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► **To cite this version:**

Veronica Sandroni, Boris Chaumette. Understanding the Emergence of Schizophrenia in the Light of Human Evolution: New Perspectives in Genetics. *Genes, Brain and Behavior*, 2025, 24 (1), pp.e70013. 10.1111/gbb.70013 . hal-04888153

HAL Id: hal-04888153

<https://hal.science/hal-04888153v1>

Submitted on 15 Jan 2025

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REVIEW ARTICLE OPEN ACCESS

Understanding the Emergence of Schizophrenia in the Light of Human Evolution: New Perspectives in Genetics

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Received: 21 September 2024 | **Revised:** 17 December 2024 | **Accepted:** 21 December 2024

Funding: This work was supported by Institut National de la Santé et de la Recherche Médicale. Agence Régionale de Santé Île-de-France. Agence Nationale de la Recherche. French Congress of Psychiatry.

Keywords: neanderthal | schizophrenia/biological evolution | schizophrenia/genetics

ABSTRACT

Schizophrenia is a frequent and disabling disease. The persistence of the disorder despite its harmful consequences represents an evolutionary paradox. Based on recent discoveries in genetics, scientists have formulated the “price-to-pay” hypothesis: schizophrenia would be intimately related to human evolution, particularly to brain development and human-specific higher cognitive functions. The objective of the present work is to question scientific literature about the relationship between schizophrenia and human evolution from a genetic point of view. In the last two decades, research investigated the association between schizophrenia and a few genetic evolutionary markers: Human accelerated regions, segmental duplications, and highly repetitive DNA such as the Olduvai domain. Other studies focused on the action of natural selection on schizophrenia-associated genetic variants, also thanks to the complete sequencing of archaic hominins' genomes (Neanderthal, Denisova). Results suggested that a connection between human evolution and schizophrenia may exist; nonetheless, much research is still needed, and it is possible that a definitive answer to the evolutionary paradox of schizophrenia will never be found.

1 | Introduction

Schizophrenia is one of the most debilitating psychiatric disorders, characterized by reality distortion (delusions, hallucinations), disorganization (disorganized behavior, for example), and negative symptoms (lack of volition and affective flattening, for example) [1]. The prevalence of the disease has been estimated to be in 1% of the population with more recent estimates of global-age-standardized point prevalence of 0.28% [1, 2]. Prevalent cases have increased from 1990 to 2016, especially in countries with growing populations, such as those in the Middle East and in North/Eastern sub-Saharan Africa [2]. Male-to-female ratios slightly greater than one

have been found in a review considering 383 studies about schizophrenia prevalence, incidence, and mortality [3]. The disease often appears gradually during adolescence and has an impact on reproductive behavior, leading to lower fertility in patients and their families [4]. Reduced fitness has also been described in schizophrenic patients before and after the onset of psychotic symptoms [5, 6]. Moreover, fertility did not seem to be either reduced or increased among siblings and offspring of schizophrenic patients, thus, likely excluding any kind of compensatory mechanism [5, 7, 8]. Questions about this “evolutionary paradox” (stable prevalence of a high burden disease) have been raised by scientists during the last century [9–11].

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1.1 | Models Explaining the Evolutionary Paradox of Schizophrenia

Because of the great impact on daily life, social relations and work capacity, and especially its early onset, questions about evolutionary advantages of schizophrenia arose during the last two-hundred years. In fact, since the publication of *The Origin of Species* written by Charles Darwin in 1859, the paradigm of natural selection has been adopted by many biologists to understand why some species disappeared and others did not. This paradigm leans on the hypothesis that transmission of features throughout generations depends on their advantages in terms of survival and reproduction.

The evolutionary paradox of schizophrenia has been addressed either by exploring its potential evolutionary advantages in the present or in the past (as suggested by the evolutionary mismatch theory) or by considering it as a byproduct [9, 12, 13]. As mentioned previously, a decrease in fitness has been found for schizophrenic patients [5, 6] and no clear compensatory mechanism has been described among patients' siblings or offspring [5, 7, 8]. Polimeni proposed that schizophrenia may have conferred advantages at the group level in the past. For instance, it could have enhanced a shaman's ability to perform religious rituals, which were essential for hunting and gathering tribes [14]. Consequently, the trait was passed down through generations despite its association with lower individual fitness [14]. Nonetheless, even though increased mating success has been reported by Lawn and colleagues [15], recent research has gradually abandoned the idea of some evolutionary advantages of schizophrenia. The hypothesis of an "evolutionary cost" diffused slowly through scientific community [16–23] and has been growing in evidence since major advance of genetics and genomics happened in the last years. Schizophrenia could be the price to pay for human evolution and achievements such as human brain complexity, language skills, and creativity. Indeed, within the families of people with schizophrenia, we find more artists, musicians, and mathematicians than in the general population [24]. Furthermore, the schizotypal personality disorder, characterized by great creativity and very specific and restricted interests, is also associated with schizophrenia [16, 25]. From a biological point of view, advocates of the "price to pay" theory argued that the primate brain, with the development of the neocortex, has become a more complex system enabling new competencies such as social cognition or language skills [16, 20]. However, this complexity also renders the brain more vulnerable to insults [16]. Phenomena of aberrant cortical connectivity could then occur and be at the origin of psychotic symptoms [16]. Schizophrenia has also been viewed as an extreme of a range of sexual fitness indicators, representing a less attractive trait in a set of psychological features that signal genetic fitness to potential mates [23]. Despite its debilitating effects, the condition could act as a warning sign of poor genetic health, with symptoms worsening with dopamine agonists (linked to pleasure) and improving with antagonists, correlating with sexual behaviors [23]. The schizophrenia evolutionary paradox may also be an apparent one, with some authors suggesting that the disease is relatively recent and that evolutionary processes have not yet had time to act on it. Adriaens [26] proposed that schizophrenia might not have existed in its current form until the nineteenth century, coinciding with the rise of

industrialization and urbanization. He speculated that schizophrenia could have infectious origins, possibly linked to viruses or *Toxoplasma gondii*, with the clustering of populations during the Industrial Revolution leading to a wider spread of pathogens [26]. With recent advances in genomics, the evolutionary hypothesis of schizophrenia has been tested through genetic analysis. Based on the complexity of the genetics underlying brain functions, Keller and Miller proposed the mutation–selection balance theory. They suggested that the persistence of harmful phenotypes, such as schizophrenia, could be explained by the high number of genetic variants involved and the action of selection on them [27]. Moreover, the concept of a "price to pay" has been translated into the idea of a "genomic trade-off," suggesting that in human evolution, the genome—considered the carrier of human traits—retains beneficial changes overall, even if they cause disease in a subset of individuals, consistent with the cliff-edge theory [28, 29]. Therefore, with genomic technology advancements, we can now move beyond testing for selection on potential adaptive traits to identifying candidate genetic regions through genome scans [30].

