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Systematic Review

DRD2/ANKK1 TaqIA Genetic Variant and Major Depressive Disorder: A Systematic Review

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Abstract: Background: Major depressive disorder (MDD) is a disease that has been increasingly affecting more people worldwide. The dopamine D2 receptor (DRD2), encoded by the DRD2 gene, plays critical roles in the brain, one of which is related to reward processes. Aims: The following systematic review aims to analyze the *DRD2/ANKK1 TaqIA* (rs1800497) polymorphism's A1 genotype frequency fluctuation in MDD patients and determine its influence on MDD. Methods: Four databases were searched, and the consequent articles were analyzed following the inclusion criteria per the PECOS strategy, resulting in five selected articles. Results: Interestingly, although two articles showed that the A1 allele presence significantly increases the risk of MDD manifestation, most articles did not find a significant association between this DRD2 gene variant and MDD. Conclusions: Most of the included studies were dated, indicating the need for more studies to address the results' non-conformity with different populations.

Keywords: DRD2; ANKK1; major depressive disorder; DRD2TaqIA; rs1800497; genetic polymorphism

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1. Introduction

Major depressive disorder (MDD) has become one of the most worrying diseases in the world, affecting about 350 million people [1]. Without taking COVID-19 into account, the World Health Organization (WHO) predicts that major depressive disorder (MDD) will be the foremost cause of global disease burden by 2030 [2].

The intensity of MDD symptoms can be debilitating and produce clinically significant distress (DSM-5). The onset of symptoms such as depressed mood, lack of concentration, feelings of worthlessness, and suicidal ideation characterizes a depressive episode [3]. On the other hand, MDD is diagnosed when at least five of the following symptoms persist for two weeks or more: those from depressive episode symptoms, decreased interest or pleasure, weight changes, altered appetite, slowed thinking, reduced physical movement, fatigue, excessive guilt, and recurrent thoughts of death [3–5].

MDD etiology and pathogenesis are complex and multifaceted, involving a combination of factors that later feed on each other, such as the person's genetic composition and physiological state, the environmental context, culture, and demographic factors, which could influence their psychosocial state and genes' expression through epigenetic changes [4,6].

Many interrelated theories, often focused on biological, psychological, and social factors, attempt to explain the causes and mechanisms behind this disease onset. Nonetheless, MDD pathogenesis is likely a combination of these theories (Biopsychosocial Model). For instance, the neurochemical theory (monoamine hypothesis) suggests that concentration imbalances in neurotransmitters such as serotonin, norepinephrine, and dopamine

affect neural functions, which in turn might cause depression. Most antidepressant treatments aim to correct these imbalances. Therefore, alterations in these neurotransmitters and their receptor genes, be they due to variants or epigenetic anomalies, could genetically predispose an individual to develop MDD (genetic theory or genetic and epigenetic anomaly hypothesis) [6].

Dopamine is a neurotransmitter and catecholamine modulator whose action occurs through binding to its receptors (DRD1 to DRD5). The dopaminergic systems are responsible for various functions and neural actions, among them motivation, motor control, maternal and reproductive behavior, reward, and cognition [7]. Dysfunctions in the dopaminergic system impair its stimulation of motivational arousal and the reward cycle. Without these functions, anhedonia occurs—one of the main symptoms of depression [8].

The dopamine D2 receptor (DRD2) is encoded by the DRD2 gene located on chromosome 11q22-23 [9] and plays a vital role in reward processes, being present in the brain's dopamine neurons' pre- and postsynaptic areas [10,11], having also been linked together with catechol-O-methyltransferase (COMT) to facilitate executive functions required for goal-directed behavior [12]. Because of this, this receptor is the main target of antipsychotics [9]. Although the *DRD2* gene's expression is known to be epigenetically modulated and thus partly connected to environmental factors [13–16], polymorphisms in this gene have been strongly implicated in various psychiatric and neurologic disorders, especially the TaqIA variant's A1 allele, which has been related to depression, post-traumatic stress disorder, substance abuse, and schizophrenia [17].

