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INVITED REVIEW

Single nucleotide polymorphisms in the cannabinoid CB_2 receptor: Molecular pharmacology and disease associations

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Abstract

Preclinical evidence implicating cannabinoid receptor 2 (CB_2) in various diseases has led researchers to question whether CB_2 genetics influence aetiology or progression. Associations between conditions and genetic loci are often studied via single nucleotide polymorphism (SNP) prevalence in case versus control populations. In the *CNR2* coding exon, ~36 SNPs have high overall population prevalence (minor allele frequencies [MAF] ~37%), including non-synonymous SNP (ns-SNP) rs2501432 encoding CB_2 63Q/R. Interspersed are ~27 lower frequency SNPs, four being ns-SNPs. *CNR2* introns also harbour numerous SNPs. This review summarises CB_2 ns-SNP molecular pharmacology and evaluates evidence from ~70 studies investigating CB_2 genetic variants with proposed linkage to disease. Although *CNR2* genetic variation has been associated with a wide variety of conditions, including osteoporosis, immune-related disorders, and mental illnesses, further work is required to robustly validate *CNR2* disease links and clarify specific mechanisms linking *CNR2* genetic variation to disease pathophysiology and potential drug responses.

KEYWORDS
biological variation, population; biomarkers; drug development; genetics; polymorphism, single nucleotide; receptor, cannabinoid, CB2; signal transduction

Abbreviations: 2-AG, 2-arachidonoyl glycerol; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; BD, bipolar disorder; BMD, bone mineral density; CD, coeliac disease; DKD, diabetic kidney disease; DM-T1, diabetes mellitus type 1; DM-T2, diabetes mellitus type 2; ECL, extracellular loop; FN, femoral neck; GGT, gamma glutamyltransferase; GIRK, G protein activated inwardly rectifying K^+-channel; GWAS, genome-wide association study; HAI, histological activity index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IBD, irritable bowel disease; ICL, intracellular loop; ITP, immune thrombocytopenia; LD, linkage disequilibrium; LS, lumbar spine; MAF, minor allele frequency; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NAGly, N-arachidonoyl glycine; ns-SNP, non-synonymous single nucleotide polymorphism; OR, odds ratio; s-SNP, synonymous single nucleotide polymorphism; SNP, single nucleotide polymorphism; TM, transmembrane domain; UC, ulcerative colitis; UTR, untranslated region.

1 | INTRODUCTION TO CANNABINOID RECEPTOR 2 (CB_2) AND SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

Cannabinoid receptor 2 (**CB_2 receptor**) is a class A (rhodopsin-like) GPCR encoded by the *CNR2* gene. CB_2 is implicated in a range of conditions, including autoimmune diseases, neurodegeneration, osteoporosis and some types of pain. The only drug with appreciable CB_2 activity used clinically is **Δ9-tetrahydrocannabinol**, which also produces effects via other targets including cannabinoid receptor 1 (**CB_1 receptor**) (Banister et al., 2019). Despite strong preclinical evidence supporting the CB_2 receptor as a promising therapeutic target, to date CB_2 receptor-selective compounds have failed to meet primary endpoints in phase 2/3 clinical trials and no CB_2-selective drug has been approved for clinical use (Whiting et al., 2022). Contributing factors to this lack of success may include poor translatability of preclinical models, and/or failure to consider individual genetic variation in disease aetiology and drug responses.

Individuals' genomes differ from each other at ~4–5 million sites, including single and multi-base substitutions, small insertions and deletions, and structural variants (1000 Genomes Project Consortium, 2015). Single nucleotide variants can be divided into polymorphisms (SNPs) which are typically defined as having a minor allele frequency (MAF) of approximately ≥1% in a population, and 'rare' variants with <1% MAF. Variants may occur in transcribed (exons), non-transcribed (introns), or intergenic regions. Within coding regions, SNPs may be synonymous and encode the same amino acid (s-SNP), or non-synonymous (ns-SNP) and produce a change in the amino acid sequence by encoding a different amino acid (missense), a premature stop codon (nonsense) or a nucleotide insertion or deletion (frameshift).