1.2 | Generalities About the Genetics of Schizophrenia

Genetic bases of schizophrenia have been widely explored, and evidence of a polygenic nature of the disease has been provided [1, 31–33]. Importantly, environmental factors are crucial in the development of the disease, and there is increasing evidence of gene–environment interactions in schizophrenia pathophysiology. Environmental risk factors such as pregnancy and birth complications, trauma, cannabis, and other substances use, and socioeconomic status have been associated with schizophrenia [1, 34]. Many schizophrenia-related genetic variants have been identified, both common and rare. Regarding common variants, schizophrenia-associated Single Nucleotide Polymorphisms (SNPs) have been identified by large genome-wide association studies (GWAS). In 2022, 287 distinct genomic loci associated with schizophrenia have been described among 76,755 people with schizophrenia and 243,649 controls [35]. Schizophrenia-associated SNPs were associated with genes expressed in central nervous system neurons, but not other tissues or cell types [35]. If we consider a SNPs-based genetic susceptibility, schizophrenia can be viewed as a polygenic disease where a single variant does not provide enough information to assess the risk. Instead, a genetic risk score, derived from the combined effect of multiple risk variants, is needed to accurately identify individuals at high risk [36]. Polygenic risk scores (PRSs) tried to meet this challenge by assigning to each variant a weighted sum based on the number of risk alleles an individual carries [36]. Clinical application of PRSs is still debated, and it goes from prediction to diagnosis and treatment decision [36]. Major concerns about PRS are limited evidence regarding its application to non-European ancestries and the challenges of converting an individual's PRS from a percentile in a normal distribution to a lifetime disease risk [36]. Efforts have been made to apply PRS to schizophrenia: the PRS analysis in the Schizophrenia Working Groups of the Psychiatric Genomics Consortium GWAS explained around 7.3% of the variance in schizophrenia liability and around 2.4% when restricted to genome-wide significant SNPs [35]. Not surprisingly, schizophrenia is subjected to familiar predisposition

with increased risk of developing the disease if relatives are affected [37]. Heritability of schizophrenia has been estimated in family studies (from 47% to 80%) and in GWAS (SNPs-based heritability, around 24%) [35, 37–39]. There is a gap between the two estimates with higher heritability in family studies. This difference has been called the “missing heritability.” Missing heritability could be multifactorial, being due to lack of power of GWAS and/or epigenetic mechanisms, for example [31].

As previously mentioned, also rare variants have been associated with schizophrenia [40], such as single nucleotide variants (SNVs), insertion–deletion (indels), and copy number variations (CNVs), such as the deletion on chromosome 22q11.2 [32, 41, 42]. The first discovered rare variants were de novo single nucleotide variants (DNVs). DNVs that can be found in offspring and not in parents [32] and have been associated with schizophrenia [31, 43].

1.3 | Mechanisms of Natural Selection and Their Impact on the Human Genome

The growing knowledge about the mechanisms of natural selection and their impact on the genome could be mobilized to test hypotheses about the evolutionary paradox. Interactions between genome and evolution forces have not been completely elucidated by scientists. The study of evolution is a complex task because of concepts definition, their partial overlap, and lack of full understanding of genome-regulating processes. Natural selection explains that traits which improve an organism's survival or reproductive success are more likely to be passed on to offspring, increasing in prevalence over time. In the genomic era, selection refers to the nonrandom spread of alleles based on their phenotypic effects [30]. Both positive and negative (purifying) selection increasing or decreasing allele frequencies have been explored [30]. Positive selection is considered the primary mechanism of adaptation [30]. In addition, random mutations are more likely to be harmful than beneficial, leading many new alleles to undergo immediate negative selection. This continual removal of harmful mutations through negative selection is known as background selection [30]. Another way natural selection acts is balancing selection which consists in the maintenance of multiple alleles at significant frequencies within the gene pool [30]. Balancing selection can conduct to opposite (only small or large body sizes, for example) or intermediate phenotypes: this phenomenon will be referred to as “diversifying/disruptive selection” or “stabilizing selection”, respectively [30]. Selective sweep could be observed as a population-wide reduction in genetic diversity due to the action of positive selection on a beneficial allele and surrounding variants on the same haplotype [30]. This reduction in diversity may be of different degrees, for example if the sweep is incomplete or if the mutation is not subject to immediate selection (complete sweep from standing variation) [30]. Importantly, the persistence of genetic variants in a population depends not only on their impact on fitness but also on the influence of random evolutionary mechanisms, such as mutations and genetic drift [32]. Genetic drift refers to random fluctuations in the frequencies of genetic variants due to the random sampling of individuals and their gametes, which transmit alleles to the next generation [32]. Genetic drift effect is supposed to be greater in small size populations where genetic variation is

lower, and sampling error is higher [32]. Moreover, migration can contribute to the introduction of novel genetic variants in the population gene pool by gene flow [32]. From a practical point of view, selection can be detected at the macroevolutionary level (interspecies selection) and at the microevolutionary level (intra-species selection) [30]. The choice of the method depends on the level of analysis. For example, comparing non-synonymous and synonymous substitutions between genomes (dN/dS ratio) can be used to study interspecies differences: If the ratio is higher than expected under the hypothesis of neutrality (absence of the action of selection, non-synonymous, and synonymous mutations occurring randomly), the region has likely been submitted to selection [30]. Identification of accelerated regions (high dN/dS ratios) can also be used to study the action of positive selection on the genome [30]. Conversely, the intra-species effect of selection can be estimated through changes in the spectrum of alleles or haplotypes frequencies (frequency-based and linkage-disequilibrium or LD-based methods, respectively), through differences between allele frequencies between two populations (population differentiation-based methods) or by the combination of at least two of these techniques (composite methods). Two examples of LD-based methods are the integrated Haplotype Score (iHS) [44] and the Cross-Population Extended Haplotype (XP-EHH), both relying on haplotype length. Indeed, recombination decreases haplotype length breaking down linkage disequilibrium [30]. On the other hand, the Composite Likelihood Ratio (CLR) is a composite method which combines multiple test scores for contiguous sites to reduce the rate of false positives [30, 45]. Another example of composite methods is the Composite of Multiple Signals (CMS) combining multiple independent tests at one site, thus integrating complementary information into one single test [30, 46].

