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REVIEW ARTICLE

Pharmacogenetics of Cannabinoids

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Abstract Although the application of medical marijuana and cannabinoid drugs is controversial, it is a part of modern-day medicine. The list of diseases in which cannabinoids are promoted as a treatment is constantly expanding. Cases of significant improvement in patients with a very poor prognosis of glioma or epilepsy have already been described. However, the occurrence of side effects is still difficult to estimate, and the current knowledge of the therapeutic effects of cannabinoids is still insufficient. In our opinion, the answers to many questions and concerns regarding the medical use of cannabis can be provided by pharmacogenetics. Knowledge based on proteins and molecules involved in the transport, action, and metabolism of cannabinoids in the human organism leads us to predict candidate genes which variations are responsible for the presence of the therapeutic and side effects of medical marijuana and cannabinoid-based drugs. We can divide them into: receptor genes—*CNR1*, *CNR2*, *TRPV1,* and *GPR55*, transporters—*ABCB1*, *ABCG2*, *SLC6A*, biotransformation, biosynthesis, and bioactivation proteins encoded by *CYP3A4*, *CYP2C19*, *CYP2C9*, *CYP2A6*, *CYP1A1*, *COMT*, *FAAH*, *COX2*, *ABHD6*, *ABHD12* genes, and also *MAPK14*. This review organizes the current knowledge in the context of cannabinoids pharmacogenetics according to individualized medicine and cannabinoid drugs therapy.

Key Points

Cannabinoids have many side effects and adverse drug reactions.

Robust genetic associations with cannabinoids efficacy and adverse effects have not yet been studied extensively.

Single nucleotide polymorphism in the *CNR1* gene and marijuana addiction is the most studied; however, the results of various studies are still not conclusive.

1 Introduction

Complexity of the cannabinoid pathway, as well as individual genetic predispositions in the population, can lead to various body responses on the cannabinoids treatment. It has been considered that long-term use of cannabis may be a risk factor for psychosis and neurocognitive disorders [1–3]. Short-term application may result in an increase in non-serious adverse events [4].

The patient's response to cannabinoid treatment may have a genetic background, which depends on genes polymorphism involved in the action, metabolism, and the transport of these substances in the organism. Based on the cannabinoid distribution and activity mechanism as well as proteins involved in their biotransformation, a set of candidate genes can be chosen which variants may determine the therapeutic effect and also the occurrence of possible

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side effects and adverse reactions. We can divide them into the following groups and contain genes encoding receptors—*CNR1*, *CNR2*, *TRPV1, GPR55, OPRM1,* and *GABRA2;* transporters and action—*ABCB1*, *ABCG2*, *SLC6A4,* and *COMT*; enzymes involved in the metabolism of cannabinoids—*CYPs* and *UGTs*; biosynthesis, and bioactivation of endocannabinoids: *FAAH*, *MAGL*, *COX2*, *ABHD6*, and *ABHD12*; and cannabinoid-related cellular processes: *MAPK14.*

This work systematizes and sums up the state of current knowledge in the field of pharmacogenetics of cannabinoids according to cannabinoids therapy and personalized medicine.

2 Methods of Literature Search

Papers published until February 2017 was included. Publication search was performed in Medline and PubMed database. The keywords: cannabinoids polymorphisms, cannabinoids candidate genes, cannabis, medical cannabis, and addiction were used.

3 Gene Variants vs Cannabinoids Use

As mentioned above, the effect of cannabis can be dependent on pharmacogenetic factors. Below, we discuss the current data according to genes polymorphisms which are involved in transport, action, and biotransformation of cannabinoids (Table 1).

3.1 Receptor Genes

3.1.1 CNR1 and CNR2

In 1990 and in 1993, the first and second cannabinoid receptors (CB1, CB2) were identified and cloned, which contributed to a significant increase in the understanding of cannabinoids. The CB1 receptor, encoded by the *CNR1* gene (cannabinoid receptor type 1, OMIM: 114610) [5], is located on the human chromosome 6q14-15 and consists of four exons, of which the latter is the largest and most commonly expressed in brain tissue [6]. Evolutionary conservatism is a characteristic feature of the CB1 receptor. It has been observed that amino acid sequences are similar in humans, mice, and rats to a degree of 97–99% [7]. Activation of the CB receptor stimulates the appetite and has antiemetic, analgesic, and sedative effects [8]. Association studies between the occurrence of single nucleotide polymorphism (SNP) in the *CNR1* gene and marijuana addiction, also including the trinucleotide repeat locus $(AAT)_n$ and insertion–deletion (-3180T) polymorphism, revealed contradictory results [9]. Comings et al. showed a correlation between $(AAT)_{>5}$ repeats with drug dependence in 206 non-Hispanic Caucasians (92 subjects and 114 controls) [10], but most studies on trinucleotide repeats $(AAT)_n$ demonstrated negative results [11–13].

