REVIEW ARTICLE

Adenosine A2a Receptor Polymorphisms and Susceptibility to Anxiety Disorders

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ABSTRACT

Anxiety disorders (ADs) are a group of mental disorders characterized by feelings of tension, fear, and excessive worrying in the face of life experiences. Aberrant signaling of adenosine A2a receptor (ADORA2A) is believed to be involved in the pathogenesis of ADs. Polymorphisms in the ADORA2A gene were shown to be associated with some of the patterns presented by ADs. The results of these studies have been inconsistent, making it hard to draw definitive conclusions. Therefore, this study performed a systematic review to clarify the associations between ADORA2A gene polymorphisms and ADs susceptibility. PubMed/Medline, Web of Science, and Scopus database using appropriate keywords, then screened for separation of suitable studies based on inclusion/exclusion criteria. Collectively, rs5751876 (1976T>C or previously 1083C>T) and rs35060421 (2592C>Tins) polymorphisms of ADORA2A were associated with an increased susceptibility to ADs. Moreover, rs2298383 TT genotype may be the causal regulatory factor, and ADORA2A T/C (rs2298383/rs3761422) haplotypes have significant susceptibility to ADs development. Additional research is needed to further define the role of ADORA2A gene polymorphisms in the pathogenesis of ADs.

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Introduction

Anxiety disorders (ADs) are complex disorders characterized by feelings of tension, fear, and excessive worrying in the face of life experiences. The worldwide prevalence of ADs ranges from 10.6% to 16.6% (1). Panic disorder with or without agoraphobia, generalized anxiety disorder, social anxiety disorder, specific disorder, and separation anxiety disorder are defined as ADs (2) and are considered the most prevalent mood and mental disorders (3). Although such disorders have psychiatric entities, the strong association between ADs and physical diseases such as cardiovascular events, hypertension, and diabetes (4) causes the high cost and burden of such diseases to the health care system.

Several epidemiological and clinical studies have demonstrated that environmental factors cause ADs, but genetic factors and specific gene polymorphisms are significant contributors (5). Adenosine A2a receptor (ADORA2A) is a candidate for genetic association studies in ADs (6). This receptor is recognized as widely distributed in the brain, with high expression rates in cortical, thalamic, hippocampal, and striatal neurons. ADORA2A involves various physiological and pathological processes in the brain, most notably regulating sleep, locomotion, anxiety, cognition, and memory (7). The main intracellular signaling branch of ADORA2A is promoted through cAMP-protein kinase A signaling cascade to adapt glial function and tune the glutamatergic information flow (6, 8). Indicatively, aberrant signaling of ADORA2A, specifically by methylxanthines such as caffeine, could induce anxiety symptoms (6).

Rodent studies have mentioned that genetic deletion of ADORA2A favors anxiety-like behaviors (9). However, evidence on the pharmacological modulation of the ADORA2A receptor by specific agonists and antagonists during anxiolytic conditions has suggested conflicting results with an uncertain conclusion about effectiveness (reviewed by (6). Variations in this receptor may influence the status of its functions, in turn affecting disease signs. In this regard, studies investigating the relationship between ADORA2A signaling and ADs have suggested that the ADORA2A gene polymorphisms are involved in the pathogenesis of ADs. The ADORA2A gene is located on chromosome 22q11.23 and consists of two exons lined about 9 kb in length. ADORA2A single nucleotide polymorphisms (SNPs) in exons, introns, and flank regions, such as rs5760405, rs2298383, rs3761422, rs2236624, rs5751876, rs35060421, rs5751862, and rs4822492 could modulate the influence of anxiogenic factors and explain differences between individuals (10-12). Studies in humans have revealed an association of single variants in ADORA2A with caffeine or D-amphetamine-induced anxiety, panic disorder, as well as individually differing sleep patterns (13). Others reported that individuals carrying the TT, CT, and CC genotypes of ADORA2A SNP rs5751876 showed different anxiogenic and alerting effects (13-16). However, no significant associations between ADORA2A SNPs and ADs were reported in Western (17) and Japanese panic disorder patients (18).