2 | Materials and Methods

Schizophrenia is a complex and highly disabling disease, and genetic research can offer valuable insights into its pathophysiology and potential treatments. Evolution may have contributed to the emergence of schizophrenia, and studying genetic regions that have undergone modification over time could provide new perspectives on understanding and treating the disorder. The objective of the present work is to question scientific literature about the relationship between schizophrenia and human evolution from a genetic point of view and to collect evidence toward or against the “price-to-pay hypothesis” of schizophrenia. Scientific literature from PubMed database has been questioned until July 2024. The inclusion criteria required publications to be in English and focused on the evolutionary genetics and/or epigenetics of schizophrenia. Initial screening based on the following keywords: “schizophren* AND evolution* AND gen*”. Because no publication of interest was found with these search terms, we enlarged the search to “schizophren* AND evolutio*”, “schizophren* AND selection”. 1838 and 13, 484 publications have been found with these queries, respectively. As different research domains emerged (human accelerated regions, segmental duplications, Neanderthal genome, Olduvai domain, ...), literature research within each domain was completed using the following specific search terms: “Human Accelerated Regions AND schizophren*”, “Segmental Duplications AND schizophren*”, “Olduvai AND schizophren*”, “Neanderthal AND

schizophren*", "introgress* AND schizophren*". References identified during the review of selected publications were also included if they met the inclusion criteria. In total, after careful review, 30 publications met the inclusion criteria and have been included.

Given the breadth and diversity of the publications, we decided to group them according to the topic and present the results as follows: First, we will consider studies comparing non-human and human genomes, leading to the identification of regions submitted to high evolutionary changes, such as human-accelerated regions, segmental duplications, and highly repetitive sequences. Then, we will go through a few studies trying to determine whether schizophrenia-associated variants have been submitted to positive or negative selection during human evolution, since their appearance on Earth hundreds of thousands of years ago.

Schizophrenia and evolutionary changes in the non-coding genome: Example of the Human Accelerated Regions (HARs).

Human Accelerated Regions (HARs) are segments of DNA which are conserved in vertebrates and showed accelerated substitution rates in humans [47]. Observed changes in HARs arose and became fixed in the human population since the human and chimpanzee lineages diverged [48]. HARs were first described in 2006 by Pollard and colleagues [49, 50]. They are mostly located in non-coding DNA [51] and near transcription factors genes [49] which may be coherent with the hypothesis of King and Wilson suggesting that differences between chimpanzees and humans could be explained by differential control of transcriptional networks [52]. The way HARs regulate gene expression is still under investigation, and it seems to be tissue specific [53, 54]; these regions are particularly involved in gene expression regulation during development [55].

Investigations have been conducted about the origin of HARs. HARs have likely been positively selected during evolution, even if evolutionary mechanisms leading to the appearance of HARs are not unique [47, 56, 57]. Among others, the phenomenon of the "enhancer hijacking¹" has recently been evocated [58]. Interestingly, when comparing modern humans and ancient hominins' genomes, Burbano and colleagues estimated that 8.3% of substitutions in HARs are not shared with Neanderthal or Denisovan [59]. Moreover, around 7% of human-chimpanzee differences in non-coding HARs occurred after divergence from archaic hominins around 500,000 years ago [51].

A recent review about HARs and their relationship with neurodevelopment, brain-related phenotypes, and psychiatric disorders has been published by Guardiola-Ripoll et Fatjo-Vilas in 2023 [60]. Authors proposed an integrated overview of connections between HARs, neurodevelopmental processes, human-specific brain phenotypes and cognition, and psychiatric diseases such as autism and schizophrenia [60]. Regarding schizophrenia, authors pointed out that first studies did not find evidence of an association between schizophrenia-associated-SNPs and HARs; these studies focuses either on specific HAR genes [61, 62] or they called in lack of power likely underlying negative results [63]. In 2015, an enrichment for schizophrenia-associated SNPs was found in primate HARs by [64]. Associations between HARs and schizophrenia-associated SNPs have also been described by

[65–68], Wei et al. [66, 67], and [68] basing on GWAS. Moreover, 4 SNPs located in HARs have been observed in two case-control Indian samples [69]. The following year, the same authors described associations between 15 HARs-located SNPs and cognition in patients with schizophrenia and controls [70].

Recent findings on HARs led scientists to affirm that changes in gene regulation, driven by the rapid evolution of non-coding regions, contribute to phenotypic differences between humans and nonhuman primates, despite the high similarity and constraints in protein-coding sequences. This supports a model suggesting that newly evolved biological mechanisms underlying human cerebral cortical evolution also heighten vulnerability to various neuropsychiatric and neurodevelopmental conditions [54].

Evolutionary driving forces such as Segmental duplication (SDs) show associations with schizophrenia.

Segmental duplications (SDs), also called Low Copy Repeats (LCRs), are regions of one to several hundred kilobases that exist in at least two copies in the haploid human genome and have a sequence identity higher than 90% [71]. SDs likely have arisen over the past 35 million years of evolution [72]. Many regions in the human genome harbor SDs [71] and a recent study estimated that they represented 7% of the human genome [73]. Cheng et al. estimated that 33% of SDs are not duplicated in chimpanzees and that genomic duplication occurred at a rate of 4–5 megabases per million years since divergence from chimpanzees [74]. Those expansion phenomena constitute a non-negligible difference between humans and great apes among euchromatic regions [75]. Therefore, SDs have been considered as candidates for adaptations during human evolution [75].