In an investigation performed on the group of 1923 individuals, a correlation of two SNPs in *CNR1* gene rs806368 ($p = 0.05$) and rs806380 ($p = 0.009$) with cannabis dependence were identified [9]. Haplotype analysis revealed stronger association by rs806380 [9]. In turn, Hopfer and his group analyzed five SNPs variants (rs2273512, rs6454674, rs806380, rs806377, and rs104935) in *CNR1* gene and demonstrated that rs806380 was significantly associated with cannabis dependence symptoms [14]. However, Herman et al. have not confirmed these observations [15]. The same conclusions were reached by Australian and American researchers [16, 17]. Moreover, Hartman group showed an association ($p = 0.029$), of rs1049353 in the *CNR1* gene with cannabis dependence symptoms in case–control samples ($n = 224$) [17]. On the other hand, Bühler et al. indicated non-statistically significant correlation of *CNR1* rs1049353, rs806368, rs6454674, and rs7766029 with cannabis use in a group composed of young individuals ($n = 91$) [18]. In case of rs806368, Zuo and co-workers analyzed 451 healthy control subjects and 550 substance dependence (including European Americans and African Americans) and showed that substance dependence increased with the number of G alleles in European Americans significantly [19]. In studies of rs2023239 *CNR1* gene variant among 105 daily marijuana smokers—students from the University of Colorado were tested [20]. Participants with CT or CC genotype were more susceptible to the negative impact of the cannabinoids action (greater withdrawal, negative affect, and higher levels of craving to smoke more). Moreover, heterozygous had 20% higher marijuana dependence checklist scores than TT subjects [20]. Di Marzo et al. demonstrated that marijuana abuse by carriers of the c.*2394A>G (rs12720071) variant of the *CNR1* gene contributes to deficits in the volume of white matter in the brains of schizophrenia patients [8].

The second gene selected through GWAS is *CNR2* encoding CB2 (OMIM: 605051). It has been actively investigated for its role in osteoporosis, inflammatory responses, leukemia, and certain forms of cancer. However, investigations on the *CNR2* gene in the context of addiction are rarely described in the literature. The Ishiguro research group showed a link between the polymorphism c.188A>G (p.Gln63Arg, rs2501432) and alcohol dependence in the Japanese population [21]. In turn, Carrasquer et al. introduced Gln63Arg, His316Tyr, and Gln63Arg/His316 mutations in recombinant human CB2 receptors. Mutant

Table 1 Association of genetic variants with response to cannabinoids

Function	Gene	Genetic variant			Study group	Effect	Reference
		RefSNP numbers	Nucleotide change	Amino acid change			
Receptor	*CNR1*	806380	c.-63-9597T>C	Intron	379 cases (EA, AA)	Cannabis dependence	[9]
					327 cases (CS, H, AA)	Cannabis dependence	[14]
					91 students (CS)	No association with drug consumption	[18]
					7452 subjects (CS)	No association with cannabis use	[16]
		806379	c.-63-6211T>A	Intron	92 cases (EA, AA)	No association with cannabis dependence	[15]
		806368	c.*3475A>G	3′ UTR	7452 subjects (CS)	No association with cannabis use	[16]
					550 cases with drug/alcohol dependence and 451 controls, (EA, AA)	Influence drug dependence	[19]
		1535255	c.-63-6152A>C	Intron	92 cases (EA, AA)	No association with cannabis dependence	[15]
					7452 subjects (CS)	No association with cannabis use	[16]
		6928499	c.-63-6233C>G	Intron	92 cases (EA, AA)	No association with cannabis dependence	[15]
		2023239	c.-63-5426A>G	Intron	92 cases (EA, AA)	No association with cannabis dependence	[15]
		–	(AAT)*n* repeats	3′near gene	92 cases and 114 controls (CS)	$(AAT)_{>5}$ associated with drug dependence	[13]
					529 cases (EA, AA)	No association with drug- or alcohol dependence	[10]
					375 Chinese	No association with heroin abuse	[11]
					40 subjects (CS)	No association with drug use and drug abuse	[12]
		1049353	c.1359G>A	Thr453=	224 cases, 108 controls (CS, H)	Association with cannabis dependence symptoms for CSS	[17]
		6454674	-64+1046T>G	Intron	550 cases, 451 controls (EA, AA)	Influence drug dependence	[19]
	CNR2	2501432	188A>G	Gln63Arg	HEK293 cells	Alterations in the CB2 receptor functions	[22]
		2229579	946C>T	His316Tyr			
Transport	*ABCB1*	1045642	3435C>T	Ile1145Ile	40 cases, 40 controls (CS)	CC genotype associated with cannabis dependence $p = 0.045$, OR = 6.61 (1.05–46.58)	[37]

Table 1 continued

Function	Gene	Genetic variant			Study group	Effect	Reference
		RefSNP number rs	Nucleotide change	Amino acid change			
Biotranformation	*FAAH*	324420	385C>A	Pro129Thr	1737 subjects	A/A genotype associated with drug drug use, abuse	[60]
					745 subjects (CS)	No association with risk for alcohol or tobacco use	[57]
					105 students at the University of Colorado	No association in marijuana smokers for dependence	[20]
	COMT	4680	472A>G	Val158Met	42 cases and 32 controls, (European-CS)	Impact of THC on memory and sustained attention	[40]
					86 cannabis users and 58 non-drug users, (European-CS)	Moderate the impact of cannabis use on executive functions	[39]
					56 subjects	Association between cannabis and psychotic phenomena	[45]
					803 individuals	Psychotic symptoms and to developing schizophrenia form disorder in cannabis users	[46]
Others	*GABRA2*	rs279858	231A>G	Lys132=	1227 (CS, AA)	Association with marijuana dependence	[33]
					4597 subjects	No association in frequency of cannabis use	[30]
	OPRM1	1799971	118A>G	Asn40Asp	891 subjects (EA, AA, H)	No significant differences	[31]
	NRG1	17664708	122-16329C>T	Intron	738 (AA, EA)	Associated with cannabis dependence in both AAs	[32]

