World Journal of Psychiatry and Mental Health Research

Review Article
Published: 06 Mar, 2020

Schizophrenia: An Evolutionary Perspective

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Abstract

Schizophrenia is a major mental illness that is partly genetic in origin. It is present in every human population that has been studied and is thought to have existed throughout history and much of prehistory. This represents an evolutionary puzzle since the expectation would be that such an adverse state would be eliminated by selection pressure. This has prompted the hypothesis that genes associated with the disorder, if not the disorder itself, confer an advantage in terms of advanced cognitive and neurological functioning. Indeed, studies utilizing DNA from *Homo sapiens*, *Homo neanderthalensis* and *Homo denisova* suggest that a tendency to schizophrenia only developed following divergence of modern humans from their nearest *hominin* relatives. However, there are other significant genetic associations with schizophrenia, such as height, Body Mass Index (BMI) and type 2 diabetes mellitus. These are likely to have been more effective than any putative intellectual superiority in conferring evolutionary advantages, probably due to more efficient energy utilization.

Introduction

Schizophrenia is associated with a number of genetic variants. It is a puzzle as to how these variants might have survived the rigors of natural selection so that the condition is now found in every human population and appears to have been present during many millennia of human history [1]. The solution to this puzzle is likely to reside in some competitive advantage conferred by associated genes rather than the condition itself. The usual explanation is that the genetic basis of schizophrenia is involved in promoting cognition, creativity and imagination; aspects of mental activity which would put *Homo sapiens* at an evolutionary advantage. However the real value of schizophrenia linked genes probably resides in their metabolic associations.

Human Family Tree and Genome Analysis

The proximal human family tree originated at least 7 million years ago. The precise relationship between various *hominins* remains a matter of controversy. Besides *H. sapiens*, more recent species, present during the past million years, include *Homo neanderthalensis* and the recently discovered *Homo denisova*. A common ancestor of all three may have lived as long ago as 800,000 years. Both the *Neanderthal* and *Denisovan* genome have been sequenced [2,3]. Also, studies have been undertaken comparing aspects of the modern human genome with those of these two *hominins*. One study revealed that genes associations with schizophrenia are found in areas of the modern human genome which diverge most markedly from their *Neanderthal* equivalents. This was not the case for genetic associations of Alzheimer's disease, bipolar disorder or major depressive disorder [4]. A more recent investigation found enrichment of schizophrenia related signals in recently evolved human specific methylated regions of the genome of *Homo sapiens* relative to both *Neanderthals* and *Denisovans* [5]. No enrichment was detected for genetic markers of bipolar affective disorder. Interestingly, these results suggest affective disorders represent a more primitive phenotype than schizophrenia, something that might not be expected from Kleinian theory. The persistence of a genetic predisposition to schizophrenia may be the price we pay for in order to speak, have abstract thoughts and be artistically creative [6]. Certainly this appears plausible, particularly as most of the recently evolved genetic markers for the condition are related to neurological functions such as neurotransmission and long term synaptic potentiation [5].

Problems with the Hypothesis

Despite apparent plausibility there are a number of problems with this hypothesis.

1. Following sequencing of the *Neanderthal* genome it became apparent that the FoxP2 gene, necessary for the production of speech, was carried by this now extinct *hominin* [2,7]. This, gene codes for a transcription factor which controls the expression of a number of genes, especially

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Received Date: *22 Jan 2020*
Accepted Date: *03 Mar 2020*
Published Date: *06 Mar 2020*

Citation:
Nicholson SD. Schizophrenia: An Evolutionary Perspective. World J Psychiatry Ment Health Res. 2020; 4(1): 1023.

in the brain, and is thought to be involved in neurotransmission and synaptic facilitation. Also there is no evidence for recent evolutionary selection of the FoxP2 gene in a number of human populations [8]. However, some doubt has been cast on the idea that *Neanderthal* man could speak by computer modeling of the sounds produced by a reconstructed *Neanderthal* vocal apparatus [9].