All variants can have functional consequences via altering gene transcription (e.g., epigenetics, chromatin structure, transcription factor binding), mRNA processing and half-life (e.g., splicing and microRNA regulation) and/or protein folding (e.g. ribosomal translation rate) (Robert & Pelletier, 2018). ns-SNPs can additionally influence biological responses via direct effects on protein folding and function. Missense variants may encode amino acids with similar (conservative) or dissimilar chemical properties (non-conservative), the latter having a greater likelihood of producing a consequential effect. Nonsense and frameshift changes have a high likelihood of altering function, typically in a deleterious manner, via significant alteration to the encoded protein and/or haploinsufficiency via nonsense-mediated mRNA decay (Mendell & Dietz, 2001).

SNPs often contribute to non-pathogenic phenotypic variability between individuals and populations, but can also influence the pathogenesis, severity, or treatment responsiveness of disease, with outcomes involving interplay with other genes and the environment (Karki et al., 2015). SNPs are frequently utilised as markers ('tags') for genetic regions with non-independent inheritance, i.e. haplotype blocks in linkage disequilibrium (LD), such as in traditional genome-wide association studies (GWAS). Thus, tag-SNPs might themselves be causative, or instead be indirect biomarkers for linked causative allele(s) at distinct loci in the same or another gene in the LD block. Notwithstanding this caveat, a number of ns-SNPs in GPCRs have been proposed to be causative in disease (Insel et al., 2007).

This review summarises the effects of *CNR2* ns-SNPs on CB_2 receptor molecular pharmacology and collates the current data informing associations between *CNR2* SNPs and human disease.

2 | CB_2 EXPRESSION AND FUNCTION

The CB_2 receptor is best known for expression in and modulation of immune cells, including B and T lymphocytes, monocytes, macrophages and NK cells (Turcotte et al., 2016). Activation is usually anti-inflammatory, though effects can be context dependent. The CB_2 receptor is also moderately expressed in various other peripheral tissues, such as the cardiovascular system, gastrointestinal tract, liver, adipose tissue, bone and skeletal muscle.

Evidence is conflicting as to whether CB_2 is expressed in the healthy human brain, with some reports suggesting low levels in microglia, neurons in specific regions, and at the blood–brain barrier (BBB). It is better established that the CB_2 receptor is up-regulated in various neuroinflammatory states due to induced expression in activated microglia and/or infiltration of peripheral immune cells, and is a promising anti-neuroinflammatory drug target (Grabon et al., 2023).

Agonist stimulation of CB_2 receptors canonically activates $G\alpha_{i/o}$-βγ heterotrimers leading to inhibition of **adenylate cyclase** with consequent reduced cAMP production, activation of signalling pathways such as MAPKs, and recruitment of β-arrestin which facilitates desensitisation, internalisation and potentially further signal transduction (Oyagawa & Grimsey, 2021). Coupling to $G\alpha_q$ and $G\alpha_s$ have also been reported, as well as biased agonism and temporal signalling signatures, which are hypothesised to influence responses downstream of CB_2 receptor activation (Oyagawa & Grimsey, 2021; Sharma et al., 2023).