EA European American, *AA* African American, *CS* Caucasians, *H-* Hispanic, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *CNR1* cannabinoid receptor 1, *CNR2* cannabinoid receptor 2, *ABCB1* ATP-binding cassette subfamily B member 1, *FAAH* fatty acid amide hydrolase, *COMT* catechol-O-methyltransferase, *GABRA2* gamma-aminobutyric acid type A receptor alpha2 subunit, *OPRM1* opioid receptor mu 1, *NRG1* neuregulin 1, *THC* tetrahydrocannabinol

CB2 receptors were than transfected into HEK293 cells. Through this study, it was demonstrated that the CB2 polymorphic receptors at both positions 63 and 316 are able to bind cannabinoid ligands and mediate signal transduction which may contribute to the etiology of certain diseases [22].

3.1.2 Trpv1

The *TRPV1* gene encodes the transient receptor potential action channel subfamily V member 1 (OMIM: 602076). So far, there have been no association studies that can demonstrate a relationship between the occurrence of *TRPV1* gene polymorphism and addiction to marijuana. Most research on the functioning of the endocannabinoid system (ECS) focuses on two well-characterized receptors: CB1 and CB2. In recent years, scientists have shown that this mechanism is much more complex and the ECS consisting of other types of receptors, which may affect the activity of ligands in many physiological processes [23]. Arnold et al. have described that Δ^9tetrahydrocannabinol (Δ^9THC) binds to CB1 and CB2 receptors with similar affinities and behaves as a partial agonist, but it does not bind TRPV1 receptors. Cannabidiol (CBD) showed a more complex profile—simultaneous blockade of CB2 and TRPV1 significantly inhibited CBD-induced *MDR1* (multidrug resistance, also known as *ABCB1* gene, which was described in the next section) mRNA expression and both CB2 and TRPV1 antagonist were not effective when tested individually. CBD in its two enantiomeric forms showed

no affinity for the CB1 and CB2 receptors (-)enantiomer or showed significant affinity for both receptor subtypes. It is, therefore, possible that the effectiveness of the CBD is related to inhibition of fatty acid amide hydrolase (FAAH) and elevates the level of anandamide (AEA). This would imply that AEA's simultaneous activation of CB2 and TRPV1 is necessary for increased *MDR1* mRNA expression following CBD exposure [23].

3.1.3 Gpr55

The human gene that encodes GPR55 protein is located on the long arm of chromosome 2 (2q37.1), encompasses 53,910 bases, and contains four exons (GeneCards, GeneBank, and Ensemble). The GPR55 receptor is consists of 319 amino acids and 7 hydrophobic domains. It belongs to a G-protein-coupled receptor superfamily, precisely to the rhodopsin-like (ClassA) family of GPCRs. The molecular mass of the protein is 36,637 Da. It is an integral membrane protein and its structure reminds structure of cannabinoid receptor. The GPR55 is de-orphanized as a CB receptor [24]. The amino acid sequence is the most similar to the GPR35 (27%), P2Y (29%), GPR23 (30%), and CXCR4 (26%) but also to CB2 (14.4%) and CB1 (13.5%) receptors [24]. It has been suggested that GPR55 is a novel CB receptor [25].

Expression of *GPR55* (OMIM: 04107) in certain areas of the human brain is responsible for binding exo- and endogenous cannabinoids [26, 27]. From the functional analysis of the sole missense polymorphism c.584G>T (p.Gly195Val, rs3749073) in the *GPR55* gene, which have a binding affinity for endocannabinoids, an association with anorexia nervosa has been observed [28].

3.1.4 OPRM1 and GABRA2

Many reports in the literature describe the possible association of polymorphisms with cannabis dependence [27, 29–32]. Particular attention is drawn to genes encoding opioid receptor (*OPRM1*, OMIM: 600018) and gamma-aminobutyric acid (GABA) receptors (*GABRA2*, OMIM: 137140).

Agraval et al. suggest cannabis dependence association with SNPs in *GABRA2* gene [33], in opposite to Lind group results [30]. They genotyped 11 SNPs within or flanking *GABRA2* in 4597 subjects and showed no correlation with alcohol, smoking, or cannabis dependence [30].

OPRM1 gene encoding the mu opioid receptor (MOR) is also considered as candidate gene for cannabis use side effect. Gelernter and co-workers analyzed two polymorphisms affecting protein sequence in exon 1, Ala6Val and Asp40Asn in African American (AA), European American (EA), Hispanic, Japanese, Ethiopians, Bedouins, and Ashkenazi Jews populations. The entire study group consisted of 891 subjects presented differences in the frequency of alleles between the AA and EA populations have been observed. For other studied subjects, they did not observe significant heterogeneity among. For all analyzed populations, neither polymorphism appears to be a direct risk factor for substance dependence [31].