The TaqIA single nucleotide polymorphism (SNP), also known as DRD2/ANKK1 rs1800497 (C/T, Glu713Lys), is one of the main genetic mutations related to the DRD2 gene and its expression that plays a crucial role in the brain's dopaminergic activities [12,18] and has been associated with motor dysfunctions (movement disorders) such as dyskinesia [19]. Located ∼10 kb downstream from the DRD2 gene's termination codon within the exon 8 of the ankyrin repeat and kinase domain containing 1 (ANKK1) gene [15,20], this genetic variant exchanges a cytosine (C) for a thymine (T), which mutates allele A2 to A1 [17]. The A1 allele is known to reduce dopamine receptor bioavailability—A1 allele carriers, compared to homozygous A2 allele carriers, have a 30–40% reduction in d DRD2 density, particularly prominent in ventral parts of brain's caudate nucleus and putamen [12] and, consequently, lower dopaminergic signals, which ends up impairing the dopamine-related reward system [18,21].

This systematic review analyzed the DRD2/ANKK1 TaqIA (rs1800497) SNP's effect on major depressive disorder and its clinical characteristics and evaluated its genotype frequency variation in MDD patients from different populations.

2. Materials and Methods

2.1. Search Strategy and Criteria for Articles' Inclusion and Exclusion

Registered in the Prospective of Systematic Reviews (PROSPERO) on 23 April 2022, under CRD42022320150, this systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, intended to assist in writing systematic reviews and meta-analyses.

The article inclusion criteria followed the PECOS strategy: (1) population, (2) exposure, (3) comparator, (4) outcome (outcome), and (5) study type. It involved (1) research participants with MDD; (2) DRD2 TaqIA (rs1800497) single nucleotide polymorphism (SNP); (3) TaqIA SNP's A1/A1 (TT) genotypic, A1 (T) allelic, or both frequency; (4) A1/A1 (TT) genotypic, A1 (T) allelic, or both frequency fluctuation in different populations; and (5) observational and interventional studies.

For this, we included full-text original articles with their complete laboratory and statistical techniques that addressed MDD in association with the *TaqIA* SNP in clinical observational/interventional studies. Studies in all languages were included in the search unfiltered by year of publication. However, studies were excluded if they were dupli-

cates; focused on pathologies other than MDD; had incomplete laboratory or statistical procedures; had incomplete data; or were congress abstracts, meta-analyses, or reviews.

The search was conducted in March 2023 in the following databases: Virtual Health Library (BVS), Pub Med, Web of Science, and Scopus. The indexed terms (descriptors) used and their Boolean operators were (Depressive disorder, major) AND (DRD2 OR ANKK1 OR rs1800497). The term "Depressive disorder, major" was based on "Medical Subject Headings" (MeSH), while the terms "ANKK1," "DRD2," and "rs1800497" were taken from the "Allele Frequency Database" (ALFRED), which provides information on DNA variants' allele frequency in defined populations, i.e., polymorphisms [22].

2.2. Article Selection

Two reviewers (IP and BR) first analyzed the articles' abstracts and titles to determine their eligibility according to the PECOS inclusion criteria using the Rayyan tool developed by the Qatar Computing Research Institute (QCRI). Then, they evaluated the full texts of previously selected articles. Restricted access articles were obtained through the Periodicos CAPES Portal, in CAFe access, using the University of Brasília's institutional access. A third reviewer (CF) evaluated the articles in case of disagreement between the reviewers.

The data from the selected studies were compiled in a table created in the Microsoft Office Excel version 2010 platform. The types of information used were authors, title, year of publication, country of study, objective, sample number, results, laboratorial test, *p*-value, and genotypic/allelic frequency.