3 | *CNR2* GENE AND SNP OVERVIEW

The human *CNR2* gene is encoded on chromosome 1, 1p36.11, on the minus (negative) strand (Figure 1a). Two mRNA transcripts have been reported, formed from four exons, here annotated 1a, 1b, 2 and 3 (Figure 1b). The canonical transcript comprises exons 2 and 3, and is found in immune cells and various peripheral tissues as described in Section 2 (NCBI/RefSeq NM_001841; Ensembl ENST00000374472; Cunningham et al., 2022; Munro et al., 1993; Sayers et al., 2023; Sherwood et al., 2009). A transcript comprising exons 1a, 1b and 3 has been detected in the testis, with lower expression in the brain and some peripheral tissues, which is a distinct expression pattern in comparison with the canonical transcript. However, to our knowledge the 1a-1b-3 transcript has only been reported once subsequently and at writing is not annotated on the latest genome assembly (GRCh38) in NCBI or Ensembl (NCBI/GenBank EU517121; Ensembl ENST00000536471; Liu et al., 2009; Nielsen et al., 2019). The presence of alternative polyA signals/sites in the 3′ untranslated region (UTR) of exon 3 results in differing lengths of mature *CNR2* mRNA (Liu et al., 2009).

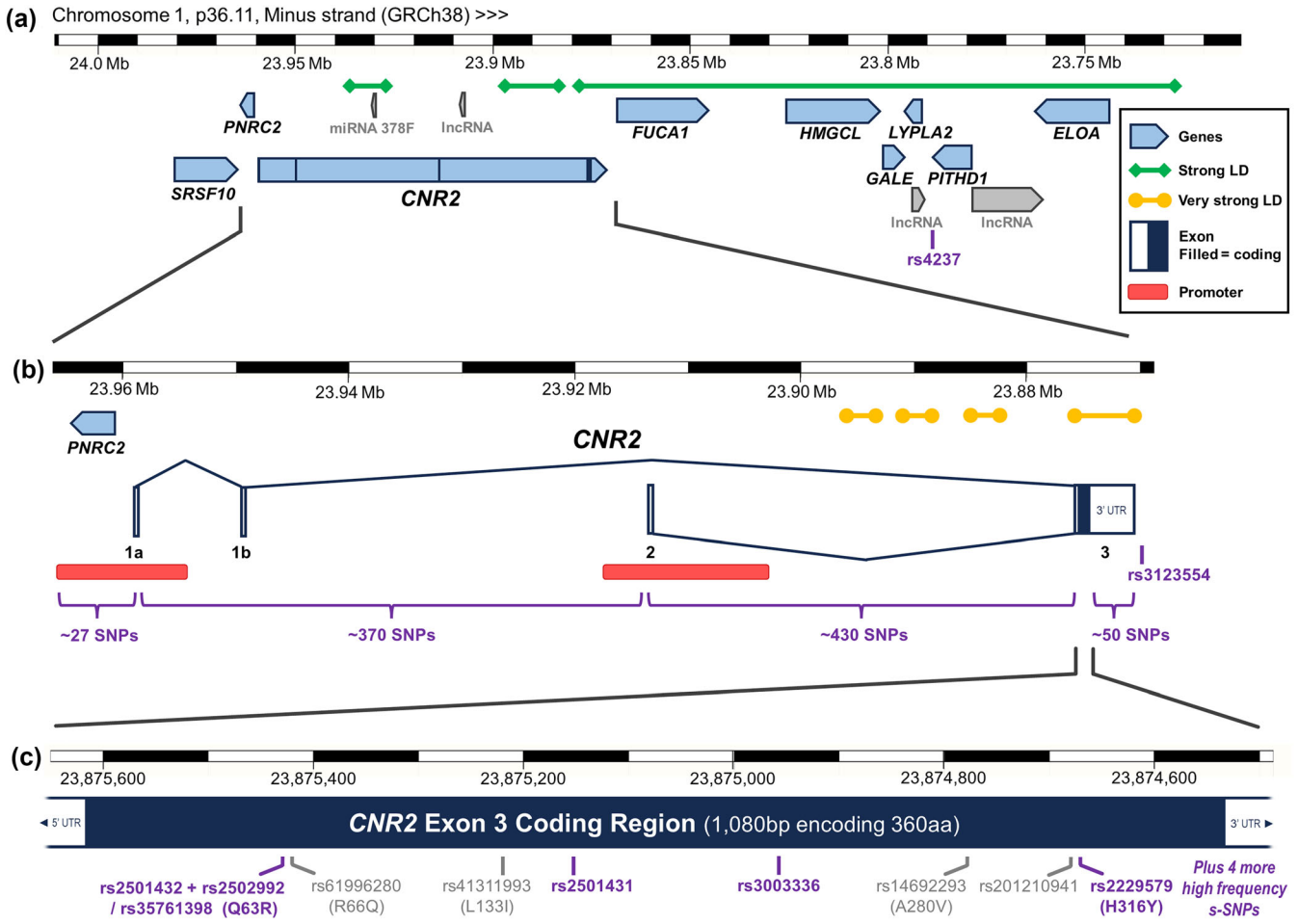

FIGURE 1 Chromosome 1 p36.11 in the region of the *CNR2* gene (a), *CNR2* exon/intron structure (b), and *CNR2* exon 3 coding region SNPs (c). The *CNR2* open reading frame is read from the minus/negative strand, presented here in the forward direction. Coordinates for genes, long non-coding RNA (lncRNA), microRNA (miRNA), *CNR2* exons and putative *CNR2* promoter/flank regions from Ensembl genome browser (http://www.ensembl.org, v109, GRCh38.p14; except exons 1a and 1b coordinates mapped from GRCh37.p13) (Cunningham et al., 2022). Strong linkage disequilibrium (LD) regions based on D′ plots (Figures S1 and S2) and published LD analysis (e.g., Karsak et al., 2005; Zhang et al., 2015). Very strong LD regions as reported by Curtis and Amos (2023). SNPs are indicated in purple (∼ ≥1% allele frequency, Table 1). Variants indicated in grey are 'rare' in most populations, but reach >1% in a specific ancestry sub-group (Tables 1 and S2).