While several case-control studies have been completed to examine the relationship of ADORA2A gene polymorphisms with ADs, systematic reviews of this topic have yet to be conducted. Therefore, to gain further insight into the relevance of ADORA2A variants for the pathogenesis of ADs, the present study aimed to perform a systematic review to

clarify the associations between ADORA2A gene polymorphisms and ADs susceptibility. By clarifying the role of ADORA2A gene polymorphisms in ADs, this review can contribute to a better understanding of the underlying genetic mechanisms and inform future research directions. Unfortunately, this study could not perform a meta-analysis because the original studies did not report their results in a fashion suitable for meta-analysis. However, the information presented may facilitate the development of targeted management and personalized approaches to ADs prevention and treatment.

Materials & Methods

Search strategy

The current study identified eligible studies for a systematic review by searching PubMed/ Medline, Web of Science, Google Scholar, and Scopus databases until January 2023. Search terms included a combination of keywords for the ADs ("anxiety disorders" OR "anxiety" OR "panic disorder" OR "panic" OR "phobia" OR "generalized anxiety disorder", OR "bipolar," OR "manic," OR "manic depression," OR "agoraphobia," OR "panic attack," OR "mental disorder," OR "mental health," OR "depression,") and for the ADORA2A gene polymorphisms ("Adenosine, OR "Adenosine receptor, "gene variation" OR "polymorphism" OR "mutation" OR "genotype" OR "allele" OR "variant).

The titles and abstracts of all original articles identified were screened for eligibility, and any abstract deemed potentially relevant was then reviewed in full text. Case-control studies were selected if data were available regarding the roles of ADORA2A gene polymorphisms in ADs. Reference lists of pertinent articles were investigated to find any further relevant studies. The search and data extraction were conducted as a collaborative effort, with two authors working independently, and any disagreements were resolved through discussion among the authors.

Inclusion and exclusion criteria

The final eligible studies were selected if they met the following inclusion criteria: 1) original articles; 2) a case-control study design (with no limitation for age and sex); 3) topic of the article focused on the association between ADORA2A gene polymorphisms and ADs; 4) comparison between participants were based on odd ratios (ORs, 95% CIs) that assess the frequency of genotypes between ADs cases and controls.

Exclusion criteria were: 1) articles not written in the English language; 2) unpublished studies or literature with unavailable full-text; 3) in the case of studies reported insufficient or missing information, the researchers contacted the corresponding authors if no answer was feedbacked the relevant study removed from further processing; 4) studies based on the *in vitro* or animal experiments; 5) reviews, meta-analyses, commentaries, letters, comments, case studies, or study protocols.

Data extraction

Two reviewers independently studied all searched articles to assess their suitability for inclusion and extracted data using a standardized form. The following data retrieved from the studies: First author's name, publication year, study design, characteristics of participants, study size, gender, age, time of sample collection, polymorphism assessment methods, type of polymorphism, and outcomes relevant to this review were tabled. In the case of missing information or specific data needed, the researchers proactively contacted

the corresponding authors. Any disagreement between reviewers was promptly resolved through discussion, ensuring the accuracy and reliability of the data extraction process.

Results and Discussion

The PubMed, Web of Science, Google Scholar, and Scopus search identified 2996 articles; of these, only 15 met our inclusion criteria (Figure 1). The reviewed studies are summarized in Table 1. No article has been identified via citation checking of included article references. Collectively, the total cases with ADs were 2103, and controls were 1927. The following SNP's were studied: rs5751862 (G>A or C or T, in the ±10 kb of 5′ flanking region ADORA2A gene located at chr22:24406596), rs5760405 (263C/T, located at the exon 1 and chr22:24417873), rs2298383 (C>T or A or G, located at the intron 1 and chr22:24429543), rs3761422 (T>C, located at the intron 1 and chr22:24430704), rs2236624 (C>T or A or G, located at the intron 1 and chr22:24440056), rs5751876 (1976C/T, formerly known as c.1083T>C, p.Tyr361Tyr: NM_000675.6: rs5751876), rs35060421 (2592T/-, (delT>dupT, located at the exon 5 and chr22:24441942-24441947)), rs4822492 ((C>G, in the 5.5 kb 3′ flank region ADORA2A gene located at chr22:24447626), rs11704959 (C>T or A, intronic SNP that located at the chr22:24424515), rs2267076 (T>C or G, intronic SNP that located at the chr22:24434627), rs148396566 (1018G/A