3.2 Transport and Action Genes

3.2.1 ABCB1 and ABCG2

According to the DrugBank data base (www.drugbank.ca), there are mainly two membrane-associated proteins from the superfamily of ATP-binding cassette (ABC) transporters involved in cannabinoid transportation: ABCB1 and ABCG2, which play the role of multidrug resistance, especially ABCB1. Both proteins transport the molecules across extra- and intra-cellular membranes [34]. *ABCB1* gene, also known as multidrug resistance gene (*MDR1*), is located in the 7q21. It encodes P-glycoprotein (P-gp) and comprised of 28 exons [35]. *ABCB1* polymorphisms—the rs2032582 (c.2677G>T/A), rs1045642 (c.3435C>T), and rs1128503 (c.1236C>T) are known to modify the drug pharmacokinetics, but there were not yet studied for their role in cannabis dependence [36]. Benyamina et al. try to determine if *ABCB1* rs1045642 polymorphism corresponds with cannabis dependence risk [37]. In this study, Caucasian patients diagnosed with isolated cannabis dependence ($n = 40$) with healthy controls ($n = 40$) were compared. Patients with cannabis dependence demonstrated significantly higher 3435C allele frequency (62.5 vs 43.8%, $p = 0.017$) and CC genotype [50 vs 20%, $p = 0.005$, OR = 4.00 (1.50–10.60)]. These researchers postulate that *ABCB1* polymorphisms may affect Δ^9THC distribution, its psychoactive effects, and individual vulnerability to dependence. Analyses indicated that the CC genotype was independently associated with cannabis dependence [$p = 0.045$, OR = 6.61 (1.05–46.58)] and also has been associated with increased expression of P-gp, whereas the TT genotype reduces P-gp expression. It can lead to the conclusion that CC genotype may increase the tendency to cannabis dependence, while the TT genotype may increase the risk of cannabis-induced psychosis development [37].

Δ^9THC has affinity for *ABCB1* and *ABCG2* gene products; notwithstanding, it is unknown whether they modulate the brain accumulation of Δ^9THC and its functional effects on the central nervous system. Spiro et al. revealed that mice lacking of *Abcb1* and *Abcg2* proteins had higher brain Δ^9THC levels and were more sensitive to cannabinoid-induced hypothermia than wild-type mice. As the authors say, these results indicate that ABCB1 and

ABCG2 proteins prolong the brain disposition and hypothermic effects of Δ^9THC which could be a new mechanism of genetic susceptibility to the psychoactive effects of cannabis and drug interactions (e.g., addiction and anxiety) between central nervous system therapies and cannabis [38]. So far, reports on role of *ABC* transporter gene polymorphisms involved in genetic susceptibility to adverse psychoactive effects of Δ^9THC or cannabis dependence are very slight. Perhaps, such research could contribute to the assessment of individual pharmacokinetic predisposition in response to cannabis use in conjunction with other genes that can modulate the pharmacodynamic actions of the drug.

3.2.2 SLC6A4 and COMT

Two other genetic polymorphisms have been associated with the neuroadaptive effects of Δ^9THC on executive functions: 5-HTTLPR (c.199G>A, rs2553) promoter polymorphism of the *SLC6A4* gene (OMIM: 182138) and c.472G>A (p.Val158 Met, rs4680) polymorphism of the catechol-O-methyltransferase (*COMT,* OMIM: 116790) gene [27, 39]. An experimental challenge study has also shown that the *COMT* gene moderates the impact of Δ^9THC on memory and sustained attention, such that individuals carrying the high-activity genotype GG in the position c.472 are more likely to show cannabis-induced cognitive deficits [40]. In healthy individuals, the neurobiological correlates of working memory encoding suggest an abnormally increased activation of the prefrontal–parietal–striatal network in homozygous GG vs AA. This network is also abnormally hyperactivated among cannabis users when performing working memory tests [41].

The 5-HTTLPR polymorphism is one of the main regulators of the serotonin transporter function [42] and the AA genotype (lower serotonin levels) has been consistently associated with poor decision-making skills in animals and humans [39, 43, 44]. Cannabis users carrying the genotype s/s 5-HTTLPR recorded worse results in the IGT decision test (Iowa Gambling Task) than the control group (non-cannabis users) with the same genotype. It was also found that the presence of *SLC6A4* and *COMT* gene polymorphisms in people taking cannabis has a moderate influence on the body's executive functions [39].

Other studies by Verdejo-Garcia et al. showed the impact of these polymorphisms on executive functions as moderate harmful effects of marijuana in young cannabis users. Cannabis users with the *COMT* c.472 (p.Val158M, rs4680) GG (Val/Val*)* genotype showed decreased attention compared to those in the control group with another genotype for this *locus*. Interestingly, the users carrying one G allele of the *COMT* gene committed more errors during the observation, monitoring, and handling of certain elements in relation to marijuana users but with the c.472 AA (Met/Met) genotype [39]. Henquet's research shows that the heterozygous c.472G>A (Val/Met) of *COMT* gene exhibits an increased hallucinogenic effect on the action of cannabis than on patients with the G/G genotype [45].