Exon 3 contains the entire protein coding sequence (Figure 1c), and as such, both proposed mRNA transcripts produce the same 360 amino acid protein (UniProt P34972; The Uniprot Consortium, 2023). The CB_2 receptor conforms to canonical GPCR topology, with an extracellular amino/N-terminus, seven hydrophobic transmembrane domains (TM1-TM7), three intracellular loops (ICL1-3), three extracellular loops (ECL1-3) and an intracellular carboxy/C-terminus (Figure 2).

SNPs in *CNR2*, here defined as single base changes with ≥1% MAF in at least one of the ancestry sub-populations represented in the gnomAD database (v3.1.2; Chen et al., 2022), are summarised in Figures 1 and 2 and Tables 1 and S1. There is one SNP in each of exons 1a and 1b, and 27 in the upstream putative promoter region. The introns between exons 1a and 2 harbour ∼370 SNPs, and there are ∼430 SNPs between exons 2 and 3. Exon 3, consisting of the coding sequence flanked by 3′ and 5′ UTRs, contains ∼63 SNPs. There are also ∼330 short multi-nucleotide variants (insertions and deletions) in *CNR2* with ≥1% MAF in at least one ancestry population; ∼14 are in the exon 3 3′ UTR and the remainder are in introns.

Thirty six SNPs in *CNR2* exon 3 are highly prevalent overall with ∼37% aggregated MAF (Table 1). Eight of these are in the coding region, and 28 in the 3′ UTR. The similar occurrence rate between these SNPs reflects that spans of the *CNR2* genomic locus are in near-complete LD, with one such span encompassing exon 3 (based on 1000 Genomes dataset, ∼2500 genomes from various ancestries; 1000 Genomes Project Consortium, 2015; Curtis & Amos, 2023; Figure 1b). Exon 3 SNPs are therefore typically co-inherited in a haplotype block, with the alternative (major) allele haplotype occurring at ∼50% to ∼83% prevalence depending on ancestral background, and ∼27% to ∼57% of individuals being homozygous for this haplotype (1000 Genomes Project Consortium, 2015; Chen et al., 2022; Tables S1 and S2). One SNP in this haplotype is non-synonymous (rs2501432; Q63R), implying that two 'versions' of the encoded CB_2 receptor protein are prevalent in human populations (see also Section 4.1).