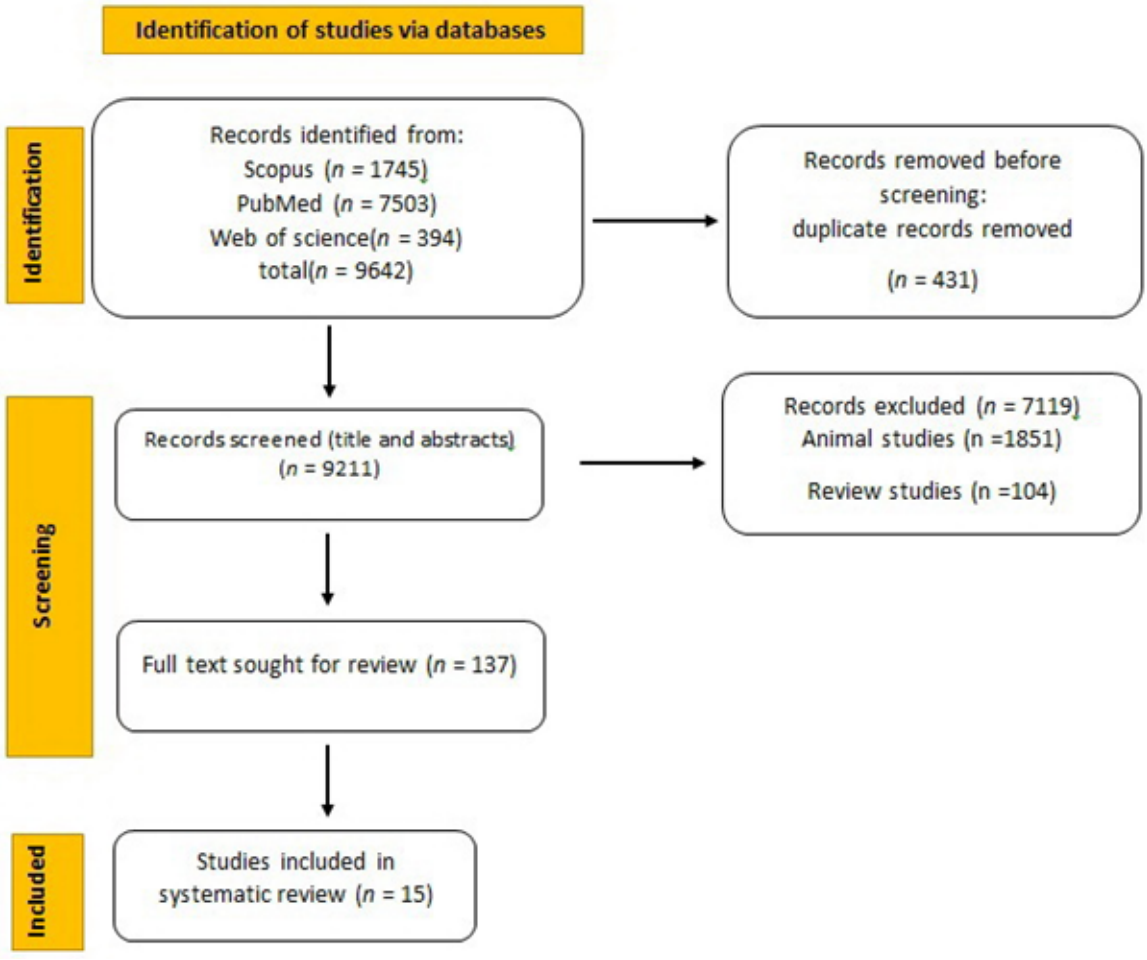

Figure 1. Flowchart of study selection and inclusion

Table 1. Studies on A2aAR gene polymorphisms with associations to anxiety disorder