Studies provided evidence of an association between SDs, recurrent chromosomal structural rearrangements (microdeletions, microduplications), and genetic diseases, such as DiGeorge syndrome, a rare disease associated with schizophrenia [71]. The mechanism likely underlying SDs-associated structural rearrangements is genomic instability that could lead to unequal crossover and nonallelic homologous recombination during meiosis [71]. Dennis and colleagues identified 218 human-specific segmental duplications (HSDs) by analyzing 322 archaic and modern genomes [76]. They identified ten gene families associated with HSDs: *ARHGAP11B*, *SRGAP2C*, *BOLA2*, *CD8B*, *CFC1*, *FAM72*, *GPR89*, *GPRIN2*, *NPY4R*, and *TISP43* [76]. As previously observed, overlap between HSDs and known disease-implicated genomic hotspots such as autism, intellectual deficiency, schizophrenia, and epilepsy have been described [76]. More specifically, an overlap between HSDs and schizophrenia-associated CNVs has been reported for microdeletions at 1q21 [41, 77], 15p13.3 [41, 77, 78], and microduplication at 16p11.2 [41, 79, 80] by authors [76].

In conclusion, segmental duplications (SDs) represent a significant evolutionary feature in the human genome, contributing to genomic diversity and potential adaptations. These duplications also overlap with genomic hotspots linked to neuropsychiatric conditions, including schizophrenia. The connection between SDs and schizophrenia-associated CNVs suggests that genomic evolutionary changes may play a role in the development of

neuropsychiatric traits. Further research is needed to explore the precise mechanisms underlying these associations and to better understand how SDs might influence both human evolution and susceptibility to disorders like schizophrenia.

The most highly amplified coding sequence in the human genome has been associated with schizophrenia.

As we already mentioned, DNA amplifications occurred during the evolution of species. The Olduvai domain, previously called “DUF1220” (“Domain of Unknown Function-1220”), is the highest amplified coding sequence in human genome with around 300 copies in humans, 125 copies in primates, and 1–9 copies in other mammals [81, 82]. Notably, the estimation of the copy number of high repeated sequences is a challenge for bioinformatics [83] and more accurate methods have been developed [83–85].

The Olduvai domain has been identified in 2006 by Popesco et al. based on a genome-wide survey on gene copy number variations among human and great ape lineages [86, 87]. Olduvai sequences are mainly located within NBPF genes on chromosome 1 (particularly on 1q21.1–2) [81], a gene family who underwent recent expansion in primate genomes [88]. Each unit of the Olduvai domain consists of two exons and one intron coding for around 65 amino acids [87]. Six subtypes (“clades”) have been described for the Olduvai domain: three of them are “conserved” among species (CON1–3) and three are “human lineage specific” (HLS1–3) [81]. HLS1–3 are tandemly repeated one after another in a “triple pattern.” The “HLS *DUF1220* triplet” (around 4.7 kb) is composed of 6 introns and 6 exons, the intronic sequence accounting for 90% [81]. Moreover, HLS 1–3 are quite similar to one another [81]. Regarding the evolutionary history of the Olduvai domain, Fiddes et al. suggested that it evolved jointly with the NBPF and the NOTCH2L genes (located in the same regions) [89]. These sequences may act together in promoting neurogenesis and brain expansion in a “dosage-related manner” [89]. More detailed hypotheses on amplification mechanisms have been evoked and a *de novo* insertion (two new copies of HLS clade in the NBPF12 gene) has been described in a sample of 16 parent–child trios, suggesting that the mechanism driving the extreme human-specific expansion of Olduvai repeats remains highly active in the human genome [90].

Nowadays, the biological role of the Olduvai domain has not been clearly identified: it has been associated with increased neuronal proliferation, brain volume, and better cognitive performance [91–95]. The copy number of the Olduvai domain has been associated with symptoms severity in autism [91,96,97] and schizophrenia [98]. Particularly, an association between positive symptoms and decreased copy number (CON1 and HLS1 subtypes) has been observed in 609 schizophrenia patients, especially for adult-onset schizophrenia [98]. Conversely, an association between negative symptoms and increased copy number (CON1 subtype) has been described in males [98]. Globally, CON1 copy number in male individuals with predominantly positive symptoms were significantly lower than controls, autistic patients, and patients with mostly negative symptoms [98].

Based on these results, Sikela and Searles Quick suggested the existence of a genomic “trade-off” between the evolution of the

human brain and some psychiatric disorders such as autism and schizophrenia [29]. More specifically, the increase in Olduvai domain copy number would be beneficial in terms of cognitive functions but also associated with chromosomal instability and the apparition of microdeletions or microduplications [29]. These structural genetic variants could lead to the development of psychiatric diseases such as autism (microduplications) and schizophrenia (microdeletions) [29]. In addition, symptom severity would be correlated to variations in copy numbers [29].

The action of natural selection on schizophrenia-associated genetic variants is diverse and complex.

Moreover, signals of natural selection on schizophrenia-associated variants during human evolution have also been studied, particularly after the sequencing of ancient hominins' genomes at the beginning of the 21st century [99–103]. In fact, the alignment of ancient and modern human genomes allowed deeper knowledge into the evolution of the disease. Associations between Neanderthal introgression and a broad range of neurological and psychiatric phenotypes have been described [99, 102, 104, 105]; interestingly, schizophrenia-associated SNPs (rs16977195 and rs950169) and another genetic variant linked to antipsychotic drugs response (rs1459148) likely introgressed from Neanderthal [101, 106]. Moreover, a recent study on 41 complex traits and their heritability found both protective effect of Neanderthal introgressed variants on anorexia and schizophrenia and a depletion for heritability among them; these results would be consistent with the effect of negative selection on these variants [107]. Nonetheless, none of these studies addressed the question about schizophrenia specifically.

