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SYSTEMATIC REVIEW

THE ASSOCIATION OF GENETIC POLYMORPHISMS AND ATYPICAL DEPRESSION IN ADULTS: A SYSTEMATIC REVIEW

Aysylu Galiautdinova, Iuliia Dolgopolova, Daria Troshina, Dmitry Petelin and Beatrice Volel

Abstract

Objective: Atypical depression (AD) is a clinical subtype of depression characterised by mood reactivity and at least two of the following features: significant weight gain/increased appetite, hypersomnia, leaden paralysis, and/or interpersonal rejection sensitivity. The role of genetics in the development of depression remains a considerable level of interest among individuals. Due to the large number of breakthrough studies in genetics, there is currently a wealth of heterogeneous data on the existence of genetic markers for depression, including AD. However, it appears that there is a gap in the literature, as we were unable to identify any systematic reviews or meta-analyses that comprehensively describe these data. Therefore, our research aims to provide high-quality, solid evidence for further studies in this area.

Method: Electronic bibliographic databases (Scopus, MEDLINE) were systematically searched from inception to September 2023. We searched for any specific genetic markers that could be retrieved associated with AD. The quality of studies has been assessed by means of the Q-genie tool.

Results: Nine studies meeting the inclusion criteria were selected, which appeared to link genetic polymorphisms to atypical depression. Four studies examined genetic polymorphisms associated with the serotonin transporter gene (5-HTT), three studies examined genetic polymorphisms associated with endocrine regulation, two studies considered genetic polymorphisms associated with immune and/or cellular regulation, specifically the melanin-concentrating hormone receptor 2 (MCHR2), mineralocorticoid receptor (MR), and fat mass and obesity-associated protein (FTO) genes involved in the regulation of energy balance.

Conclusions: The extracted data confirm that the atypical type of major depressive disorder is heritable to a certain extent. Individual risk markers for developing this type of depression may be identified in the future.

Key words: atypical depression, depression with atypical features, genetic marker, single nucleotide polymorphism, weight gain, hypersomnia, increased appetite

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1. Introduction

Depression is a common, highly debilitating disease affecting up to 310 million people worldwide (Vos et al., 2020). Major depressive disorder (MDD) is currently considered the primary cause of disability around the world and is predicted to generate the greatest global burden by 2030 (Hock et al., 2012).

Depression is a highly heterogeneous disease encompassing a wide range of clinical subtypes that have been identified based on their chronological features (e.g., age of onset), treatment response (e.g. treatment-resistant depression), progression over time, and clinical presentation (Cai et al., 2020).

One commonly recognized clinical subtype is atypical depression (AD) which differs from the classical "melancholic" type in that it lacks the typical features of insomnia and weight loss. According to DSM-V criteria, AD is characterised by mood reactivity and at least two of the following features: significant weight gain/increased appetite, hypersomnia, leaden paralysis, and/or interpersonal rejection sensitivity (American Psychiatric Association, 2022). Data from large community-based studies suggest that up to one third of patients with MDD present with atypical features, with a 1-year prevalence of AD estimated at 1 to 4% (American Psychiatric Association, 2022; Grant & Booth, 2009; Thase et al., 2007). Epidemiological research also points to a higher proportion of females, and a younger age of onset for AD (Łojko & Rybakowski, 2017). Apart from having a distinctly different clinical presentation and demographic characteristics, AD was

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shown to be associated with higher rates of psychiatric comorbidity, primarily anxiety and substance use disorders, suicidal ideation, and disability as compared to non-AD (Blanco et al., 2012; Gili et al., 2012; Matza et al., 2003). In addition to psychiatric implications, individuals with AD appear to be at a higher risk of cardiovascular disease (CVD) (Case et al., 2018), compared to those with non-AD, which may be attributed to the lifestyle changes in AD, i.e., increased appetite and carbohydrate craving that may result in metabolic disturbances, and some shared pathological mechanisms involving chronic inflammation observed in both AD and CVD (Refisch et al., 2023; Sen et al., 2021). Indeed, recent studies suggest there might be a bidirectional relationship between common CVD factors of increased BMI, obesity, and dyslipidemia and AD (Beurel et al., 2020), highlighting the importance of recognizing AD in general medical practice.