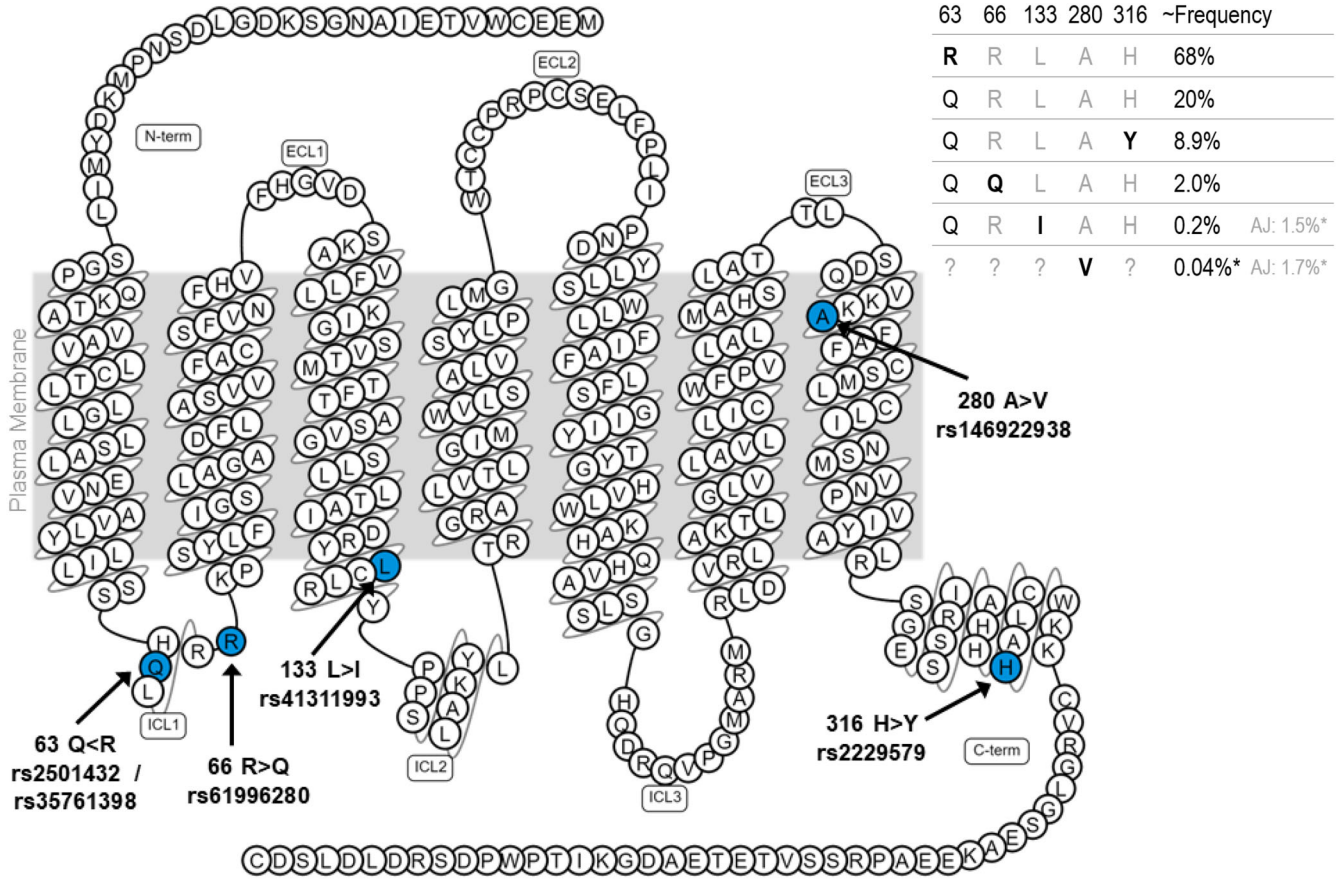

FIGURE 2 Snake plot representation of the human CB_2 receptor and locations of ns-SNPs. Snake plot adapted from GPCRdb (Munk et al., 2016). 'N-term', amino/N-terminal tail; 'C-term', carboxy/C-terminal tail. Inset table summarises ns-SNP haplotypes and approximate average frequencies (1000 Genomes Project Consortium, 2015; Cunningham et al., 2022). * indicates approximate haplotype frequencies based on MAFs in gnomAD database v3.1.2 (Tables 1 and S2); AJ—Ashkenazi Jewish ancestry. A280V haplotype unknown.

CNR2 exon 3 also contains 27 lower frequency SNPs, occurring at ~0.04%–8% MAF in overall population analysis (Table 1). Four of these are ns-SNPs. rs2229579 (H316Y) is the most prevalent (~8% MAF), while the other three have <1% MAF in aggregated analysis but reach >1% in specific ancestry population(s) (Tables 1, S1 and S2; see also Section 4). Synonymous variant rs201210941 is rare (<0.01%) in most ancestries but has ~1.8% MAF in those with South Asian ancestry and is linked to the 63R haplotype (Tables 1 and S2). Various rare non-synonymous variants have also been reported, including rs150233022 that introduces a stop codon roughly half way through the coding sequence found at 0.2% MAF in those of East Asian ancestry, but <0.02% MAF or undetected in other gnomAD ancestry populations (Chen et al., 2022).