In the first decade of the 21st century, many studies aimed to assess the action of natural selection on genes associated with schizophrenia or schizophrenia-related biological pathways. Results suggested that positive selection could have favored alleles both increasing and decreasing the risk of having schizophrenia. For example, the ancestral allele of the MAOB (Monoamine Oxidase B) gene at rs5905512 showed signs of positive selection and has been associated with an increased risk of schizophrenia in males [108]; conversely, a polymorphism (rs6280) of a common protective haplotype in the *DRD3* (Dopamine D3 Receptor) gene, has likely been submitted to positive selection [109]. Moreover, recent alleles of four SNPs in the *GABRB2* gene (rs6556547, rs187269, rs1816071, and rs1816072) showed evidence of positive selection in humans compared to primates, more in controls than in schizophrenic patients [110]. In 2007, Crespi et al. looked for positive selection signal among 76 genes that had been associated with schizophrenia in association or family-based transmission-disequilibrium studies² [111]. They found that 14 genes had been submitted to positive selection in human population based on haplotype length; they also described more ancient positive selection (between primates and human) for other few genes through the estimation of the non-synonymous/synonymous substitution ratio [111]. In addition, no signal of positive selection has been detected for three brain-related and schizophrenia-associated genes (*DAOA*, *PPP1R1B*, and *APOLI*), whose possible rising in frequency could have been due to an overall selective advantage (hypothesis of the antagonistic pleiotropy) [112]. Major studies providing evidence for selection and genes associated with schizophrenia

have been collected by Crespi et al. [111]. More recently, evidence of negative selection of variants associated with lower tolerance to psychosocial stress and increased risk of schizophrenia has been provided for the promoter of the *ST8SIA2* gene [113]. Based on biological and clinical data, higher promoter activity of the *ST8SIA2* gene has been associated with increased risk of schizophrenia [114].

We will now briefly review results from studies about the action of selection on schizophrenia-associated common variants (SNPs), either through archaic genomes comparisons or other statistical methods to detect natural selection. More details can be found in Table 1. In 2016, Srinivasan and colleagues tried to determine whether schizophrenia risk alleles appeared in modern human genomes after the divergence from Neanderthal or if these variants were more ancient [115]. Authors based on the first complete sequencing of Neanderthal genome from Green et al. [99] who established a score, the “Neanderthal Selective Sweep” (NSS) score, by the alignment of modern human, Neanderthal, and primate reference sequences [115]. Every SNP was assigned a score (a z-score more or less its standard deviation) quantifying the abundance in ancestral/non-ancestral SNPs in Neanderthal and in modern human genomes, the primate sequence representing the ancestral variant [115]. NSS negative values indicated scarcity of non-ancestral alleles in Neanderthal compared with modern humans and therefore a likely recent appearance of the genetic variant and possible positive selection of the latter in modern humans (represented in the third line of Table 2) [115]. On the contrary, positive values of NSS indicated abundance in non-ancestral SNPs in Neanderthal compared to modern humans, suggesting an action of negative selection in modern humans (represented in the second line of Table 2) [115].

To select SNPs, authors referred to the GWAS study from the Psychiatric Genomics Consortium of 2014, including up to 36,989 cases and 113,075 controls and identifying 108 schizophrenia-associated SNPs. Results showed an enrichment for schizophrenia-associated SNPs among negative-NSS SNPs (“human divergent stratum”) [115, 122]. Significance was reached independently of the presence or absence of Major Histocompatibility Complex (MHC) genes in the analysis [115]. When considering only genes associated with brain-related functions or another Neanderthal genome sequencing [102], results did not change. Conversely, results were not significant regarding other phenotypes such as bipolar disorder and Alzheimer's disease [115]. Underpowered GWAS studies were evoked by authors as one possible cause of lack of significance regarding the latter analyses. Authors concluded that schizophrenia likely appeared recently during human evolution, due to the enrichment for schizophrenia-associated SNPs among non-ancestral SNPs [115]. Moreover, 27 genomic loci associated with negative-NSS SNPs were identified; interestingly, some of the genes harbored in these loci are related to schizophrenia (SNPs located in following genes: *NRG3*, *NRXN1*, *VRK2*, and *ZNF804A*), autism, bipolar disorder, intellectual deficiency, and depression [115].

Two years later, Pardinás et al. published a new GWAS identifying 145 schizophrenia-associated SNPs in 11,260 cases and 24,542 controls [116]. Authors also found that loss-of-function (LoF) intolerant genes were enriched for schizophrenia-associated

SNPs [116]. This association was robust to the inclusion of brain-associated genes as covariate [116]. Interestingly, authors reminded that GWAS often found enrichment for disease-associated SNPs in LoF-intolerant genes and that LoF genes are submitted to high selection pressure [116]. Moreover, schizophrenia SNPs-based heritability was enriched in SNPs under background selection and depleted in SNPs under positive selection [116]. Finally, SNPs in LoF genes account for around 30% of schizophrenia SNPs-based heritability [116]. According to Pardinás and colleagues, the fact that schizophrenia variants continue to persist at common allele frequencies even if mapping to LoF-intolerant genes could be partially explained by background selection [116]. Indeed, previous works showed that when selection eliminates deleterious variants in regions of low recombination rates, haplotypes are removed from the gene pool and genetic diversity decreases, leading alleles with small deleterious effect (schizophrenia-associated variants, for example) rise in frequency [123–125]: this phenomenon is called “background selection.” Moreover, genomic architecture of complex human traits could be compatible with background selection [126] and an enrichment for loci submitted to this selection and for LoF-intolerant regions has been described in SNPs-heritability in schizophrenia and other brain-related traits [127]. Therefore, according to authors, the persistence of schizophrenia-associated deleterious variants in modern humans could derive from the action of negative selection on deleterious variants located in regions of low recombination rates, thus leading to the background selection phenomenon, and ultimately to the maintenance of schizophrenia-risk SNPs [116]. This would be consistent with the evidence of the action of negative selection on the genetic architecture of complex traits [128, 129]. In addition, Neanderthal introgression for schizophrenia variants did not reach significance in the study [116]. Interestingly, many statistical methods have been used by authors: B-statistics has been used to detect background selection, CLR, CMS, XP-EHH, and iHS to investigate positive selection and LA (average posterior probability) to estimate Neanderthal introgression [116]. Therefore, these methods aiming to detect intra species evolution are not taking Neanderthal into account [30] and Neanderthal introgression has been identified through a probabilistic technique [116, 117], differently from Srinivasan et al. [115]. Finally, B-statistics relies on the comparison between human and primate genomes to detect reduction in genetic diversity in the former [116, 130].