2.3. Risk of Article Bias

Genetic risk prediction studies try to predict disease risk, prognostic outcome, treatment response, or treatment-related harms by examining genetic variants or analyzing genetic and environmental risk factors. Hence, the Genetic Risk Prediction Studies (GRIPS) guideline was employed to assess the risk of bias in the selected studies and verify their quality and completeness [23]. Twenty of the twenty-five GRIPS items—the ones that evaluated the article's methods, results, discussion, and conclusion—were considered to assess the quality of this review's selected articles. An article was classified as of good quality when it presented 75% (15) of the evaluated items. Two reviewers (IP and BR) independently evaluated each article selected using the GRIPS guideline, and, in case of disagreement, a third reviewer (CF) was consulted.

3. Results

3.1. Articles' Search and Selection

First, 266 articles were identified using the chosen descriptors after searching four databases. Excluding duplicates, 130 articles remained. Of these, seven were selected for full-text analysis per the PECOS strategy's inclusion and exclusion criteria, leaving only five articles eligible for this systematic review (Figure 1). Of the five selected articles, 40% (2) are from the American continent, 40% (2) are from the European continent, and the remaining 20% (1) is from the Asian continent.

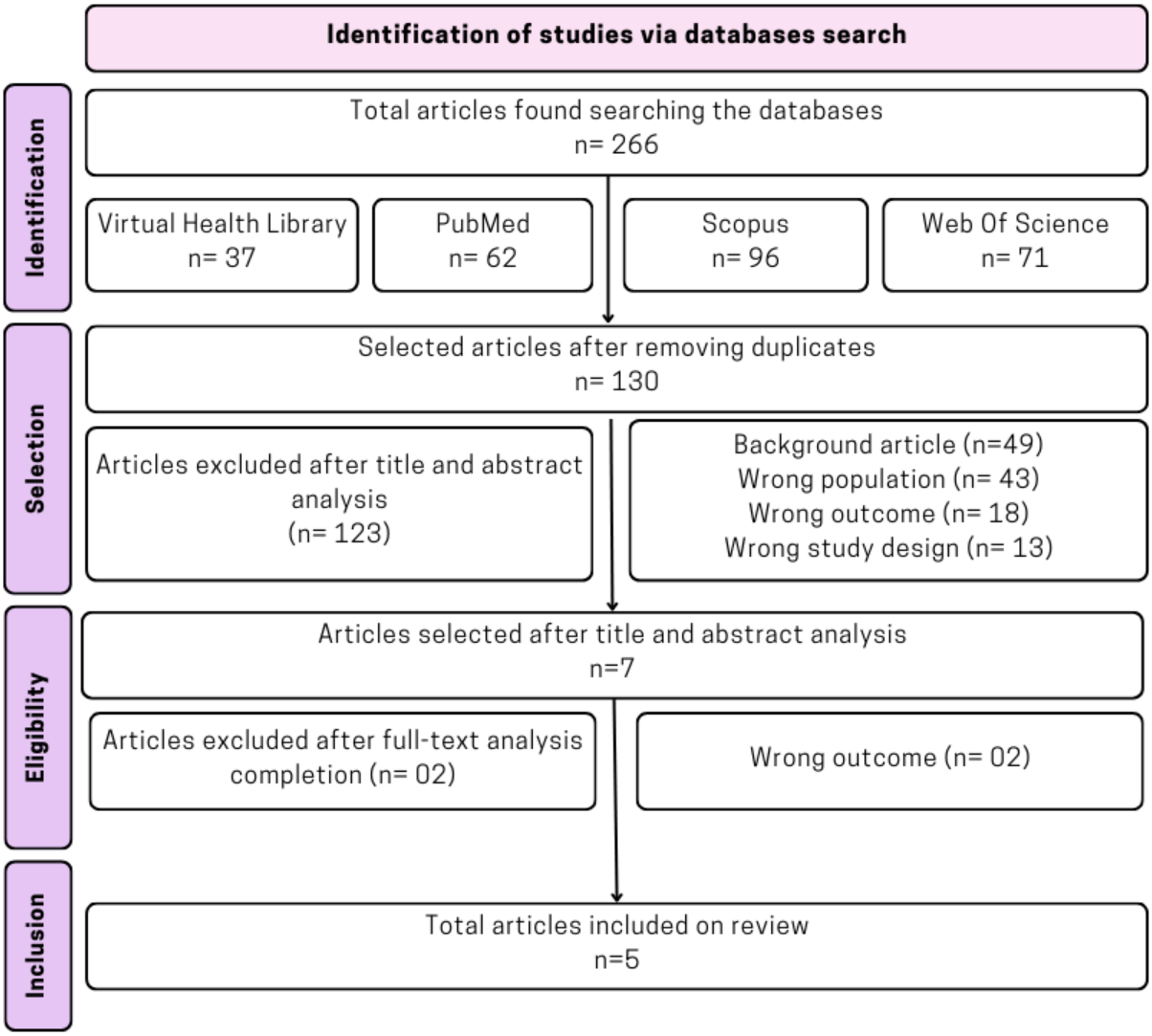

Figure 1. Bibliographic search flowchart.

3.2. Selected Studies' General Characteristics

Table 1 compiles the data extracted from the selected articles. Only two articles found a statistically significant association between the DRD2 TaqIA (rs1800497) SNP and MDD, and the A1 allele varied significantly among sampled populations (Table 1).

Figure 2 presents DRD2/ANKK1 TaqIA SNP's genotype frequencies from the selected articles (Table 1), although two of these articles were not included in the figure as they did not present genotype frequencies, only allelic frequencies. The Rafikova et al. article from Russia presented three genotype frequencies for patients with depressive episodes, recurrent depressive episodes, and a mixture of anxiety and depression (see Table 1). Figure 2 only presents the genotype frequency referring to recurrent depressive disorder, which was chosen as the sample group and was similar to symptoms and duration of other groups' studies. In summary, the frequencies vary depending on the study and country.

Table 1. Selected articles related to the DRD2/ANKK1 TaqIA (rs1800497) single nucleotide polymorphism (SNP) and major depressive disorder (MDD).