Exon 3 sits within a broader strong LD region spanning ~170 kb that encompasses multiple downstream genes (Figures 1a, S1 and S2; Karsak et al., 2005; Machiela & Chanock, 2015). SNPs up to ~146 kb downstream of *CNR2* have been associated with CB_2 receptor expression levels in lymphoblastoid cells and in post mortem brain tissue (e.g., rs4237, rs12744386; Dixon et al., 2007; Ishiguro, Horiuchi, et al., 2010). Strong LD across this region also implies that *CNR2* exon 3 SNPs are linked to inheritance of SNPs in neighbouring genes downstream, including ns-SNPs in *FUCA1* which encodes alpha-L-fucosidase 1, mutation of which causes fucosidosis (Machiela & Chanock, 2015). This linkage pattern is important to consider when interpreting both genome-wide and gene-of-interest disease association studies.

No SNP or rare variant in *CNR2* has been found to be fully penetrant in causation of any disease or phenotype to date. This is consistent with rodent knockout models that exhibit relatively subtle phenotypes, and the generally observed modulatory role of the endocannabinoid system and the CB_2 receptor on physiological responses (Turcotte et al., 2016). Nonetheless, the potential remains that genetic factors altering CB_2 receptor expression and/or function may influence traits and diseases.

4 | CB_2 NS-SNP MOLECULAR PHARMACOLOGY

4.1 | rs2501432 + rs2502992 / rs35761398, Q63R

The ns-SNP encoding glutamine (Q) versus arginine (R) at position 63 in CB_2 ICL1 (Figure 2) is the most widely studied CB_2 receptor SNP. Codon [CAA] (minus strand) is the genomic reference codon at this

TABLE 1 Summary of SNPs and rare variants in the *CNR2* gene region.