More recently, based on Pardinás et al.'s results being in favor of an action of negative selection on schizophrenia-associated variants, Liu and colleagues tested the hypothesis of negative selection operating on schizophrenia risk alleles during human evolution [118]. To “track” the history of genetic variants, authors identified modern and archaic-human-specific sites (called “MD” and “AD”, respectively), based on Neanderthal and Denisovan genomes available on the Max Planck Institute's Evolutionary Anthropology website [118]. Archaic human specific sites (AR) are shared by chimpanzees and modern humans but not by Denisovan or Neanderthal; conversely, modern human-specific sites (MD) can be found only in modern humans and not in Neanderthal, Denisovan, or chimpanzees. No enrichment for MD nor for AR was found among schizophrenia-associated SNPs [118]. On the contrary, an enrichment for schizophrenia-associated SNPs was found in AM and an enrichment for protective SNPs was observed

TABLE 1 | Studies looking for signals of selection on schizophrenia during human evolution.

Reference	Methodology	Phenotype	Results
[115]	<ul style="list-style-type: none"> – Enrichment analysis for schizophrenia-SNPs in negative and positive NSS-SNPs^a – The Neanderthal selective sweep (NSS) score is based on [99, 102] – The NSS estimates the divergence between modern humans and Neanderthal respective to chimpanzees – Enrichment analysis for schizophrenia-SNPs in LoF genes – Background selection measured through B-statistics. – Positive selection measured through: CLR, CMS, XP-EHH, and iHS – Neanderthal introgression estimated using the “average posterior probability” (L/A), a probabilistic method based on Conditional Random Fields [117] 	<p>GWAS (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014): 36989 cases and 113,075 controls, 108 schizophrenia-associated SNPs</p> <p>GWAS [116]: 11260 cases and 24,542 controls, 145 SNPs identified through GWAS and GWAS metaanalysis [116]</p>	<ul style="list-style-type: none"> – Negative-NSS SNPs are enriched for schizophrenia-associated SNPs <p>INTERPRETATION: Schizophrenia-associated SNPs have been submitted to positive selection in modern humans /appeared recently during evolution</p> <ul style="list-style-type: none"> – Loss-of-Function genes are enriched for schizophrenia-associated SNPs – Schizophrenia SNPs-based heritability is enriched in SNPs under background selection – Schizophrenia SNPs-based heritability is depleted in SNPs under positive selection – SNPs in LoF genes account for around 30% of schizophrenia SNPs-based heritability – No evidence of Neanderthal introgression nor positive selection in schizophrenia-associated SNPs <p>INTERPRETATION: Background selection could explain the persistence of schizophrenia-SNPs despite they are in LoF genes (genes submitted to high selection pressure). In fact, background selection could explain the rise in frequency of alleles with small deleterious effect due to the action of selection on regions of low recombination rates</p> <ul style="list-style-type: none"> – AD sites are enriched for schizophrenia-associated SNPs – MD sites are enriched for schizophrenia-protective SNPs – Schizophrenia-associated SNPs are not enriched for MD nor AD sites <p>INTERPRETATION: Schizophrenia-associated SNPs appeared before the divergence of modern humans from Neanderthal. These variants have been submitted to negative selection then</p>
[118]	<ul style="list-style-type: none"> – Enrichment analysis for schizophrenia-SNPs in modern (MD) and ancient-human (AD) specific sites – Enrichment analysis for MD and AD sites in schizophrenia-SNPs – MD and AD sites have been determined according to hominins’ genomic sequences (Neanderthal and Denisovan) from the Max Planck Institute’s Evolutionary Anthropology website^b – MD sites: Present only in modern humans, not in Neanderthal, Denisovan nor in chimpanzees – AD: Present in modern humans and chimpanzees, not in Neanderthal nor Denisovan 	<p>GWAS (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014): 34241 cases and 45,604 controls</p>	<ul style="list-style-type: none"> – AD sites are enriched for schizophrenia-associated SNPs – MD sites are enriched for schizophrenia-protective SNPs – Schizophrenia-associated SNPs are not enriched for MD nor AD sites <p>INTERPRETATION: Schizophrenia-associated SNPs appeared before the divergence of modern humans from Neanderthal. These variants have been submitted to negative selection then</p>

(Continues)

TABLE 1 | (Continued)

Reference	Methodology	Phenotype	Results
[119]	<ul style="list-style-type: none"> – Positive selection: Bayesian conjugate beta-binomial analysis based on high-frequency derived alleles, reduction in genetic diversity, long haplotypes, and differences between populations (Wang et al. 2016)^c 	<p>Randomly selected schizophrenia-associated SNPs from GWAS (Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2014 and [116]).</p>	<ul style="list-style-type: none"> – No evidence of widespread positive selection of schizophrenia-associated SNPs (10 SNPs out of 105 are submitted to positive selection); 5 SNPs out of 10 submitted to positive are protective against the disease <p>INTERPRETATION: Little support in favor of positive selection of schizophrenia-associated SNPs</p>
[120]	<ul style="list-style-type: none"> – Neanderthal introgression estimated through the NeanderScore (enhanced D-statistic based on [102]) 	<p>Three different studies:</p> <ul style="list-style-type: none"> – 3837 schizophrenic patients and 5525 controls – 49 unmedicated patients – 172 healthy individuals—FDOPA PET scanning 	<ul style="list-style-type: none"> – Lower Neanderthal introgression in cases than in controls – Negative correlation between Neanderthal introgression and positive symptoms severity – Negative correlation between Neanderthal introgression and dopamine synthesis capacity in the pons and striatum. <p>INTERPRETATION: Schizophrenia may be a modern human-specific condition</p>
[121]	<ul style="list-style-type: none"> – Differences in the population structure between East Asians and Europeans: F-statistics (Weir et al. 1984)^d – Positive selection measured through: XP-EHH, and iHS – Neanderthal introgression inferred using gArchaicSeeker 2.0 (Yuan et al. 2021)^e 	<ul style="list-style-type: none"> – 1007 unrelated individuals from the 1000 Genomes Project Phase III (5 European populations and 5 East Asians populations) – high-coverage genomes of Altai Neanderthal and 8872 worldwide Neolithic-to-Paleolithic ancient human genomes – 3987 schizophrenia-associated SNPs from the GWAS Catalog 	<ul style="list-style-type: none"> – Stronger selection signals on the schizophrenia-associated genes in East Asians than in Europeans. – Differential natural selection on some schizophrenia-associated genes between Europeans and East Asians. – Different impact of the Altai Neanderthal introgression on schizophrenia risk between Europeans and East Asians. <p>INTERPRETATION: The action of natural selection on schizophrenia-associated genetic variants differs according to ancestry. These differences may be due to the selection of adaptive variants in response to the local environment.</p>

^a<http://genome.ucsc.edu>.