Caspi et al. analyzed 803 individuals. Carriers of the *COMT* Val158 allele showed more often psychotic and schizophrenic symptoms when they used cannabis and, however, did not observed that in patients with two copies of the methionine allele [46]. Whereas Tunbridge et al. studied effect of *COMT* c.472G>A (p.Val158Met) genotype on the cognitive and psychotic effects of Δ^9THC. They tested 78 suffered from paranoia participants (non-clinical cohort) in Digit Span Backwards task. Δ^9THC was administered intravenously in a double-blind, placebo-controlled manner. The results showed a correlation between the occurrence of genotype and study group on working memory and indicate a similar relationship that Verdo-Garcia received in his research, namely, that Δ^9THC has an effect on the loss of efficiency for the *COMT* Val/Val, but not Met carriers but interestingly not on psychotic experiences. The results suggest that *COMT* genotype can moderate the cognitive, but not the psychotic, effects of Δ^9THC [47].

3.3 Cannabinoids Metabolism Genes

Cannabinoids metabolite formation is enzyme-depended, what was confirmed by simple experiment of synthetic cannabinoid FUBIMINA incubation for 3 h in hepatocyte samples and in buffer only [48]. The Δ^9THC biotransformation is mainly based on oxidation, decarboxylation, and conjugation with glucuronic acid.

3.3.1 CYPs Genes

Cytochrome P450 (CYP, EC1.14.14.1) superfamily enzymes, namely, CYP3A4 (significant metabolic pathway for Δ^9THC and CBD) and CYP2C9 (significant contributor to Δ^9THC metabolism) encoded by *CYP2C9* (OMIM: 601130) and *CYP3A4* (OMIM: 124010) genes, are predicted to play a major role in the primary metabolism of Δ^9THC, where THC serves as a substrate for these two CYP enzymes. Studies of Δ^9THC, CBD, and cannabinol (CBN) inhibition and induction of CYP-450 indicate a low clinical importance with interactions with hemp use; however, there is a lack of relevant data on humans [49].

The *CYP* gene family includes 57 putatively functional genes and 58 pseudogenes in humans [50]. *CYP* gene mutation and polymorphism can lead to altered or cancelled enzyme activity. Phenotypically, it manifests as poor, intermediate, efficient, or ultrarapid drug metabolizers (UMs). To date, 60 alleles of the *CYP2C9* gene (Human

Cytochrome P450 Allele Nomenclature Committee, www.cypalleles.ki.se) have been described in the literature, with the two most frequently occurring being *CYP2C9*2* (c.430C>T, p.R144C) and *CYP2C9*3* (c.1075A>C, p.I359L), which lead to decreased enzyme activity and poor metabolism. In the case of the *CYP3A4* gene, 26 alleles are known. *CYP3A4*2*, *11*, *12*, *17* are the most common cause of lower enzyme activity. Δ^9THC biotransformation may occur via the following pathways: 7-OH-Δ^8THC by CYP3A4 enzyme, 11-OH-Δ^9THC and 11-nor-9-carboxy-Δ^9THC by several UGT isoforms, 11-oxo-Δ^8THC by primarily CYP2C9; and some epoxide metabolites of Δ^8THC by epoxide hydrolase [49]. In vitro research data characterize cytochrome P-450 (CYP-450) enzymes as potential significant contributors to the primary metabolism of several exogenous cannabinoids: Δ^8THC (CYP2C9, CYP3A4), CBD (CYP2C9, CYP3A4), CBN (CYP2C9, CYP3A4), JWH-018 (CYP1A2, CYP2C9), and AM2201 (CYP1A2, CYP2C9). CYP-450 enzymes may also contribute to secondary metabolism of Δ^9THC [49].

3.3.2 UGTs Genes

Cannabinoids are the subject of UDP-glucuronosyltransferase (UGT)-dependent glucuronidation. UGTs have been identified as capable of catalyzing both primary (CBD and CBN) and secondary (Δ^9THC, JWH-018, and JWH-073) metabolizers of some cannabinoids [49]. Mazur et al. demonstrated that the most important in this process are UGT1A9, UGT1A7, UGT1A8, and UGT1A10 enzymes encoded by genes with the same names: *UGT1A9* (OMIM: 606434), *UGT1A7* (OMIM: 606432), *UGT1A8* (OMIM: 606433), and *UGT1A10* (OMIM: 606435), respectively [51] and found that the glucuronidation of CBN and Δ^9THC-OH was carried out at similar rates by UGT1A9. In contrast, UGT1A10 was threefold more effective at CBN conjugation than Δ^9THC-OH. UGT1A1 and UGT1A3 demonstrated the only measurable activity toward Δ^9THC-COOH. Moreover, CBN was glucuronidated at high levels by UGT1A10 and to a lesser extent by UGT1A7, UGT1A9, and UGT2B7. Activity toward CBD was limited, and the UGT1A9, UGT2B7, and UGT2B17 formed a minimal amount of a glucuronidated CBD product [51].

UGTIA genes are a part of a complex locus that encodes several UDP-glucuronosyltransferases with a specific sequence of the first exon and common exons 2–5. Most studies concern the *UGT1A9* gene. The first exon encodes the substrate binding and regulation of gene expression is performed by means of its own promoter preceding the exon 1. A number of polymorphisms changes occur mainly in the promoter region and exon 1 of the gene *UGT1A9* (https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature). Previous studies have shown the variable activity of the UGT1A9 enzyme. The most important alleles of *UGT1A9*3*, *4,* and *5 lead to the reduction or elimination of the enzymatic activity of the protein product.