It is now well established that genetic factors are important contributors to depression. In the last decades, substantial advances have been made in understanding the genetic architecture behind depression owing to the adoption of new technologies enabling a paradigm shift from historical twin studies to modern molecular genetic research looking at the contribution focused on investigating gene polymorphisms and their association with the condition (McIntosh et al., 2019; Norkeviciene et al., 2022). Given the heterogeneity of depression, multiple studies have been conducted to explore potential genetic markers of specific depression subtypes, including AD. However, to our knowledge, no systematic review or meta-analysis of data from AD studies has been conducted to date. Our study was therefore aimed at producing high-quality, solid evidence to enable further research into genetic markers of AD given its high psychiatric burden and the potentially shared mechanisms with a range of medical conditions putting the highest strain on healthcare nowadays such as CVD and metabolic disorders.

2. Materials and methods

2.1. Protocol registration

This systematic review is reported in accordance with the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2015). The review was registered with the National Institute for Health Research's PROSPERO (PROSPERO 2022 CRD42022333639. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022333639 on May 29, 2022.

2.2. Literature search strategies

An extensive electronic search of Scopus and MEDLINE databases was performed to retrieve relevant literature up to June 2022. Additional searches were conducted in September 2023 to identify recent papers published during the systematic review process. The search strategy included a combination of keywords and MESH terms "depression or depressive disorder", and "atypical or atypical features or atypical symptoms", and "genetic or polymorphism or variant or SNP or allele or genetic association or polygenic or mutation" and "epigenetics". Additionally, we manually searched reference lists of the retrieved papers.

2.3. Eligibility and selection criteria

2.3.1. Types of studies. Observational studies (prospective/retrospective cohort, case-control, and cross-sectional), randomised controlled trials as well as cluster randomised trials, and quasi-experimental trials were included. All original studies had to report any genetic factors and their association with AD. We did not include studies with 1) no available data reported; 2) invalid study design (reviews, case reports, letters, or abstracts); 3) overlapped data sets; 4) in vitro studies and non-human studies. The articles were required to be written in English. We also included studies written in Russian in the review, as all researchers are native speakers of the language.

2.3.2. Participants/population. Participants of any sex over the age of 18, were diagnosed with AD. We included all studies that evaluated conditions limited to the criteria for AD according to the international diagnostic tools (ICD, DSM, etc.). We also considered conditions that were characterised by depression with atypical symptoms, such as significant weight gain or increase in appetite, hypersomnia, leaden paralysis, and a long-standing pattern of interpersonal rejection sensitivity.

2.3.3. Interventions/Exposures. We searched for any specific genetic markers that could be retrieved associated with AD. We did not restrict the explored genes, alleles, genotypes, etc.

2.3.4. Comparators. Healthy controls and individuals without atypical or atypical-like features depression were assigned as comparators.

2.3.5. Outcomes. We considered the evidence for an association between genetic factors and AD in adults; the evidence for genetic markers which can be used to detect AD in adults; specific genetic markers associated with AD in adults when compared to a population with other clinical subtypes of depressive disorder (melancholic). We also identified the evidence for an association between genetic factors and specific symptoms of AD (weight gain or increased appetite, hypersomnia, leaden paralysis, interpersonal rejection sensitivity) or metabolic features (hyperglycaemia, hyperlipidaemia, dyslipidaemia, hypercholesterolemia) and BMI in adults with AD.