^b<http://cdna.eva.mpg.de/neanderthal/>.

^cWang G, Speakman JR. 2016. Analysis of Positive Selection at Single Nucleotide Polymorphisms Associated with Body Mass Index Does Not Support the “Thrifty Gene” Hypothesis. *Cell Metabolism* 24: 531–541.

^dWeir BS, Cockerham CC. 1984. ESTIMATING F-STATISTICS FOR THE ANALYSIS OF POPULATION STRUCTURE. *Evolution* 38: 1358–1370.

^eYuan K, Ni X, Liu C, Pan Y, Deng L, Zhang R, Gao Y, Ge X, Liu J, Ma X, et al. 2021. Refining models of archaic admixture in Eurasia with ArchaicSeeker 2.0. *Nat Commun* 12: 6232.

TABLE 2 | Schematic illustration of the interpretation of the Neanderthal Selective Sweep score.

Primate (Ancestral variant)	Neanderthal	Modern humans	Interpretation
A	A	A	No differences between Neanderthal and modern humans
A	B	A	Non-ancestral alleles in Neanderthal Positive NSS score Negative selection of non-ancestral variant in modern humans
A	A	B	Ancestral alleles in Neanderthal (scarcity of non-ancestral alleles) Negative NSS score Positive selection of non-ancestral variant in modern humans Human divergent stratum
A	B	B	No differences between Neanderthal and modern humans

in MD, suggesting that negative selection may operate on schizophrenia risk alleles [118]. Moreover, authors proposed an explicative framework about origins of schizophrenia: brain evolution led to the accumulation of deleterious variants being submitted to purifying selection starting from a certain time in the past [118]. This “turning point” could be likely situated before the Out-Of-Africa phenomenon.³ Therefore, when Sapiens met Neanderthal in Eurasia, schizophrenia-associated deleterious variants were already submitted to negative selection [118]. This framework is just a hypothesis, and it is incomplete due to lack of knowledge about ancient population demography and genetics [118].

Similarly, Yao and colleagues found no widespread positive selection signatures among common schizophrenia-associated variants. Schizophrenia-associated SNPs were randomly selected from the partially overlapped results from two different GWAS [116, 122] and positive selection was estimated through a probabilistic method, the Bayesian conjugate beta-binomial analysis. Authors did not find signals of widespread positive

selection of deleterious variants; conversely, signals of positive selection of protective variants were found [119].

More recently, associations between Neanderthal scores, positive symptoms, and dopamine-synthesis capacity have been described by Gregory and colleagues [120]. Neanderthal introgression was estimated through “enhanced D-statistic” (the NeanderScore metric) for each patient and each SNPs [120]. The NeanderScore has previously been shown to have a linear relationship with the amount of Neanderthal ancestry in an individual [120, 131]. Lower Neanderthal scores have been found in schizophrenia (3837 cases compared to 5525 controls), indicating less introgression in affected individuals than healthy ones [120]. Moreover, in 49 unmedicated inpatients, a negative correlation between positive symptoms severity and Neanderthal scores was described. Lastly, higher Neanderthal introgression was associated with lower dopamine synthesis capacity in 172 healthy individuals, dopamine synthesis being measured through 18F-fluorodopa PET scanning [120].

The action of natural selection on schizophrenia-associated SNPs across ancestries was recently studied using the genomes of individuals of European and East Asian origin [121]. The results suggested stronger selection signals on schizophrenia-associated genes in East Asians than in Europeans and differential natural selection on some schizophrenia-associated genes between these populations. Additionally, Neanderthal-introgressed variants showed a protective role in Europeans but a deleterious role in East Asians. For example, haplotypes in a region of around 150 kb at 1q21.2 were likely inherited from Altai Neanderthal introgression in Europeans, and the archaic allele was in high linkage disequilibrium with the schizophrenia protective rs140505938 allele. Conversely, the non-ancestral allele showed signals of positive selection in East Asians. In addition, the region at 3p21.31 contained Altai Neanderthal-like adaptive haplotypes specifically among East Asians. These haplotypes carried a schizophrenia risk allele that was rare among Europeans. The reason for this phenomenon of positive selection in the East Asian population could have been due to an adaptive role of these haplotypes to the local environment, such as latitude-dependent ultraviolet-B irradiation [121,132].

In summary, there is no clear evidence supporting positive selection on schizophrenia-associated variants, but stronger evidence exists for negative selection. The role of Neanderthal introgression in schizophrenia risk remains unclear, with data suggesting both possibilities, particularly when considering different ancestries.

3 | Differentially Methylated Regions Suggest a Recent Origin of Schizophrenia

Epigenetic differences between modern humans and archaic hominins have also been investigated and evidence is in favor of evolutionary changes in methylation patterns during evolution [133]. Banerjee and colleagues found enrichment for schizophrenia-associated SNPs in human differentially methylated regions (DMRs), but not in Neanderthal or Denisovan DMRs [134]. Authors affirm that the enrichment seen in

human DMRs is comparable to that of genomic regions tagged by NSS markers and stronger than that for HARs [134]. The following year, authors compared human and great ape methylation patterns. They found that regions that are hypomethylated in humans compared to great apes show an enriched association with schizophrenia, but only when the Major Histocompatibility Complex (MHC) region is included. When the MHC region is excluded from the analysis, only a modest enrichment for low-effect SNPs remains [135]. Authors then suggest that schizophrenia appeared more recently in human evolution due to lower differences between humans and great apes compared to differences between modern humans and archaic hominins [135]. Moreover, evidence about the potential link between evolutionary constraints (purifying selection) and schizophrenia has been provided by the analysis of gene and enhancers expression alteration in post-mortem brain specimens from schizophrenic patients [136]. In conclusion, while epigenetic studies exploring the relationship between schizophrenia and evolution remain limited, existing research points to a recent origin for the disorder, particularly through the identification of DMRs.