Author	Year	Title	Country	Objective	Sample (*n*)	Results	Laboratorial Test	*p*-Value	Genotypic/ Allelic Frequency
Rafikova et al. [24]	2020	Influence of Polymorphic Gene Variants of the Dopaminergic System on the Risk of Disorders with Depressive Symptoms	Russia	Locate genetic risk factors for individuals diagnosed with a depressive episode, recurrent depression, and anxiety and depressive disorder.	DE *: *n* = 108 RD *: *n* = 149 MADD * *n* = 100 Control group: *n* = 163	There was no statistical difference in the *DRD2* rs1800497 SNP's allelic and genotypic distributions and the risk of manifesting disorders with depressive symptoms.	PCR *; Electrophoresis andenzymatic digestion by TaqI.	G *: 0.644 A *:0.432	DE: A2/A2: 72 (66.7%) A1/A2: 34 (31.5%) A1/A1: 02 (1.9%) A1 allele: 38 (17.6) A2 allele: 178 (82.4%) RD: A2/A2: 96 (64.4%) A1/A2: 45 (30.2%) A1/A1: 08 (5.4%) A1 allele: 61 (20.5%) A2 allele: 237 (79.5%) MADD: A2/A2: 64 (64%) A1/A2: 33 (33%) A1/A1: 03 (3.1%) A1 allele: 39 (19.5%) A2 allele: 161 (80.5%) Control group: A2/A2: 95 (58.3%) A1/A2: 63 (38.6%) A1/A1: 05 (3.1%) A1 allele: 7 (22.4%) A2 allele: 253 (77.6%)
He et al. [25]	2013	Genetic distribution and association analysis of *DRD2* gene polymorphisms with major depressive disorder in the Chinese Han population	China	Screen and analyze the *DRD2* gene's TaqIA, C957T, and -141C polymorphisms among the Chinese population and their association with MDD.	MDD * group: *n* = 114 Control group: *n* = 224	No evidence that the *DRD2* gene's TaqIA SNP * is associated with major depressive disorder was found.	PCR; Electrophoresis and enzymatic digestion by TaqI.	0.200	MDD group: A2/A2: 14 (12.2%) A1/A2: 50 (43.9%) A1/A1: 50 (43.9%) A1 allele: 66 (66%) A2 allele: 34 (34%) Control group: A2/A2: 28 (12.5%) A1/A2: 114 (50.9%) A1/A1: 82 (36.6%) A1 allele: 62 (62%) A2 allele: 38 (38%)
Savitz et al. [26]	2013	*DRD2/ANKK1* TaqIA polymorphism (rs1800497) has opposing effects on D2/3 receptor binding in healthy controls and patients with major depressive disorder.	United States	Investigate the TaqIA polymorphism effect on the dopamine D2 receptor in healthy controls and MDD patients during dopamine release.	MDD group: *n* = 12 Control group: *n* = 24	MDD patients with the A1 allele had increased BPND, while controls with the A1 allele had reduced BPND.	PCR; Electrophoresis and enzymatic digestion by TaqI.	MDD group: 0.033 Control group: 0.009	MDD group: A2/A2: 05 (41.7%) A1/A2: 06 (50.0%) A1/A1: 01 (8.3%) Control group: A2/A2: 14 (53.8%) A1/A2: 10 (38.5%) A1/A1: 02 (7.7%)
Vaske et al. [27]	2008	The interaction of DRD2 and violent victimization on depression: An analysis by gender and race	United States	Analyze whether the relationships between DRD2, violent victimization, and depression statistically differ between men and women.	2380 participants	Although no statistical difference was found between the male and female groups, statistical significance existed between the TaqIA SNP and depressive symptoms in the male group.	PCR; Electrophoresis and enzymatic digestion by TaqI.	Male × female = 0.968 TaqIA male group × depressive symptoms = 0.005	A1 allele mean: Total = 0.532 ± 0.63 F * = 0.532 ± 0.63 M * = 0.532 ± 0.63
Kõks et al. [28]	2005	Analysis of SNP * Profiles in patients with major depressive disorder	Estonia	Find associations with MDD by examining 91 single nucleotide polymorphisms located in 21 genes.	MDD group: *n* = 177 Control group: *n* = 160	There was no statistical significance between the *DRD2* TaqIA SNP and MDD manifestation.	PCR and GenoramaTM 4.1 genotyping software (Asper Biotech Ltd.) for identification of polymorphisms.		A1 allele frequency = 0.80

* DE = depressive episode; RD = recurrent depression; MADD = mixed anxiety and depressive disorder; PCR = polymerase chain reaction; G = genetic; A = allelic; MDD = major depressive disorder; F = female; M = male; SNP = single nucleotide polymorphism.

Figure 3 shows DRD2/ANKK1 TaqIA SNP's A1 and A2 allelic frequencies from the selected articles (Table 1). Interestingly, the allelic predominance differs between countries (Russia, Estonia, and China) and within the same country (United States).