3.4 Endocannabinoids Biosynthesis and Bioactivation Genes

The two most studied endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Changes in the AEA and 2-AG concentration in various tissues may be the cause of many diseases of the immune, neurological and neuropsychic system, as well as obesity, cancer, and cardiovascular diseases [52]. They initiate downstream signaling by binding to their target receptors: CB1, CB2, GPR55, and TRPV1 [53]. There are several paths for the formation and metabolism of AEA and 2-AG. 2-arachidonoylglycerol is produced by the hydrolysis of diacylglycerols DAGs, almost exclusively by one-selective DAG lipases α and β. AEA is metabolized by the fatty acid amide hydrolase (FAAH), whereas 2-AG does this via monoacylglycerol lipase (MGL). 2-AG is also metabolized to some extent by other lipases, such as αβ-hydrolase domain 6 (ABHD6) and 12 (ABHD12), as well as FAAH (Fig. 1).

Level of endocannabinoids is elevated at key sites involved in pain processing, such as neuropathic pain. Exploiting the potential therapeutic properties of cannabinoids may be possible by maximizing the effects of endocannabinoids in which are terminated by re-uptake and metabolism by different enzymes as FAAH, MAGL, and cyclooxygenase type 2 (COX-2). Prevention of metabolism or uptake of endocannabinoids would result in raising the level of these lipid compounds in the tissues and likely to affect the analgesic response in models of acute pain [54].

3.4.1 FAAH

Fatty acid amide hydrolase gene (*FAAH*; OMIM: 602935), located on the 1p35-34 human chromosome [55], encodes enzymes of ECS, which catabolize the conversion of both AEA and 2-AG to arachidonic acid, ethanolamine, or glycerol. A variant p.P129T in the *FAAH* gene results in reduced enzyme activity among obesity patients [56]. Tyndale et al. demonstrated that inhibition of this enzyme, which decreases the intensity of endocannabinoid degradation, enhances analgesia not induced by opioids [57].

Other studies have shown a link between the *FAAH* gene missense mutation c.385C>A (p.Pro129Thr, rs324420), which results in the conversion of proline into threonine in exon 3. Many researchers have demonstrated that this sequence variation may be related to the dependence of