Reference	Age[#]	Sample	Type of SNP	Type of illness	Genotyping	Outcome
Freitag et al. 2010 (9)	10.5 (5.7)	nP=98 (8 F, 90 M), nC=234 (20 F, 214 M); Caucasian	rs5751862, rs5760405 (263C/T), rs2298383, rs3761422, rs2236624, rs5751876 (1976C/T), rs35320474 (2592T/-), rs4822492	ASD	PCR-RFLP	A2aAR rs2236624 was associated with autism spectrum disorder. And, replicated A2aAR variants (rs3761422, rs5751876 and rs35320474) as risk factors for anxiety were reported in healthy and ASD individuals.
Hohoff et al. 2010 (10)	18-65	nP=457 (290 F, 167 M), nC=457 (290 F, 167 M) for panic disorder subgroup and nC=422 (222 F, 202 M) for anxious personality subgroup; German*	rs5751862, rs5760405, New3, rs11704959, rs2298383, rs3761422, rs2267076, rs5751876	Panic disorder, Agoraphobia, Anxious personality	TaqMan SNP genotyping assay	The rs5751876 was found to be associated with panic disorder, particularly agrophobia. The rs5751876, rs5751862, rs2298383 and rs3761422, as well as the corresponding haplotypes were associated with anxious personality. The rs2298383 showed functional potential and might therefore represent the true underlying causal variant.
Domschke et al. 2012 (15)	26.01 (5.75)	nP=110 (54 F, 56 M), nC=NA. German	rs5751876 (1976T>C)	Startle reflex	PCR-RFLP	1976TT risk genotype increased startle magnitudes; women seem to be more affected.
Hohoff et al. 2020 (22)	34.2 (14.1)	nP=43 (11 F, 32 M), nC=NA; German*	rs5751876 (1976T>C)	Healthy volunteers	PCR	The rs5751876 impact sleep and might be involved in regulating anxiety disorders.
Childs et al. 2008 (12)	18-35	nP=162 (83 F, 81 M), nC=NA; European-American, African-	rs5760405, rs2298383, rs3761422,rs2236624, rs5751876, rs35320474,	Caffeine-induced anxiety	TaqMan SNP genotyping assay	The T/T genotype of the rs5751876 1976C/T polymorphism was associated with anxiogenic responses to 150 mg caffeine, significantly.

Continued Table 1.

		American, Asian-American, and other	rs5751862 and rs4822492			
Rogers et al. 2010 (13)	18-65	nP=416 (218 F, 198 M), nC=NA; German*	rs5751862, rs5760405, New3, rs11704959, rs2298383, rs3761422, rs2267076, rs5751876	Anxiogenic effect of habitual caffeine intake	TaqMan SNP genotyping assay	The rs5751876 TT and rs3761422 genotype were associated with effects of caffeine on anxiety, alertness, or headache.
Yamada et al. 2001 (17)	41.2 (11.2) (M), 36.9 (10.8) (F)	nP=91 (48 F, 43 M), nC=100 (50 F, 50 M); Japanese	405C>T (exon 2), 432C>T (exon 2), 1018G>A (Gly340Ser), 1083C>T (rs5751876)(exon 2)	Panic disorder	PCR-RFLP	No evidence of association between the A2aAR variants and panic disorder was found.
Lam et al. 2005 (16)	39.1 (10.8)	nP=104 (61 F, 43 M), nC=192 (104 F, 88 M); Chinese	rs5751876 (1976T>C)	Panic disorder	PCR-RFLP	No significant association was found between the distribution of the A2aAR 1976T>C genotypes (P = 0.296) or alleles (P = 0.864), nor the age of onset (P = 0.719) either for mitral-valve prolapse or agoraphobia in panic disorder patients.
Gaiewska et al. 2013 (14)	26.86 (5.7)	nP=114 (57 F, 57 M), nC=129 (68 F, 61 M); Caucasian	rs5751876 (1976T>C)	Healthy subjects	PCR-RFLP	In A2aAR 1976TT homozygotes females an impaired ability was reported to selectively process very early information and to gate irrelevant sensory information, in response to caffeine as compared to male A2aAR 1976TT

Continued Table 1.