2. It is mistaken to regard *Neanderthal* as having been lacking in culture and the ability for abstract and symbolic thought. There is evidence that they used relatively sophisticated tools cared for their injured; acted cooperatively; and buried their dead. With a degree of ceremony; used pigments and adorned their bodies [10]. These features of complex *Neanderthal* behavior seemed to have increased between about 160,000 and 40,000 years ago. In addition there is a modicum of evidence that *Denisovans* were capable of producing art: Rib fragments were recently discovered in northern China with apparent engravings, one of which was decorated with ochre [11]. It seems that genetic markers for schizophrenia are not a sine qua non for symbolic thought and creativity.

3. Genes other than those related to schizophrenia were probably more important in the development of cognition. The recently discovered families of Notch Homolog 2 N-terminal-like (NOTCH2NL) genes are involved in the development of the human cerebral cortex [12]. These genes delay the development of neurons from cortical stem cells and these results ultimately in the production of more neurons during brain development. These genes originally arose due to a repair of a non-functional version of NOTCH2NL which in turn arose from partial duplication of NOTCH2, another neurodevelopmental gene. This repair only happened in humans and is estimated to have occurred 3 to 4 million years ago, at a time when the *hominin* brain was expanding. Before we diverged from our common ancestor with *Neanderthal,* NOTCH2NL had been duplicated twice over. This would suggest that selection of genes associated with schizophrenia is not the evolutionary price paid for higher cognition in modern humans but that brain evolution was dependent upon separate genetic mechanisms.

4. A review of the connection between mental illness and creativity found that the evidence for a connection is thin. Most studies examining this question, and which find a positive association, use flawed methodologies and inadequate criteria for determining causal connections [13]. However, this leaves open the possibility of a predisposition, rather than an illness per conferring an advantage.

Alternative Hypotheses

If it is true that no competitive advantage in terms of cognition is associated with a genetic loading for schizophrenia at least two alternative hypotheses may be reasonably considered.

Fertility

The fertility of patients with schizophrenia is reduced relative to those without the condition. However it has been suggested that a genetic tendency to schizophrenia may increase fertility. Evidence concerning this issue is contradictory. An early study looking at the number of offspring produced by the first degree relatives of schizophrenia found that the parents of schizophrenic patient stented to have more children than average, as did the siblings, although the effect for the latter was small [14]. A more recent study suggests there is no association between the liability to schizophrenia and number of offspring. However, the same study indicated that those with a genetic predisposition may have a greater number of sexual partners [15]. In sum, the evidence connecting a tendency to schizophrenia with increased fertility is sparse.

Stature, energy economy and metabolism

About 80% of variation in human height is determined genetically and there are over 40 genetic loci associated with normal variation in human stature [16]. *Neanderthal* is often envisaged as being of shorter stature than Early Anatomically Modern Humans (EAMHS). There isn't a consensus on this issue but a study employing maximum femur length to calculate stature found *Neanderthal* to be shorter than both Homo erectus and EAMHS [17]. The shorter stature of *Neanderthal* is accepted by most if not all authorities [18]. A recent painstaking anatomical reconstruction of a *Neanderthal* skeleton tends to confirm this impression, giving a height of 163.8 cm [19]. A more extensive study employing long bones from various *hominin* species revealed an overall mean stature of 160.6 cm for *Neanderthal* and 177.4 cm for early modern humans [20]. There is a genetic overlap between schizophrenia and stature [21]. Patients with the illness are shorter on average than unaffected individuals. However, three of the six overlapping genetic regions are concordant for stature and schizophrenia. These regions are involved in cell division and proliferation. One of these concordant regions, on Chromosome 3 (IT1H cluster), is the locus most strongly associated with schizophrenia. This raises the interesting possibility that the putative inferior stature of *Neanderthal* and their lack of genetic markers for schizophrenia may be connected. One factor contributing to smaller *Neanderthal* stature is the relative shortness of the *Neanderthal* tibia, which is just over 50% of the femoral length (compared with 85% in *H. Sapiens*) and there is evidence from treadmill studies that short tibiae are associated with greater energy utilization per distance traversed [22]. This would put *Neanderthal* at a disadvantage compared with longer legged *Homo sapiens* when searching for or pursuing prey. In harsh climatic conditions this relative *Neanderthal* inefficiency would reduce chances of survival.