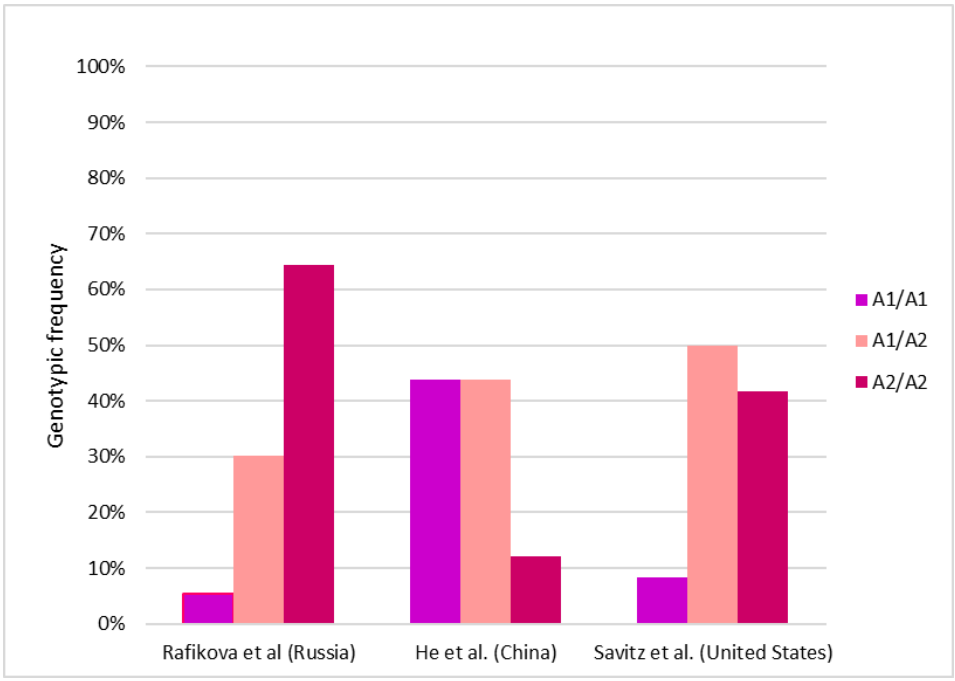

Figure 2. DRD2/ANKK1 Taq1A (rs1800497) single nucleotide polymorphism (SNP)'s genotypic frequency in patients with major depressive disorder by the selected articles [24–26].

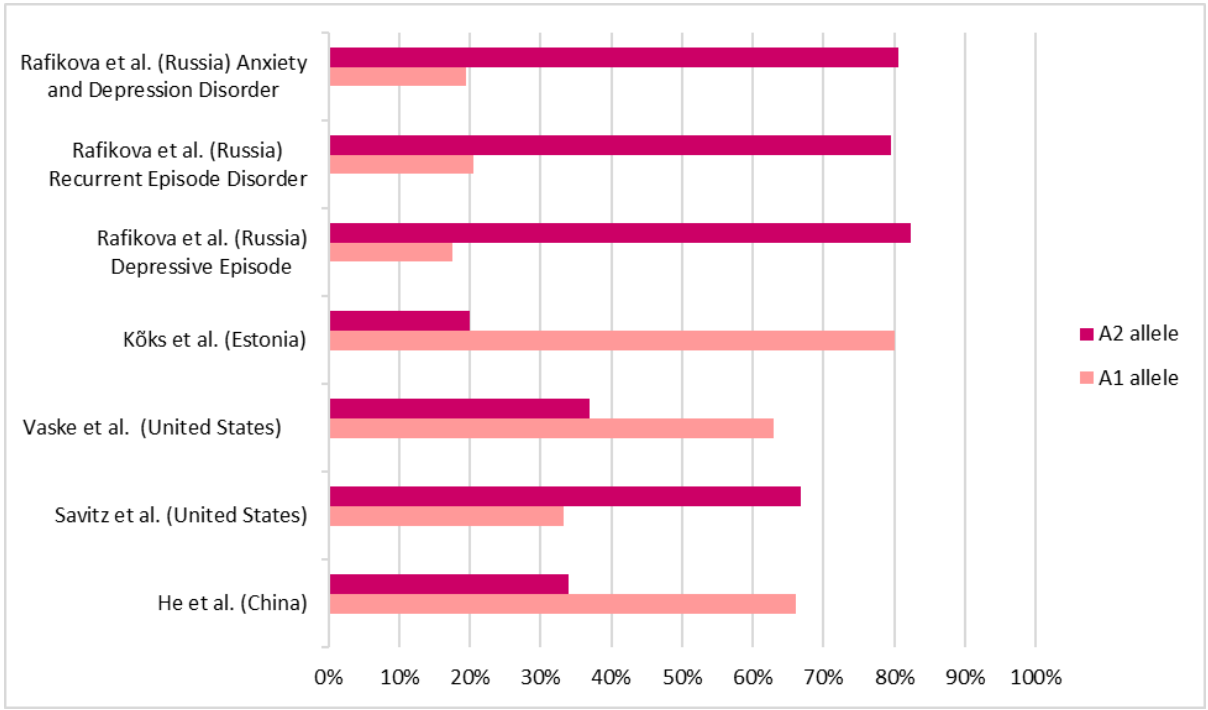

Figure 3. DRD2/ANKK1 Taq1A (rs1800497) allelic frequency in patients with major depressive disorder by the selected articles [24–28].