4 | The Evolutionary Paradox of Schizophrenia in Light of Recent Findings in Genomics

The study of evolutionary genetics in schizophrenia offers valuable insights into the complex relationship between this disorder and human evolution. The discovery of common genetic variants associated with schizophrenia, some of which have ancient origins, along with evidence of selective pressures acting upon them, such as background selection, supports the mutation–selection balance theory [27]. The resulting phenotype is shaped by the action of selection on multiple genetic variants. Given the high number of variants involved, it is unlikely that the disease will ever be eradicated from the population. The cliff-edge theory is also consistent with these findings [28], suggesting that schizophrenia represents one extreme of a spectrum corresponding to varying genetic loads. Similar to the mutation–selection balance theory, the polygenic nature of schizophrenia makes its elimination unlikely.

Furthermore, discoveries about Human Accelerated Regions (HARs) support the “price-to-pay” hypothesis, which suggests that while high brain complexity is advantageous, it also increases vulnerability to damage [16–23]. Some schizophrenia-associated genetic variants are located within HARs, regions relevant to vertebrates and involved in gene regulation processes linked to neurodevelopment, human-specific brain phenotypes, and cognition. The Olduvai domain and segmental duplications (SDs) also support the “price-to-pay” hypothesis. Genetic redundancy arising from random duplication events can lead to the emergence of new sequences or genes with potentially beneficial functions. However, repeated regions increase the probability of non-allelic homologous recombination, resulting in deletions or duplications. These genetic variants, known as copy number variants (CNVs), are less common but have been associated with schizophrenia. Additionally, epigenetic studies, though limited, tend to support a recent emergence of schizophrenia, aligning with the

hypothesis that the disorder is linked to recent advancements in human brain development.

It would also be challenging to either refute or confirm the hypothesis of genetic advantages associated with the disease. Indeed, more information on phenotype and past environments would be needed to gather additional evidence for the evolutionary mismatch hypothesis [14]. Regarding the suggestion of a contemporary advantage associated with schizophrenia, epidemiological data do not seem to support this notion [5–8].

Finally, Adriaens’ theory [26] of an infectious origin for schizophrenia is not widely supported by genetic data, which primarily implicates genetic sequences unrelated to infectious agents. While this hypothesis cannot be definitively ruled out, current evidence favors primarily genetic etiology. Moreover, Shaner’s suggestion [23] that schizophrenia may indicate low fitness aligns with the broader understanding of the disorder’s negative impact on individual health and reproductive success. However, it remains difficult to definitively support this idea using genetic findings.

5 | Conclusion

Genetics has interrogated the evolutionary paradox of schizophrenia, trying to understand if and to what extent schizophrenia is associated with human evolution. Genetic markers of evolution have been identified through comparative studies based on human and non-human genomes, such as HARs and SDs; their relationship with schizophrenia has been investigated and literature on the subject is steadily increasing. Moreover, recent advances in paleogenomics led to deeper insights into the evolution of the human genome and the emergence of schizophrenia, through the comparison between archaic hominins and modern humans’ genomes and the study of archaic introgression. An even more recent action of selection on schizophrenia-associated variants has also been investigated using different statistical methods applied to genomes from different populations of the *Sapiens* species. Literature is still relatively scarce and results in non-immediate interpretation, probably because of methodological differences, ongoing improvements in archaic genomes sequencing and heterogeneity among ancestral populations, such as more Denisovan introgression in Asians than in Europeans. Globally, schizophrenia seems to be genetically linked to human brain evolution as the “price-to-pay” hypothesis suggested around thirty years ago and would be a *Sapiens*-specific condition. We could then assume that rapid changes in brain-related genes allowed the emergence of new skills such as abstraction, language, and social communication. Such a great number of “attempts” has been mostly observed in brain-related genes and has been relatively well supported during evolution. Because of the relatively limited number of genes and the large number of brain connections and functions, some mutations could have had a deleterious effect on phenotype, leading to the apparition of hallucinations, delusions, and loss of the coherence of thought. Higher complexity could then have increased the risk of possible mistakes and dysfunctions. In addition, no clear signal of positive selection has been detected on schizophrenia-associated variants. On the contrary, natural selection would likely have acted against these alleles or even more deleterious ones, thus leading the formers to rise in frequency due to

background selection. In light of these findings, we propose a more dynamic conceptualization of the evolutionary paradox of schizophrenia, one that incorporates the fluidity of environmental and social pressures, the complexity of human brain architecture and its genetics, and the multifaceted actions of selection. This framework views schizophrenia not simply as an evolutionary anomaly or a “price-to-pay” but as the result of a complex interplay between genetic mutations, brain and behavioral complexity, and shifting environmental contexts. By recognizing the polygenic nature of schizophrenia, its relationship to evolutionary mismatching, and the role of selection, we gain a deeper understanding of how schizophrenia may have emerged as a consequence of human cognitive and social evolution, with both adaptive and maladaptive features. Furthermore, studying the evolutionary genetics of schizophrenia offers an invaluable tool for identifying genomic regions associated with the disorder. These insights can advance our understanding of the biological underpinnings of schizophrenia, providing avenues for research and therapeutic strategies that remain relevant regardless of the broader theoretical framework.

Acknowledgments

Veronica Sandroni received a grant from the ARS Ile de France (Année Recherche) and from the Congrès Français de Psychiatrie. This work was supported by a Young Researcher grant (ANR JCJC ANR-22-CE16-0029), by a grant from Inserm and the French Ministry of Health (Inserm-AAP Messidore2022-N°9), and by a French government grant managed by the Agence Nationale de la Recherche under the France 2030 program, reference ANR-22-EXPR0013.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Endnotes

¹The action of an enhancer on a new target-gene is called “enhancer hijacking”.

²Family-based transmission-disequilibrium studies aim to identify alleles that are transmitted from parents to the affected offspring.

³Out-of-Africa event: Sapiens out-of-Africa dispersal.

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