2.4. Data extraction

All the available data from each study were extracted using a review manager Covidence by three independent investigators (A.G., D.T. and Y.D.) in accordance with the inclusion criteria listed above. In the event of any disagreements, a fourth investigator (D.P.) was consulted to resolve the discrepancy. A final decision was made based on the majority of votes. All information was tabulated and included the first author's name, publication year, country and setting, study design, number of participants, described diagnosis and classification of diagnosis, symptoms, comparator group if any and explored outcome.

2.5. Quality assessment of primary studies

We applied the Quality of genetic Studies (Q-Genie) tool version 1.1 (Sohani et al., 2015). The eleven questions in the Q-genie tool cover the following areas of research methodology: study design, outcome, comparability, exposure, bias, sample size, analyses, statistical procedures and control for confounding, conclusions for genetic analysis, and conclusions

derived from data.

A quality assessment is scored on the 7-point Likert scale ranging from 1 (poor) to 7 (excellent). For studies with control groups, total scores of 35 indicate poor quality studies, >35 and 45 indicate studies of moderate quality, and >45 indicate good quality studies. For studies without control groups, total scores of 32 indicate poor quality studies, >32 and 40 indicate studies of moderate quality and >40 indicate good quality studies.

3. Results

3.1. Study selection

The process of study selection is shown in the PRISMA flow diagram (see **figure 1**). A comprehensive search revealed a total of 374 references. After the removal of duplicates, a total of 328 titles and abstracts were independently screened and a total of 40 references were selected for comprehensive evaluation of their full texts. The rationales for excluding studies that meet the criteria for full-text evaluation are provided in the chart (see **figure 1**). After completing the final eligibility evaluation phase, only 9 studies met the criteria and were included in this systematic review (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Kang et al., 2021; Kumsta et al., 2019; Mikhalitskaya et al., 2021; Milaneschi et al., 2014; Praschak-Rieder et al., 2005; Willeit et al., 2003).

3.2. Study characteristics

Characteristics of the included studies are summarised (see **table 1**). Based on our search, we identified studies investigating genetic polymorphisms