4. Discussion

Genes' coded information, hence, their product, is expressed differently depending on each individual and population, and these differences might alter the products' overall function. Studies on this help us to understand, at the molecular level, not only how physiological systems work and interact but also the possible causes/origins of these systems' dysfunctions and diseases [29].

He et al. [25] analyzed a Chinese population sample's *DRD2 TaqIA* (rs1800497) polymorphism's genotypic and allelic frequency in patients with major depressive disorder (MDD) and found the following frequencies: 43.9% for the A1/A1 and A1/A2 genotypes (each) and 12% for the A2/A2 genotype (Table 1 and Figure 2). The most frequent allele in MDD patients was A1, with a 66% frequency (Figure 3). Differently, Rafikova et al. [24], in the Russian population, found a 64.4% frequency for the A2/A2 genotype, 5.4% frequency for the A1/A1 genotype, and 30.2% frequency for the A1/A2 genotype (Table 1 and Figure 2). Their depressive episodes, recurrent depressive disorder, and mixed anxiety and depressive disorder groups had a higher A2 allele presence (82.4%, 79.5%, and 80.5%, respectively) (Figure 3). These populations likewise present different *DRD2 TaqIA* (rs1800497) allele frequencies, with the Chinese population having a higher A1 allele frequency, and the Russian population having a higher A2 allele frequency (Figure 3). Similar to China's study, the Estonia study had the highest A1 frequency (80%) [28], while the United States study had an A1 frequency of 0.53 [16] (Figure 3).

Vaske et al. [27] examined if the *DRD2 TaqIA* variant modulates the effect of violent victimization on depression by analogizing this SNP in the United States (US) population (aged between 11 and 27) by biological sex and race. Noteworthily, the TaqIA polymorphism and victimization probably have an additive effect on depression as their interaction is insignificant. Concentrating on the SNP influence, their results indicate that TaqIA SNP significantly affects depressive symptoms for males (b = 0.540, p = 0.005) and African-American females (b = 1.03, p = 0.033). Compared to the A2 allele, the A1 allele seems to be a risk factor for depression. Individuals with one or both A1 alleles in the sample report higher depressive symptom levels (b = 0.410, p = 0.009). Regarding depressive symptom levels, the A1 allele seems to have a dominant effect on depression as the A2/A2 genotype differs in terms of average depression levels from the A1/A2 (t = −2.208, p = 0.027) and A1/A1 (t = −2.442, p = 0.015) genotypes, but these do not differ between each other (t = −1.141, p = 0.254); this phenomenon was also observed when analyzing only the male sample. Interestingly, the A1 allele frequency in African-American women was higher than in Caucasian women (x2 = 26.32), which might explain why African-American women have a higher risk of developing depressive symptoms than Caucasian women and their depressive symptoms seem to be a function of the TaqIA SNP (b = 1.03, p = 0.033) and its interaction with violent victimization (b = 1.77, p = 0.006).