Due to paucity of *Denisovan* remains a reconstruction of their anatomy has been attempted using DNA methylation maps but the authors do not comment upon their subject's stature or the relative sizes of lower limb bones [23]. Consequently an analogous argument to that made concerning *Neanderthal* locomotion cannot at present be made for the *Denisovan*. If the above reasoning is correct, genetic loading for schizophrenia may indeed be a price paid for evolutionary advantage but it would have been an advantage based on metabolic factors rather than cognition. Furthermore, there is some evidence that the Body Mass Index (BMI) of *Neanderthal* was larger than that of modern Canadians and Americans [18]. The maintenance of a greater BMI requires a larger caloric input. If *Neanderthal* were of greater BMI than EAMHS, their energy requirements would have been correspondingly greater. A negative correlation has been discovered between the genes for schizophrenia and those for Body Mass Index (BMI) [24], suggesting that schizophrenia genes confer another energy advantage on *H. sapiens* by giving them a tendency towards lower body mass index. There is also a positive genetic association between schizophrenia and diabetes mellitus type 2 [25]. This too may be of evolutionary significance. The thrifty gene hypothesis suggests that modern humans evolved mechanisms for storing lipids in times of relative plenty for use in leaner times. A high calorie modern diet leads to excessive fat deposition, predisposing to insulin resistance and diabetes whereas in the Pleistocene the ability to store lipids would have been a kind of metabolic investment. Another hypothesis, the "carnivore connection" proposes that insulin resistance evolved

to maintain blood glucose levels at a time during the Paleolithic when diet was high protein and low carbohydrate [26,27]. This putative importance of insulin resistance in our prehistory is speculative but it does suggest there is a deep connection between evolution, schizophrenia and metabolism in *H. sapiens*.

Discussion

A number of hypotheses might explain why evolution has not selected against schizophrenia. The classic explanation is couched in terms of a cognitive advantage for *H. sapiens*. However, growing evidence of *Neanderthal* culture has tarnished this hypothesis. There is a reasonable body of evidence to support the idea of a more efficient energy economy for *H. sapiens* compared with our closest *hominin* relatives. This efficiency relates to genes for stature, BMI and possibly those related to Type 2 diabetes. The genes for all of these overlap with the genetic basis of schizophrenia. However there are plausible objections to this idea. Firstly, evolutionary competition and success are complex affairs involving more than genetic factors. For Example; climate change, food supply, size of the social group, physiology and anatomy, the range of technologies available, to name but a few. Any or all of these factors might swamp the effect of a particular group of genes. Secondly, much of the above argument concerning stature and energy use depends upon calculations of height utilizing regression equations based on the study of modern samples. Thirdly, even when *hominin* remains are available they are fragmentary and rare. It is therefore difficult to make definitive statements concerning stature. In addition, although it is customary to regard *Neanderthal* as having become extinct, it is possible that they simply lost their identity by interbreeding with *H. sapiens* and other *hominin* groups. Most Europeans have 2% to 4% of DNA which is distinctly *Neanderthal*. Furthermore one study, not entirely reliant upon genetics, suggests that *Neanderthal* energy requirements were more moderate than previously supposed [28]. Another puzzle is that risk alleles for schizophrenia are being steadily eliminated from the genome since the advent of modern humans, whereas the number of protective alleles has been increasing [29]. It is possible that risk genes conferred an edge early in the prehistory of modern humans but that following the elimination of evolutionary competitors the advantages associated with these alleles has diminished. Perhaps the major objection to the foregoing discussion is that an apparent genetic overlap between schizophrenia, stature and BMI does not necessarily imply causality. There is a possibility of a common underlying cause and a deeper study of how the various relevant genes interact and the control of gene expression are required.

Conclusion

Schizophrenia, a condition with a polygenic basis, has persisted for millennia; suggesting an evolutionary advantage for the genes underlying this condition. After surveying the evidence, it seems likely that a tendency to schizophrenia is the price *H. sapiens* pay for relatively efficient energy metabolism. This efficiency would have given our distant ancestors an evolutionary edge and enabled them to compete more successfully with their nearest evolutionary relatives for scarce food resources, perhaps at times of adverse climate change. In this way a proclivity to schizophrenia may have played a part in the success of our species.

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