Figure 1. *PRISMA flow diagram*

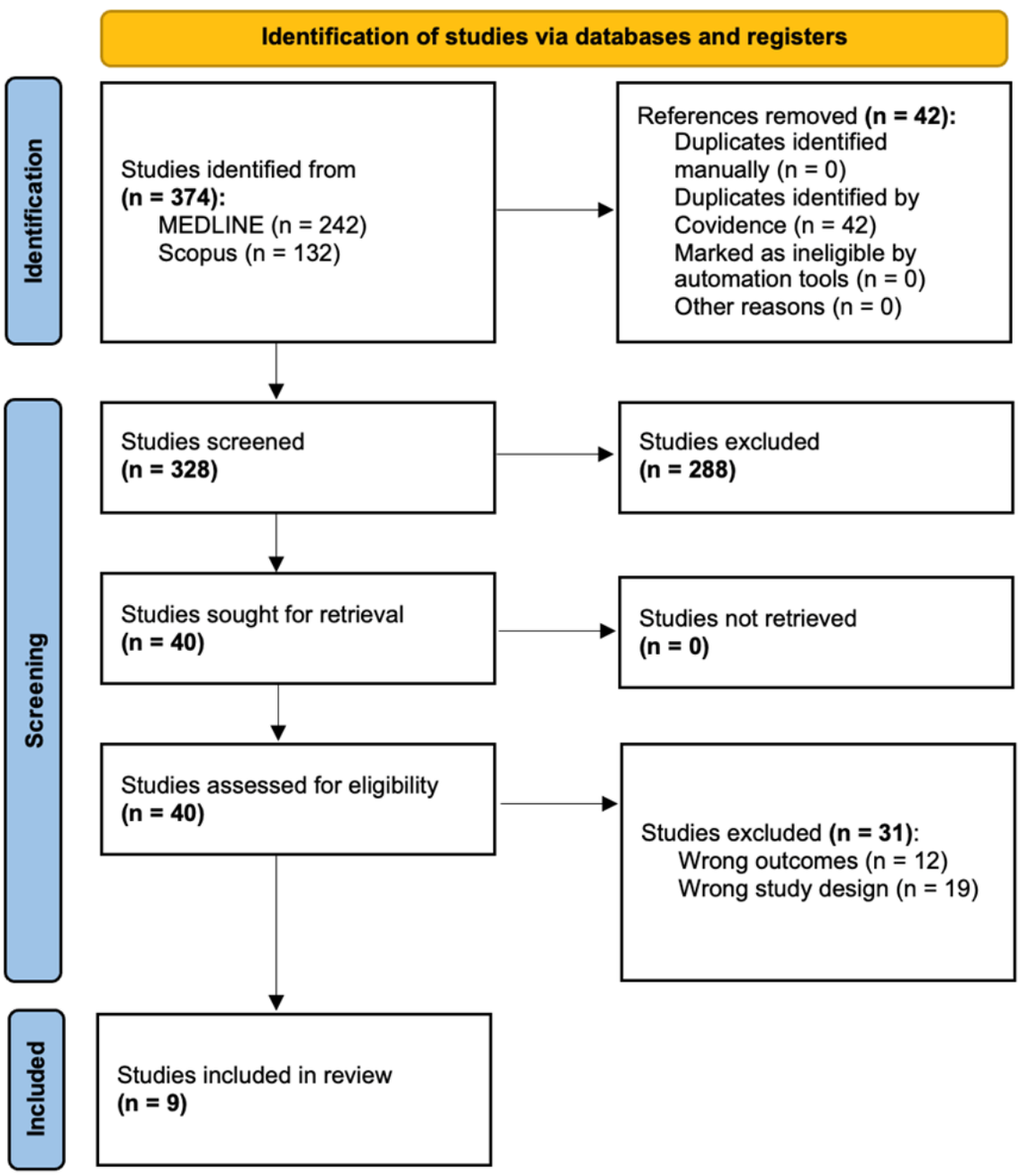

Table 1. *Study Characteristics provides details on the studies included in the analyse*

Year and author	Country (-es)	Study design	Race/ ethnicity	Data Set	N of participants		Principal diagnosis	Diagnostic Approach for AD	Other reported symptoms of AD, if any[1]	Comparator group	Genes	Genetic marker	Main findings	Total score for quality assessment
					Total included	Total of AD patients, if reported								
Neurotransmitter regulation														
Baune et al., 2008	Germany	Cross sectional	Caucasian	Sample	340	30	MDD, BD	DSM IV	N/R	Melancholic depression (n = 100)	Serotonin transporter gene (5-HTT)	5-HTTLPR and 5-HTTLPR/ rs25531	No association with AD (p = 0.13)	50, Good
Praschak-Rieder et al., 2005	Austria, Canada	Cross sectional	Caucasian (Austrian sample), Caucasian and non-Caucasian (Canadian sample)	Sample	413	211	SAD	DSM-IV	N/R	Female healthy controls (N=161)	Serotonin 2C receptor gene (5-HT2C)	Cys23Ser (Cys/Cys genotype)	Direct association with AD features: weight (p = 0.039), BMI (p = 0.038), and seasonal appetite change (p = 0.031)	52, Good
Willeit et al., 2003	Austria	Cohort, retrospective	Caucasian subjects with central European origin	Sample	284	104	SAD	DSM-IV	N/R	Healthy controls (N=146)	Serotonin transporter gene (5-HTT)	5-HTTLPR (short-[S] allele)	Direct association with AD (two-sided Fisher's exact test: genotype distribution: p =0.0038; allele frequencies: P=0.007)	43, Moderate
Aklillu et al., 2009	Sweden	Cross sectional	Caucasian (Scandinavian)	Sample	118	27	MDD, Dysthymia	DSM IV	N/R	Non-AD (n = 91)	Monoamine oxidase-A (MAO-A) gene	MAOA-uVNTR (short [S]-allele)	Direct association with AD in females (p = 0.005; OR = 4.76; 95% CI = 1.5–13.1; statistical power = 80.0%)	39, Moderate
Endocrine regulation														
Delacretaz et al., 2015	Switzerland	Cross sectional	Caucasian	Sample	736	N/R	MDD	DSM-IV	N/R	N/R	Melanin-concentrating hormone receptor 2 gene (MCHR2)	rs7749425C>T (proxy of rs7754794C>T)	Inverse association [of rs7754794-TT] with BMI in AD (p = 0.04)	40, Moderate