						homozygotes, while no significant effects were observed in the A2aAR 1976CC/CT non-risk genotype.
Hamilton et al. 2004 (20)	NA	nP=153, nC=NA; Caucasian	Five SNPs (sequence not available) in or near the A2aAR gene	Panic disorder	SNPs fluorescence polarization	Only one SNP with a silent substitution (1083C/T, SNP-4) in the second coding exon showed high LOD score (2.98 (ɵ=0)). No significant association tests were reported for any of the five A2aAR SNPs. Moreover, SNP haplotypes in the triads revealed one 3-marker haplotype (SNPs 1, 4, 5) was associated with panic disorder (P = 0.029).
Hohoff et al. 2005 (23)	23.9 (4.4)	nP=99 (49 F, 50 M); nC=NA; German*	263C>T (rs5760405), 1976T>C (rs5751876), 2592C> Tins	Anxiety response of healthy volunteers to the amphetamine	PCR-RFLP	Significant associations were reported for just 1976C/T and 2592C/Tins polymorphisms with increases in anxiety after amphetamine administration.
Hohoff et al. 2009 (21)	32.5 (12.8)	nP=17 (9 F, 8 M), nC=NA; German*	rs5751876 (1976T>C)	Anxiety response to blood-injury phobia	PCR-RFLP	Patients homozygous for the A2aAR 1976T allele have anxiety related arousal in blood-injury phobia as compared to patients carrying at least one 1976C allele.
Fraporti et al. 2019 (28)	10.37 (0.27)	nP=133 nC=304;White Brazilians and European immigrants	rs2298383, rs3761422	Attention deficit/hyperactivity disorder	TaqMan SNP genotyping assay	The rs2298383 TT genotype of A2aAR was associated with the presence of anxiety disorders (P = .004) in patients with attention deficit/hyperactivity disorder.

Continued Table 1.

Deckert et al, 1998 (19)	NA	nP=98, nC=98; German	432C>T and 1083C>T (rs5751876)	Panic disorder	PCR-RFLP	The silent mutation, 1083C/T with the 1083T allele (P = 0.01) and 1083T/T genotype (P = 0.024) in the A2aAR gene was related to panic disorder.
Alsene et al. 2003 (18)	21.3 (2.7)	nP=100 (46 F, 54 M), nC=NA; Caucasian	263C>T (rs5760405), 1976T>C (rs5751876), 2592C> Tins	Caffeine-induced anxiety	PCR-RFLP	Significant association was reported between 1976C>T and 2592C>Tins A2aAR gene polymorphisms and self-reported caffeine-induced anxiety.

Abbreviations: A2aAR, adenosine A2a receptor; ASD, autism spectrum disorder; nP, number of patients; nC, number of controls; M, male; F, female; SNPs, single nucleotide polymorphisms; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; NA, not available.

#Age (year) are presented as mean (SD) or range.

*According to the authors affiliation

(Gly340Ser) as a missense variant located at the chr22:24441268) and other silent mutations such as 405C/T, 432C/T.

As shown in Table 1, Caucasians and Germans were the groups of people that were genotyped for interested ADORA2A SNPs in the included studies. According to the results, ten studies detected the ADORA2A gene using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Moreover, the TaqMan SNP genotyping assay was also used to determine the association between ADORA2A gene polymorphisms and ADs. Most of the included patients were affected by panic disorder, agoraphobia, or caffeine-induced anxiety.

Moreover, an interrelationship between gender, ADORA2A SNPs, and the risk of ADs was mentioned only in three studies (15, 16, 19). Indeed, both Domschke et al. (16) and Gaiewska et al. (15) indicated a significant risk of rs5751876 (1976TT) genotype and progress of ADs in females compared with male subjects. However, Alsene et al. (19) found no statistically significant relationship.

Polymorphisms at coding sequences of ADORA2A

ADORA2A rs5751876 polymorphism and ADs susceptibility

The rs5751876 (1976C/T or previously 1083C/T) polymorphism is a restriction fragment length polymorphism (RFLP) of RsaI enzyme (20) in that the T allele of a silent polymorphism in exon 5 of ADORA2A gene (13). Of 15 included articles in the current systematic review, fourteen studies provide the necessary information on the specific association between the ADORA2A rs5751876 polymorphism, as one of the main predisposing polymorphisms, and ADs (10-24).