dbSNP ID[a]	Genome base(s)[b]	*CNR2* region	Alleles Reference > alternative		Alternative allele (%)[c]	Alternative allele 63Q/R link[d]	Disease association[e] (# studies significant association/total)
			DNA	Protein			
27 SNPs	23,959,818-23,959,132	Promoter for Exon 1a	(various)	-	0.6–48[f]	-	
2 SNPs	23,959,031	Exon 1a & 1b (non-coding)	(various)	-	41.2, 0.6	No	
rs75459873	23,929,822	Intron between Exons 1b & 2	G > A	-	3.2	No	Schizophrenia & psychosis (1/1)
rs35675064	23,925,161	Intron between Exons 1b & 2	C > T	-	24.1	No	Haematological traits (1/1)
rs16828926	23,888,640	Intron between Exons 2 & 3	G > A	-	11.8	Q	Osteoporosis/BMD (1/4)
rs2501432	23,875,430	**Exon 3, Coding**	T > C	**Gln>Arg (Q63R)**	63.4	(NA)	Osteoporosis/BMD (2/3); autoimmune disorders (9/11); chronic liver disease (7/7); viral & respiratory (3/4); metabolism (2/2); affective disorders (3/4); schizophrenia & psychosis (2/2); substance use disorder (2/4); eating disorders (1/1)
rs2502992	23,875,429	Exon 3, Coding	T > C	Synonymous	63.4	R	
rs35761398[h]	23,875,430-23,875,429	Exon 3, Coding	TT > CC	Gln>Arg (Q63R)	63.4	(NA)	
rs61996280[g]	23,875,421	**Exon 3, Coding**	C > T	**Arg>Gln (R66Q)**	0.94[g]	Q*	
rs41311993[g]	23,875,221	**Exon 3, Coding**	G > T	**Leu>Ile (L133I)**	0.27[g]	Q*	Affective disorders (depression, anxiety, BD) (1/2)
rs2501431	23,875,153	Exon 3, Coding	G > A	Synonymous	63.4	R	Osteoporosis/BMD (7/7); cardiovascular (1/2); affective disorders (2/3)
rs3003336	23,874,958	Exon 3, Coding	C > T	Synonymous	63.4	R	Osteoporosis/BMD (3/4)
rs146922938[g]	23,874,779	**Exon 3, Coding**	G > A	**Ala>Val (A280V)**	0.04[g]	(ND)	
rs201210941[g]	23,874,679	Exon 3, Coding	G > A	Synonymous	0.06[g]	R*	
rs2229579	23,874,672	**Exon 3, Coding**	G > A	**His>Tyr (H316Y)**	7.7	Q	Osteoporosis/BMD (3/7); schizophrenia & psychosis (2/3); substance use disorder (1/1)
4 SNPs	23,874,867-23,874,604	Exon 3, Coding	(various)	Synonymous	63.5	-	
rs2229583	23,874,493	Exon 3, 3′ UTR	C > T	-	64.1	R	Osteoporosis/BMD (2/3)
27 SNPs	23,874,479-23,871,022	Exon 3, 33′ UTR	(various)	-	59.0–64.1	-	Haematological traits (5/5)
22 SNPs	23,874,479-23,871,022	Exon 3, 33′ UTR	(various)	-	0.07–6.0	-	
~800 SNPs	23,958,922-23,875,663	Introns	(various)	-	0.002–50[f]	-	Viral & respiratory (1/1); metabolism (obesity, DM-T2) (2/2); eating disorders (1/1); Haematological traits (2/2)
rs3123554	23,869,911	~0.6 kb downstream of *CNR2*, ~1.6 kb upstream of *FUCA1*	A > G	-	63.4	R	Metabolism (obesity, DM-T2) (6/6)
rs4237	23,787,639	~83 kb downstream of *CNR2*; *PITHD1* 3′ UTR	G > A	-	64.1	R	Osteoporosis/BMD (3/5)

locus, encoding 63Q. The rs2501432 alternative allele changes the codon second position to [G] to encode 63R. 1000 Genomes Project data indicates this SNP is in perfect LD (always co-inherited) with rs2502992, a synonymous variant that modifies the third codon position to [G] (Tables 1 and S1). rs35761398 refers to the double base change, [CAA > CGG].

