradigm and hypothesis testing. Any experiment/research must have both an experimental hypothesis and a null hypothesis. If there is insufficient or contradictory or no evidence, after appropriate evidential and statistical analysis then researchers should accept the null hypothesis. A null hypothesis states that there is no relationship between the variables under investigation, that is, the IV and the DV.

In many of the studies into genetic causes of schizophrenia, it has not been possible to replicate studies and come up with the same results, as noted by Farrell et al. [21] and it is this fact that has caused the proliferation of gene studies each falsely claiming an extra gene that is causative leading to the idea that schizophrenia is caused by multiple genes. For example, twenty years on, only the Edinburgh group have found evidence of DISC1 and DISC2. Nor have researchers been objective as was demonstrated in all studies cited above. There has also been an absence of control groups in some studies including the Edinburgh group, and an absence of a lack of willingness to accept the null hypothesis, namely that there is no relationship between the IV and DV. They did not demonstrate that the IV affected the DV.

It must be concluded that much of this research into a genetic basis has been ill advised and as stated above, a waste of money. Lack of scientific rigor has not enhanced the reputation of the discipline nor served the public well as funds are being misdirected, and cause has still not been found with certainty leaving many people to continue to suffer due to a lack of understanding by professionals. Empirical evidence of no genetic cause should be accepted and research moved forward to investigating environmental causes. Money ought to be used on projects that are fit for purpose such as undertaking research investigating family relationships and in particular reconsidering and further advancing the work begun by researchers such as David Cooper, Bateson, Esterson and Laing and Leff to name a few.

The real question is why medical researchers continue their unwinnable quest into finding responsible genes. So many academic reputations and indeed whole university departments and research institutes have been built around studies based on false premises that researchers are reluctant to admit that they are mistaken. This myopia to some extent is possibly a reflection on funding practices and the conservatism and indeed sometimes incompetence of journal editors who accept papers from established universities and researchers simply because they are highly ranked, such as Edinburgh University, for example, while themselves having inadequate knowledge of subject matter or research methods.

A second issue possibly is the paradigm encompassing conservatism of psychiatry itself. There have been many studies that have concluded that there are serious problems within this discipline that remain unaddressed beginning with Rosenhan [36]. Rosenhan found that many medical staff could not tell the difference between the behaviour of psychotic patients and pseudo-patients. There have been suggestions of need for improvement Naslund et al. [37] and that a paradigm change is needed et al. [38]. Many studies quoted here [13] demonstrate a lack of understanding of psychosocial issues within the family as well as insensitivity towards people in general [36]. In essence, psychiatry would benefit from more modules on communication studies, sociology and psychology being incorporated into training.

Finally, it is clear that research method training is inadequate. Many studies cited above reveal an absence of a basic knowledge of research methods such as for example, not understanding the fundamental principles behind research process including the need for a null hypothesis, the need to be objective, the need to have control groups, the need for reliability, and so on. Moreover, knowledge of inferential statistics is inadequate. Researchers do not understand that high levels of association between variables do not demonstrate cause and effect. There may well be other confounding, intervening and ignored variables that impact on both the IV and DV. Clearly inferential statistics in particular have been badly taught as has the entire theoretical underpinning of what scientific research is all about. It is mind boggling that researchers still consider genes to be responsible, given the substantial evidence that this is not possible.

Moreover, clinical implications must be profound. Psychiatrists still do not know cause, consequently do not understand the problem, and sometimes lack empathy [39]. Treatment could probably improve were there a greater understanding of the problem.

Conclusion

There is still no genuine scientific evidence of a genetic cause of schizophrenia as distinct from false claims of evidence, and never has been, yet medical researchers continue to wrongfully assert that genes are responsible, although the focus has now moved to genome wide studies, rather than searching for individual genes. Multiple intra-familial and intergenerational diagnoses of schizophrenia alone are not evidence of genetic cause as environment has not been controlled for and indeed it is difficult to control for, as families are complex. They are more likely to be evidence of dysfunctional familial relationships, but this observation or conclusion is wilfully ignored by medical researchers. Thus, there must be significant clinical consequences for such irrational beliefs.

Training in research methods for medical researchers in psychiatry is highly inadequate and needs to improve in order to undertake more useful studies, make fewer mistakes in research choice and practice and therefore become more cost effective. Psychiatrist paradigms need to modernise.
There is an old proverb that says that there is none as blind as he who will not see. Sadly, the emperors continue to be naked, albeit they now wear shoes.

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