Table 1. *Continued*

Kumsta et al., 2019	Germany	Cohort study, prospective	N/R	Sample	451	N/R	Depression	the Neuropattern diagnostic	Other: muscle weakness, lethargy, adynamia, inactivity, fatigue, exhaustion	N/R	Mineralocorticoid receptor gene (MR, NR3C2)	rs2070951 G/C and rs5522 A/G	Direct association with AD features[2]: depressivity (p = 0.013), hypersomnia (p = 0.037), muscle weakness (p =0.021), feeling as being paralyzed (p = 0.032), lethargy (p = 0.007), adynamia (p = 0.003), exhaustion (p = 0.011), weight gain, (p = 0.031)	36, Moderate
Milaneschi et al., 2014	the Netherlands	Cross sectional study	European ancestry	NESDA cohort; the Netherlands Twin Registry	4,350	256	MDD	DSM-IV	N/R	Healthy controls (n = 2806)	Fat mass and obesity-associated protein (FTO)	rs9939609	Direct association with AD (p = 0.003)	48, Good
Immune and/or cellular regulation														
Kang et al., 2021	the Republic of Korea	Cohort study, retrospective	Korean	Sample	1,000	N/R	MDD, dysthymic disorder or any other depressive disorder	DSM-IV	N/R	N/R	Chemokine (C-C motif) ligand 14 (CCL14), FYN Binding Protein (FYB), G Protein-Coupled Receptor Associated Sorting Protein 1 (GPRASP1), Catenin Delta 2 (CTNND2)	rs75238886 (CCL14), rs35384751 (FYB), rs201921260 (GPRASP1) and rs202234398 (CTNND2)	No association with AD.	50, Good
Mikhailitskaya et al., 2021	Russia	Cohort study, prospective	N/R	Sample	936	N/R	MDD, BP I, BP II, Dysthymia	ICD-10, SIGH-SAD	N/R	Healthy controls (n = 356)	Phosphatidylinositol-5-phosphate 4-kinase type-2 alpha (PIP5K2A)	rs10828317	Direct association with the severity of AD symptoms (p = 0.039).	34, Poor

Abbreviations: AD = atypical depression; MDD = major depressive disorder; BD = bipolar disorder; BMI = body mass index; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; ICD-10 = International Classification of Diseases 10th Revision; SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version, N/R = not reported.

[1] - Other than the four DSM-V criteria: (1) significant weight gain or increase in the appetite, (2) hypersomnia, (3) leaden paralysis, and (4) long-standing pattern of interpersonal rejection sensitivity

[2] - the Neuropattern CRF hypoactivity type consistent with AD

and their association with AD. However, our search for other relevant genetic and epigenetic markers yielded no results, and such studies were not included in our review.

A total of nine studies (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Kang et al., 2021; Kumsta et al., 2019; Mikhalitskaya et al., 2021; Milaneschi et al., 2014; Praschak-Rieder et al., 2005; Willeit et al., 2003) examined the association between genetic polymorphisms and AD. Studies were published between 2003 (Willeit et al., 2003) and 2021 (Kang et al., 2021; Mikhalitskaya et al., 2021). Seven studies were conducted in Europe (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Kumsta et al., 2019; Milaneschi et al., 2014; Willeit et al., 2003), one study in Asia (Kang et al., 2021), one study carried out simultaneously in Europe and North America (Praschak-Rieder et al., 2005). Five of the included studies were cross-sectional (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Milaneschi et al., 2014; Praschak-Rieder et al., 2005), and four were cohort studies (Kang et al., 2021; Kumsta et al., 2019; Mikhalitskaya et al., 2021; Willeit et al., 2003).