Focused on DRD2 TaqIA's A1 allele, Savitz et al. [26] investigated the TaqIA polymorphism effect on striatal dopamine D2/3 receptor (DRD2/3)'s binding potential in unmedicated MDD patients and healthy controls (12 MDD patients and 24 healthy controls) from the United States during reward-associated dopamine release. The results revealed opposite effects: while in the controls with the A1 allele, there was a decreased baseline DRD2/3 binding potential in both the middle caudate (r2 explained = 0.20, β-weight = 0.47, t = 2.9, p= 0.009) and ventral striatum (r2 explained = 0.20, β-weight = 0.46, t = 2.6, p= 0.016) in MDD patients, this potential was increased in the middle caudate (r2 explained = 0.40, β-weight = 0.65, t = 2.6, p= 0.033) and tended towards significance in the ventral striatum (r2 explained = 0.28, β-weight = 0.54, t = 2.0, p = 0.086). Interestingly, TaqIA polymorphism is uncorrelated to changes in BNDF during reward-associated dopamine release in both groups (p-values > 0.35). Their results suggest that the A1 allele is a risk factor for depression and addiction disorders, although the exact mechanism due to the difference between the baseline DRD2/3 binding potential and reward-associated dopamine release remains unclear. Further studies should analyze the possible mechanism of the TaqIA effect on binding potential and dopamine release.

Many genes have a single nucleotide polymorphism (SNP) that may be related to various diseases. In an Estonian population, Kõks et al. [28] selected 91 SNPs in 21 genes to analyze which ones were associated with MDD. However, with regard to *TaqIA* polymorphism, they found no statistical significance (p-value unmentioned). This result is similar to that of Rafikova et al. [24], who researched five polymorphisms in four genes in the Russian popula-

tion and found a statistical association between the *TaqIA* SNP and MDD (neither depressive episodes, recurrent depressive disorder, and mixed anxiety nor depressive disorder).

The *TaqIA* SNP was also studied in association with other diseases. Wang et al. [30] found no association with schizophrenia when analyzing allele frequency in an Asian population, unlike Cordeiro's [31] results in a Brazilian population, which showed an association between the A2 allele and schizophrenia (p = 0.06). Regarding genotypes associated with Parkinson's disease, McGuire et al. [32] found that non-Hispanics with the A1/A1 genotype were 1.5 times more likely to develop Parkinson's disease compared to A2/A2 genotype individuals, unlike results from Yu et al.'s [33] systematic review that found no statistical significance with the same comparison.

Regarding the selected articles' quality assessment, all [24–28] had at least 15 of the 20 evaluated items and, consequently, were considered of good quality (Table S1). They also all described the laboratory techniques performed and specified the eligibility criteria for their study participants' selection. Most articles [24–27] (80%) addressed the importance of their treated subject and results for health care. None of the articles explained how they handled missing data in their study, and only two [24,25] (40%) discussed the limitations that affected their research.

5. Conclusions

The present systemic review found contrary evidence of an association between the dopamine D2 receptor (*DRD2*)/ankyrin repeat and kinase domain containing 1 (ANKK1) gene's *TaqIA* (rs1800497) single nucleotide polymorphism (SNP) and major depressive disorder (MDD), even though our search found few and mostly dated studies on the subject. These limitations indicate a need for further research, with different populations, on this SNP associated with MDD to address the non-conformity in the results.

The A1 allele presence proved to be a vital component for the increase in depressive symptom levels and can be called a risk factor, especially for populations where it appears more frequently, such as the Chinese and American populations. Contrary to the Russian population, depressive episodes, recurrent depressive disorder, and mixed anxiety and depressive disorder groups had a higher A2 allele presence. Other studies presented no association between TaqIA SNP and MDD. Besides populations being different, these discrepancies may be due to the environment and how people's lives differ (culture and socioeconomic class, among other factors), i.e., epigenetic regulation of the *DRD2* gene, which may lead to the change in the risk factor reflected in the alleles of this SNP.

MDD is a debilitating illness affecting an increasing number of people worldwide. The *DRD2* gene plays a crucial role in DRD2 availability and, therefore, dopamine—a relevant neurotransmitter in the pathophysiology of depression. Further studies in different populations and with significantly larger samples are necessary to deepen the understanding of *TaqIA* (rs1800497) SNP's correlation with MDD and its alleles' roles in different populations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/dna4040024/s1, Table S1: The systematic review selected articles' quality assessment according to the Genetic Risk Prediction Studies (GRIPS) guideline.

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