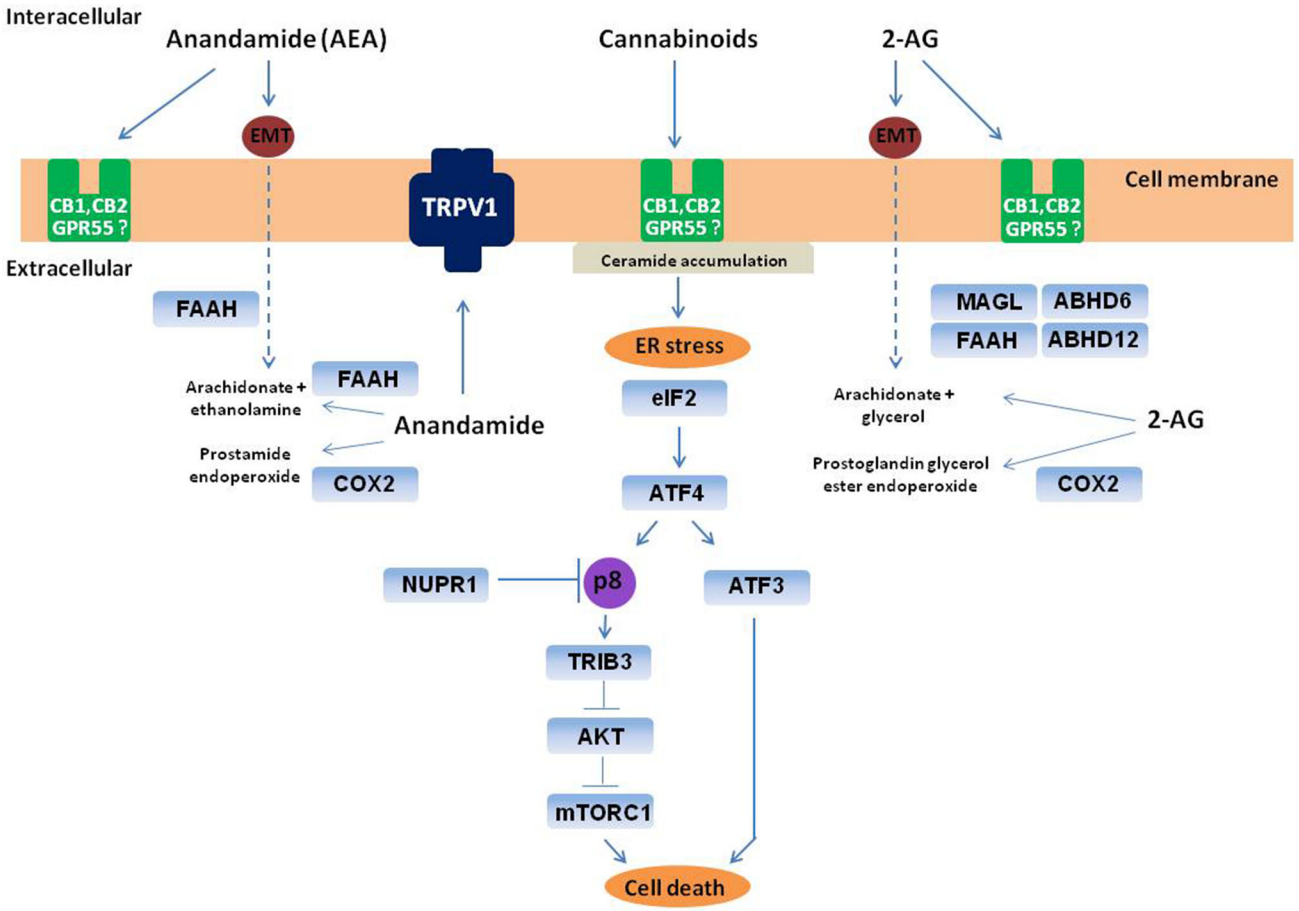

Fig. 1 Breakdown and action scheme of two endocannabinoids: AEA and 2-AG. After AEA and 2-AG cellular re-uptake, AEA is metabolized via FAAH, and 2-AG via MAGL as well as FAAH, ABHD6, and ABHD12. AEA and 2-AG under conditions, in which the activity of MAGL or FAAH is suppressed, might become substrates for COX2 and give rise to the corresponding hydroperoxy derivatives. AEA and 2-AG hydroperoxy derivates can then be converted to prostaglandin ethanolamides (prostamides) and prostaglandin glycerol esters, respectively, by various prostaglandin synthases. AEA also interacts with several non-cannabinoid receptors, such as TRPV1, GPR55 as well as 2-AG. Ceramide accumulation is also demonstrated, illustrating accumulation in tumor cells which mediates cannabinoid-induced apoptosis. ABHD6, ABHD12—αβ-hydrolases domain-containing protein 6 and 12, respectively, *AEA* anandamide, *2-AG* 2-arachidonoylglycerol, *AKT* (also known as *PKB*) protein kinase B, *mTORC1* mechanistic target of rapamycin complex 1, *ATF3* and *ATF4* transcription activator of the integrated stress response, *CB1*, *CB2* cannabinoid receptor, *COX2* cyclooxygenase 2, *eIF2* eukaryotic initiation factor 2α, *EMT* endocannabinoid membrane transporter, *ER stress* endoplasmic reticulum stress, *FAAH* fatty acid amide hydrolase, *GPR55* orphan G-protein-coupled receptor, *MAGL* monoacylglycerol lipase, *p8* (also known as Nupr1) small chromatin protein, *TRIB3* human tribbles homolog 3, *TRPV1* transient receptor potential action channel subfamily V member 1

addiction in the Caucasian and African-American, but not in the case of the Japanese population and other Asian populations [58, 59]. Sipe et al. showed that genotype AA in locus c.385 decreases the expression of the *FAAH* gene in Caucasians and is associated with the abuse of alcohol and drugs (OR = 4.54; 95% CI = 2.15–4.54) [60]. These results were also confirmed by Flanagan et al. (OR = 3.2; 95% CI = 1.86–5.51) [61]. The same genotype was associated by Tyndale et al. with the reduced likelihood of an impact on the dependence of Δ^9THC (OR = 0.25; 95% CI = 0.07–0.88) than for those carrying genotypes CC or CA [57].

3.4.2 *MAGL*

The monoglyceride lipase (MGL) enzyme encoded by the *MAGL* gene is also responsible for the hydrolysis of 2-AG and other lipids (OMIM: 609699). Monoglyceride lipase is part of the endocannabinoid pathway, responsible for the inactivation of endogenous cannabinoids. It is suggested that ECS strengthens the action of drugs. This finding, in combination with other studies on the variability of genes involved in the endogenous cannabinoid system (such as *GABRA2*), may result in the relationship of dependence on cannabis being clarified [33, 62]. There is considerable

evidence that *MAGL* with CB1 and *FAAH* plays a significant role in behavioral experiences related to Δ^9THC. Harismendy et al. [56] identified five rare and common regulatory variants in the population sequencing of the *MAGL* gene (c.47C>T, p.Ser16Phe; c.256G>A, p.Asp86Asn; c.427G>A, p.Ala143Thr; c.819T>G, p.Ile273Met; and c.919G>A, p.Ala307Thr) associated with extreme obesity and metabolite level. These variants are described only in the HGMD® Human Gene Mutation Database. In 2015, Carey et al. published a work which involves analysis of SNPs in six endocannabinoid genes (anabolism: *DAGLA, DAGLB,* and *NAPEPLD*, catabolism: *MAGL* and *FAAH*, and binding: *CNR1)* in cannabis dependence symptoms. There was an evidence that *MAGL* rs604300 (c.263-1443T>C) polymorphism interacts with early life adversity to predict threat-related basolateral amygdala habituation, a neural phenotype linked to the ECS and addiction ($\Delta R^2 = 0.013$, $p = 0.047$). This may be an evidence linking epigenetic modulation of *MAGL* expression which affirms the results achieved in rodents assuming that 2-AG is metabolized by the enzyme encoded by the *MAGL* gene, as a causes of stress adaptation associated with cannabis dependence [63].