3.3. Description of participants in included studies

The total number of participants in the included studies ranged between 118 (Aklillu et al., 2009) and 4,350 (Milaneschi et al., 2014). Seven studies provided a description of ethnicity (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Kang et al., 2021; Milaneschi et al., 2014; Praschak-Rieder et al., 2005; Willeit et al., 2003). Five studies included Caucasians (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Milaneschi et al., 2014; Willeit et al., 2003), one study included Caucasians and Non-Caucasians simultaneously (Praschak-Rieder et al., 2005), one included Koreans (Kang et al., 2021). Two studies lacked data on ethnicity (Kumsta et al., 2019; Mikhalitskaya et al., 2021). Eight studies analysed data from patients' blood samples (Aklillu et al., 2009; Baune et al., 2008; Delacrétaz et al., 2015; Kang et al., 2021; Kumsta et al., 2019; Mikhalitskaya et al., 2021; Praschak-Rieder et al., 2005; Willeit et al., 2003), one study employed data from mixed cohorts – NESDA and the Netherlands Twin Registry (Milaneschi et al., 2014). Four studies used healthy controls as a comparison group (Mikhalitskaya et al., 2021; Milaneschi et al., 2014; Praschak-Rieder et al., 2005; Willeit et al., 2003), two studies included patients with "non-AD" (Aklillu et al., 2009) or "melancholic depression" (Baune et al., 2008). Three studies lack a comparator group (Delacrétaz et al., 2015; Kang et al., 2021; Kumsta et al., 2019).

3.4. Assessment of the quality of studies

We accomplished the assessment of study quality using the Q-Genie tool (Sohani et al., 2015). Four studies demonstrated "good" scores (Baune et al., 2008; Kang et al., 2021; Milaneschi et al., 2014; Praschak-Rieder et al., 2005), four studies indicated "moderate" scores (Aklillu et al., 2009; Delacrétaz et al., 2015; Kumsta et al., 2019; Willeit et al., 2003) and one study "poor" quality (Mikhalitskaya et al., 2021). The majority of studies sufficiently provided a rationale for the selected gene or genes and drew a conclusion supported by the presented results. The absence of data regarding the blinding of the assessor who performed the genotyping made it challenging to assess the non-technical evaluation of exposure. The prior statistical power and sample size analysis were insufficient in most of the studies, and not all assumptions related to the genetic analysis were tested.

3.5. Description of genetic polymorphism studies

Among the nine papers looking at the role of specific genetic polymorphisms, five studies (Aklillu et al., 2009; Delacrétaz et al., 2015; Kumsta et al., 2019; Mikhalitskaya et al., 2021; Milaneschi et al., 2014), demonstrated an association between genetic polymorphisms and AD, with one study (Delacrétaz et al., 2015) having shown an inverse association. The remaining two studies (Baune et al., 2008; Kang et al., 2021) found no evidence of a significant correlation.

Four studies examined genetic polymorphisms related to neurotransmitter regulation, primarily within the serotonin transporter gene (5-HTT), as explored by Baune et al., 2008 and Willeit et al., 2003. One study investigated the 5-HT2C receptor gene polymorphism (Praschak-Rieder et al., 2005) and another explored a monoamine oxidase A gene polymorphism (Aklillu et al., 2009).

In three studies, genetic polymorphisms associated with endocrine regulation were assessed, namely melanin-concentrating hormone receptor 2 (MCHR2) (Delacrétaz et al., 2015), mineralocorticoid receptor (MR) (Kumsta et al., 2019), and fat mass and obesity-associated protein (FTO) genes involved in the regulation of energy balance (Milaneschi et al., 2014).