The rs5751876 polymorphism is a synonymous

variant leading to a silent codon change (Tyr/Tyr) (25); therefore, it may not functionally change ADORA2A signaling. Nonetheless, according to the present systematic review, the TT homozygote genotype of this SNP was more prevalent and overrepresented in individuals with ADs compared to controls, as well as T/T homo- and C/T heterozygotes scored higher in the anxiety-related personality scores than C/C homozygotes, indicating that such genetic variation in the ADORA2A gene may be associated with susceptibility to anxiety.

Moreover, an essential and noticeable issue in this systematic review is that susceptibility to ADs in individuals carrying rs5751876 polymorphism may be ethnicity-dependent. Seemingly, carrying this SNP in Asian populations (Japanese (18) and Chinese (17)) is not associated with ADs susceptibility. However, Americans and European races (mainly Caucasian) appear to be more affected by this SNP (Table 1). Notably, the reproducibility of such results should be confirmed in larger sample sizes.

Furthermore, proposedly, the rs5751876 TT genotype might be associated with alterations in the fronto-insular connectivity in the synopsis, leading to dysfunction of the attentional network in processing both salient exteroceptive and interoceptive information. These alterations could reflect as enhanced processing of interoceptive information in rs5751876 TT carriers causing ADs (26). However, the interpretation of these results may be complicated, as rs2236624 and rs5751876 polymorphisms of the ADORA2A gene may modify regional adenosine A1 receptor availability (specifically at the fear network), which in turn increases anxiety (12).

Notably, the rs5751876 is not specific to panic disorder signs, but also anxious personality showed relevant associations (11). Indeed, this is confirmed in the different studies (13, 19, 27) implicating a broader impact of rs5751876 on different forms of Ads, such as increased anxious modality in different challenge tests or even elated anxiety arousal in blood-injury phobia. It can be deduced that rs5751876 may considered an excellent primary risk factor that increases the susceptibility to anxiety reactions despite anxiogenic situations. Therefore, screening persons who carry its alleles in combination with a specific set of environmental factors might be a potential strategy for managing ADs.

ADORA2A rs35060421 polymorphism and ADs susceptibility

The rs35060421 polymorphism (synonymous exonic exchange Tyr361Tyr, formerly known as 1976C/T or 1083C/T) is an RFLP of the MboII, and this polymorphism is located at exon 5 of the ADORA2A gene (10). Four studies (10, 13, 19, 24) provide evidence for the correlation of rs35060421 and ADs. All these studies implicated that rs35060421 is in nearly complete linkage disequilibrium ($P<0.05$). In silico assessment showed that 2592Tins/Tins polymorphism probably changed ADORA2A expression (19). Although the 1976C/T and 2592C/Tins polymorphisms themselves are not clinically relevant polymorphisms (2592C>Tins located in the 3′UTR region of ADORA2A gene any potential functional relevance), as compared with 1976C/T–2592C/Tins genotype, individuals with 1976T/T (rs5751876) and 2592Tins/Tins genotypes experience a more significant increase in anxiety after caffeine (19, 24). These SNPs may be the genetic risk factors for anxiety not only in healthy but also in individuals with autism spectrum disorders (10).

Other exon-embedded polymorphisms

The rs5760405 (263C>T) polymorphism, as an RFLP of the BseNI enzyme, is located at exon 1 of the ADORA2A gene. The genotype of this SNP and the risk of ADs were addressed in six studies (10, 11, 13, 14, 19, 24). None of these studies reported significant differences between individuals carrying rs5760405 and controls. The evidence suggests that the frequency of rs5760405 alleles conforms to Hardy-Weinberg equilibrium (P>0.05), and having this SNP is not linked to ADs phenotypes. Notably, Hohoff et al. (11) reported a strong correlation between 263C>T polymorphism and anxiety-related personality scores (TPQHA4) without significant association with panic disorder. Additionally, according to the literature review, the 432C>T (silent mutation) (18, 20), 405C>T (18), and 1018G>A (Gly340Ser) (18) SNPs (as an RFLP of the RsaI, MobI, and Hae III enzymes, respectively) showed no significant relationship with ADs.