3.4.3 ABHD6 and ABHD12

It was discovered that 2-AG can be degraded to glycerol and arachidonic acid with the participation of FAAH and other hydrolytic enzymes, such as αβ-hydrolase domain-containing protein 6 (ABHD6) and αβ-hydrolase domain-containing protein 12 (ABHD12). Blankman et al. described that ~85% of brain 2-AG hydrolase activity can be ascribed to MAGL, with the remaining 15% being mostly catalyzed by two hydrolytic enzymes, such as ABHD6 and ABHD12 [52, 64]. The authors speculate that MAGL, ABHD12, and ABHD6 may regulate different cellular or subcellular pools of 2-AG, thereby making unique contributions to endocannabinoid signaling in vivo [64]. Chromosomal localization, genes sequence of both ABHD6 (OMIM: 616966) and ABHD12 (OMIM: 613599) were characterized first in 2009 and 2010. There is a lack of functional investigations regarding their genetic variants; however, it is certainly an interesting field in the context of research on the effects of cannabinoids.

3.4.4 COX2

Recent research indicates a significant role of cyclooxygenase-2 (COX-2) in the mechanisms of intraneuronal CB1 signaling transduction and modulation of expression of *COX2* (*PTGS2*, OMIM: 600262) and *CNR1* genes. It has also been found that Δ^9THC increases expression and activity of COX-2. Taurisano et al. genotyped 242 healthy subjects for *COX2* and *CNR1* gene variants, rs20417 and rs1406977, respectively. Results suggested specific interaction between C carriers of *CNR1* gene, C carriers of *COX2* as well as homozygous *CNR1* TT and *COX2* GG, which indicate the lower cortical response. It was associated with dorsolateral prefrontal cortex (DLPFC) activity, which in turn is correlated with frequency of cannabis use. The results suggest that the balance in the signaling COX-CB1 pathway by genetic factors may influence the prefrontal activity during working memory process. This would mean that the use of cannabis affects the *CNR1*/*COX2* genes modulation of cortical processing in the cognitive process [65].

3.4.5 MAPK14 and NGR1

The Onwuameze group investigated the potential interactions between *MAPK14* and *CNR1* gene variants [66]. *MAPK14* (OMIM: 600289) is a family member of mitogen-activated protein kinase encoding the MAPK family factor, which is involved in various cellular processes, such as apoptosis (similar to *CNR1*). The study included 235 patients with schizophrenia, characterized by abuse/addiction to marijuana. The patients were analyzed in terms of *MAPK14* SNPs; however, only the c.117-10981A>G (rs12199654) variant and the interaction of homozygotes AA vs marijuana abuse had a significant effect on the change in volume of white matter in the brain [66]. The effects of having *MAPK14* rs12199654 variant on white matter volume deficits in the brain remained significant even when the simultaneous control by the *CNR1* gene and c.*2394A>G variant (rs12720071).

Other interesting observations relate to neuregulin 1 gene (*NRG1,* OMIM: 142445) encoding glycoprotein membrane that mediates cell–cell signaling. Han and colleagues performed a genome-wide linkage scan in 384 African American ($n = 384$) and European American ($n = 354$) for genetic studies of cannabis dependence. The results showed strong association between rs17664708 variant of *NRG1* gene and cannabis dependence in both European Americans (OR = 1.38, $p = 0.02$) and African Americans [(OR) = 2.93, $p = 0.0022$]. The next step which they have done was the replication of the association of rs17664708 with cannabis dependence in independent African American sample (OR = 2.81, $p = 0.0068$). Common analysis of two African American samples showed a strong association between rs17664708 polymorphism and cannabis dependence in both the global ($p = 0.00044$) and the local ancestry ($p = 0.00075$). They suggest, therefore, that *NRG1* may be likely susceptibility gene possessing cannabis dependence based on the evidence of linkage and associations replicated in two independent samples AA [32].

4 Conclusions and Prospects in the Pharmacogenetics Context

In recent years, we can observe increasing interest of the medicinal qualities of cannabis. There is an intense discussion of health benefits and risk of medical marihuana. However, everything varies over time. As of March 2015, 23 US states and the District of Columbia had medical marijuana laws in place [67]. However, in many countries in Europe and around the world, its use in medicine is unlawful. First, this is due to the many side effects and adverse use reactions of cannabinoids. On the other hand, we are witnessing incredible technological advances in molecular biology. Research carried out by molecular methods constitutes the most recent, rapidly growing field of laboratory tests. DNA sequence analysis and GWAS are important strategies for almost all biological research, also in the case of pharmacogenetics, which is based on candidate gene association studies.

Consistent and robust results in the context of genetic associations have not yet been shown so far, and for most of considered genetic variants, the observations are controversial (Table 1.) Moreover, previous studies mainly focused on *CNR1* gene which perhaps is dictated by relatively good knowledge of its function in endocannabinoid system. Molecular biology allows universal access to the comprehensive pharmacogenetic analysis of individual genomes. Current methods of sequencing already allow the whole genome DNA sequence to be recognized within a few days. There is a feeling that the next milestone, after legal acceptance of medical marijuana, will be intensive pharmacogenetic-oriented study of individual populations, which hopefully explain the previous contradictory results and identify in the future genetic markers to personalize cannabinoids treatment.

Compliance with Ethical Standards

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Conflict of interest Hryhorowicz S, Walczak M, Zakerska-Banaszak O, Slomski R, and Skrzypczak-Zielińska M declare that there are no financial or other relationships, which could lead to the conflict of interest. The manuscript has been read and approved by all the authors. Each author believes that the manuscript represents honest work.

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