Finally, two studies considered genetic polymorphisms associated with immune and/or cellular regulation: chemokine (C-C motif) ligand 14 (CCL14), FYN binding protein (FYB), G protein-coupled receptor associated sorting protein 1 (GPRASP1), catenin delta 2 (CTNND2) (Kang et al., 2021) and phosphatidylinositol-5-phosphate 4-kinase type-2 alpha (PIP5K2A) (Mikhalitskaya et al., 2021).

3.6. Statistical analysis

However, the small number of included studies and the fragmentation of findings, combined with the lack of a uniform genetic statistical model, precluded any statistical analysis.

4. Discussion

The goal of this systematic review was to determine associations between genetic polymorphisms and AD. We found that genetic variations (SNPs) in the pathways of neurotransmitter regulation, endocrine system function, and immune and cellular regulation appear to play important roles in the development of the atypical subtype of depression. We also found studies in which the association of genetic polymorphisms with AD was not identified.

4.1. Neurotransmitter regulation

In our systematic review, contradictory findings regarding the role of serotonin transporter gene (5-HTT) polymorphisms were obtained. Specifically, M. Willeit demonstrated a significant association of the short allele with AD, while Baune et al. found the long allele to

have been associated with melancholic depression, with the short allele not being statistically significant (Baune et al., 2008; Willeit et al., 2003).

Praschak et al. identified a significant association of AD, according to DSM-IV criteria, with the Cys/Cys variant of the serotonin receptor 2C (5-HT2C) in samples of women with SAD from Austria and Canada (Praschak-Rieder et al., 2005).

However, not all symptoms of AD were equally associated with the Cys/Cys variant of the Cys23Ser polymorphism. A significant association was found for weight, BMI, and seasonal appetite changes.

This result is consistent with available data on the significant role of this subtype of serotonin receptors SNPs in weight gain associated with the use of a variety of psychopharmacological drugs, primarily atypical antipsychotics (Wallace et al., 2011).

However, further research is warranted into the role of genes involved in neurotransmitter regulation in the development of AD. Specifically, it is unclear whether the inclusion of exclusively patients with SAD, where atypical features are significantly more common, influenced the results of the studies by Willeit et al., 2003 and Praschak-Rieder et al., 2005 (Michalak et al., 2002; Tam et al., 1997; Westrin & Lam, 2007).

Finally, Aklillu et al. identified an association of AD in women with the short allele of the MAOA-uVNTR polymorphism of the MAO-A gene (Aklillu et al., 2009).

These findings are of scientific and practical interest, as in a significant number of publications, polymorphisms of this gene are more strongly associated with aggression and antisocial behaviour (Kolla & Bortolato, 2020).

4.2. Endocrine regulation

Expected and logically consistent findings also included the presence of significant associations of AD with polymorphisms of genes involved in endocrine and neuroendocrine regulation – MCHR2, MR, NR3C2, and FTO.

Moreover, all three identified markers – melanin-concentrating hormone (MCH) receptors (Torterolo et al., 2015), mineralocorticoid receptors (MR) (de Kloet et al., 2016), and the protein associated with obesity (FTO) (Liu et al., 2021) – are involved not only in the regulation of homeostasis but also mood. Therefore, all three markers may be considered mediators between pathologically reduced mood and weight gain. It is noteworthy that alongside the direct association of the FTO gene polymorphism with AD (Milaneschi et al., 2014), authors also demonstrate a reverse association of the MCHR2 gene polymorphism with BMI in patients with AD (Delacrétaz et al., 2015).

The alteration of mineralocorticoid receptors and melanin-concentrating hormone receptors activity also aligns well with their role in the regulation of the sleep-wake cycle (Born et al., 1991; Potter & Burgess, 2022). For instance, in the study by Kumsta et al., 2019, among the AD symptoms associated with polymorphisms rs2070951 G/C and rs5522 A/G, alongside “depressivity”, “muscle weakness”, “feeling as being paralyzed”, “exhaustion”, “adynamia” and “weight gain”, “hypersomnia” and “lethargy” were identified (Kumsta et al., 2019).