Polymorphisms at non-coding sequences of ADORA2A

ADORA2A rs5751862 polymorphism and ADs susceptibility

The rs5751862 polymorphism is located at the 5′flank of the ADORA2A gene and could be genotyped by the 5′exonuclease assays using different colored fluorophores for allele labeling (28). In the current systematic review, four included studies investigated the relationship of the rs5751862 genotype with the risk of ADs (10, 11, 13, 14). Rogers et al. (14) and Freitag et al. (10) showed that the frequency of rs5751862 genotype has no significant association with ADs phenotypes. However, Childs et al. (13) revealed a trend for the main effect of the rs5751862 genotype on anxiety. Furthermore, a significant interaction was reported between rs5751862 and D2 dopamine receptor (DRD2) rs1079597 Taq1B. Indeed, such combinations of ADORA2A and DRD2 polymorphisms may be related to more variability in caffeine-induced anxiety than the individual SNPs alone. Ultimately, strong correlations were reported by Hohoff et al. (11) between rs5751862 polymorphism and anxiety-related personality scores (TPQHA4) without significant association with panic disorder. They also reported high Linkage Disequilibrium (LD) between rs5751862 and rs5751876 polymorphisms.

ADORA2A rs2298383 and rs3761422 polymorphisms and ADs susceptibility

The rs2298383 (as a RFLP of the HpaII enzyme) and rs3761422 polymorphisms are located in the promoter region of ADORA2A gene, suggesting the regulatory role of these polymorphisms in ADORA2A expression (29). By the way, rs2298383 SNP probably has the highest score for regulating ADORA2A function compared to other variants (30). Therefore, this SNP might represent a true causal variant underlying ADs development.

Five studies (Table 1) evaluated the correlation of rs2298383 and rs3761422 genotypes with the risk of ADs development (10, 11, 13, 14, 30). These studies implicated that these variants are in high linkage disequilibrium (LD), and rs2298383 TT and rs3761422 (T/T homo- and C/T heterozygotes) genotypes were nominally associated with ADs. Moreover, patients carrying ADORA2A T/C (rs2298383/rs3761422) haplotypes have significant susceptibility to ADs. In contrast, Rogers et al. (14) found no clear association between rs2298383 genotype and

caffeine-induced anxiety.

The anxiolytic effect of rs2298383/rs3761422 is probably due to the simultaneous presence of ADORA2A T/C (rs2298383/rs3761422) and DRD2 (dopamine receptor 2) A/T (rs1076560/rs2283365) risk haplotypes, which are associated with anxiety. Fraporti et al. (30) suggest that 40% of the effect of these variants on anxiety was attributable to synergism.

Other intro-embedded polymorphisms

Other investigated ADORA2A SNPs include i) rs2236624 (as a RFLP of the MnlI enzyme) evaluated by Freitag et al. (10), who showed a nominal relationship between rs2236624-CC genotype and ADs. In contrast, Chance and Childs et al. (13) revealed no associations; ii) rs4822492 is a 3′flank SNP of ADORA2A gene, assessed by Childs et al. (13), who showed a significant association between caffeine-induced anxiety and rs4822492 polymorphism. However, Freitag et al. (10) reported no associations; iii) rs2267076 that investigated two studies, one indicated a nominal association between ADORA2A rs2267076 polymorphism and PD (11), and other reported no significant associations (14); iv) rs11704959 and NEW3 polymorphisms showed no significant relations with ADs (11, 14).

Conclusion

The current systematic review showed that the rs5751876 (1976T>C or previously 1083C>T) and rs35060421 (2592C>Tins) polymorphisms of the ADORA2A gene were associated with an increased susceptibility to the ADs. Moreover, the rs2298383 TT genotype may be the causal regulatory factor of ADORA2A function in individuals with ADs. This conclusion may be quite race-dependent, as Asian populations carrying such SNPs did not show any significant correlations with ADs. Undoubtedly, more investigations are needed to robust these implications.

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Author's Contribution

Haniyeh Karami, and Ilia Abrishami searched data bases. Mohammad Keyvaloo Shahrestanki and Milad Khorasani involved in the screening and data extraction. Mohammad Keyvaloo Shahrestanki and Hadi Lotfi prepared the drafts of the manuscript. Mohammad Keyvaloo Shahrestanki and Zeinab Babaei finalized the manuscript, and provided funds.

Conflict of interest

No conflict of interests declared.

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