4.3. Immune and/or cellular regulation

Polymorphisms of the genes CCL14, FYB, GPRASP1, and CTNND2, involved in the regulation of intracellular processes and inflammation, according to the results of Kang et al., did not demonstrate a significant association with AD (Kang et al., 2021). In line with the accumulated understanding of the biological and physiological underpinnings of chronic inflammation, it is conceivable that there might be an association between depression in general and its atypical subtype. Particularly noteworthy are studies that pinpoint common pathways in the pathogenesis of AD and metabolic disorders (Sen et al., 2021). Therefore, additional research is imperative to elucidate the genetic predisposition to immune disorders and its implication in the development of AD.

In the study by Mikhaltskaya et al., a significant association between AD and the rs10828317 polymorphism of the PIP5K2A gene was identified (Mikhalitskaya et al., 2021). PIP5K2A plays a crucial role in transmitting neural signals across membranes by regulating the activity of potassium channels, which in turn are involved in maintaining the membrane potential of dopamine neurons (Koch & Holt, 2012). However, we did not find data in the English-language scientific literature regarding the association of polymorphisms of this gene with AD and affective disorders in general. However, the investigation of the association of PIP5K2A polymorphisms with the AD continues a series of studies by several groups of authors who have found a connection of this gene with various aspects of affective and other mental pathology, as well as the effectiveness of therapy for depressive disorder, alcohol dependence, and others (Mikhalitskaya et al., 2019; Vyalova et al., 2017). The mechanism of such associations deserves further investigation.

The diversity and ambiguity of the data obtained on markers of AD confirm the multifactorial nature of this disorder, involving neurotransmitter, metabolic, and immune pathways. In this regard, the results of genome-wide studies (GWAS) conducted on samples of patients with AD are of great interest.

The goal of GWAS studies is to investigate whether depression characterised by atypical features exhibits distinct heritability and varying degrees of genetic overlap with polygenic risk score for psychiatric and immunometabolic traits compared to other subtypes of depression, particularly melancholic depression.

From the studies available for analysis, it can be found that AD, compared with depressive disorder without atypical features (or symptoms uncharacteristic of AD – insomnia, weight loss, etc.) exhibit a higher polygenic risk for metabolic and immune markers such as BMI and C-reactive protein (Badini et al., 2022; Milaneschi et al., 2016; Nguyen et al., 2022). At the same time, the relatively limited number of studies on this topic, along with the majority being conducted on UK Biobank data which may not facilitate analysis across diverse ethnic groups, underscores the necessity of further research.

However, the findings could potentially be interpreted in other ways. Some recent studies have suggested that the concept of atypical depression may be less valid than previously thought. In particular, the syndromic division of depressive disorders may not provide an accurate classification of the symptomological profile of depressed patients (Buss et al., 2023). Moving away from the works discussed above, the results of our review can be interpreted in a slightly different way – a significant part of the identified genetic markers may actually determine the formation of individual symptoms, and not atypical depression as an independent disorder (Lorenzo-Luaces et al.,

2021). This interpretation is in accordance with the findings of Kumsta et al., which were included in our review. Further discussion of the validity of identifying subtypes of depressive disorder is beyond the scope of this work, and in the genetic aspect requires separate systematic work.

5. Conclusions

We found several potentially important associations of SNPs related to neurotransmitter, endocrine and immune/cellular regulation with AD and separate symptoms of AD. The data we extracted generally confirm the fact that the atypical type of major depressive disorder is heritable to a certain extent. Nevertheless, we found no evidence of genetic markers that could be used to detect AD in adults. In this regard, it may be possible in the future to identify individual risk markers for developing this type of depression. However, at the current level of knowledge, the genetic prerequisites for the formation of AD appear to be extremely heterogeneous and involve a number of metabolic pathways that are poorly connected to each other. This fact predetermines the need for further study of genetic markers of AD.

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