As introduced in Section 3, both alleles for these variants are highly prevalent, with MAF ~20% to ~48% depending on ancestry (Table S2). Although reference genome GRCh38 and standard consensus sequences encode 63Q (e.g. RefSeq NM_001841.3, UniProt P34972), this allele is ~27% *less* prevalent than the alternative allele encoding 63R (on average, in aggregated populations; Tables 1 and S1). The vast majority of consensus sequences for CB_2 orthologues are 63R (Carruthers & Grimsey, 2023).

The amino acid substitution at this residue is relatively conservative in terms of chemical properties; glutamine is polar and uncharged, whereas arginine is also polar but positively charged. Molecular dynamics structural analysis of a CB_2 homology model predicted no structural rearrangement as a result of the substitution (Turu et al., 2021). The role of ICL1 in GPCR activation has not been investigated widely, but studies have suggested involvement in receptor signalling via interactions with the intracellular helix 8 domain (Winfield et al., 2021), or with G proteins (Qian et al., 2022).

A handful of studies have investigated the molecular pharmacology of CB_2 63Q versus 63R when heterologously expressed in cell lines. In HEK293 cells, CB_2 63R was initially assessed as having equivalent ligand binding affinity and constitutive activity to CB_2 63Q, but slightly lesser efficacy for inhibiting cAMP synthesis (with no change in potency) in response to endocannabinoid 2-arachidonoyl glycerol (**2-AG**) and synthetic agonist **WIN55,212-2** (Carrasquer et al., 2010). This effect was ligand-selective, as signalling in response to **anandamide**, **CP55,940** and **HU-210** was equivalent between variants.

This potential for reduced activity of CB_2 63R was mirrored in two studies expressing CB_2 receptor variants in CHO cells. In the first, there was a complete lack of detectable agonist response of CB_2 63R to 2-AG or **JWH-015** in a cAMP assay, and a smaller inverse agonist window (**AM-630**), suggesting lesser constitutive activity, though comparative expression levels were not reported (Ishiguro, Horiuchi, et al., 2010). Subsequently, in transiently-transfected CHO cells, CB_2 63R produced somewhat reduced efficacy but equivalent potency of ERK phosphorylation in response to CP55,940 and reduced potency but equivalent efficacy with 2-AG stimulation in single-timepoint analysis (Wang et al., 2018).

In contrast, the most recent study found that inhibition of cAMP synthesis and $G\alpha_i$ activation in response to 2-AG and **JWH-133** were equivalent between CB_2 63Q and 63R when expressed in HEK293T cells (Turu et al., 2021). Meanwhile, GRK2/3 interaction, β-arrestin-2 recruitment, and internalisation in response to both ligands were slightly greater for CB_2 63R than 63Q. It was hypothesised that while CB_2 63R may be activated similarly upon ligand stimulation, desensitisation might be more rapid or complete than 63Q, which could result in an overall reduced signalling response when integrated over time.

Note: Variants are listed in the direction of *CNR2* open reading frame (minus/negative strand). Non-synonymous variants in bold. Further detail provided in Table S1, including: gnomAD ID, homozygote prevalence, alternative allele linkage supporting data and more detail for disease associations. BD, bipolar disorder; BMD, bone mineral density; DM-T2, Diabetes mellitus type 2.

[a]'rs' numbering from NCBI dbSNP; https://www.ncbi.nlm.nih.gov/snp/ (Sherry et al., 2001).

[b]All on chromosome 1. Base numbering per genome assembly GRCh38.p14 (NC_000001.11).

[c]Allele frequency data from gnomAD database v3.1.2 for aggregated populations of various ancestries; https://gnomad.broadinstitute.org/ (Chen et al., 2022).

[d]Indicates LD correlation (high likelihood of co-inheritance) of the alternative allele with the rs2501432 allele encoding CB_2 63Q or 63R. 'No'—SNP is not significantly correlated with rs2501432 (in linkage equilibrium); 'ND'—no data available; *—LD correlation not significant, but SNP only in haplotype with 63Q or 63R. LD correlation calculated with the LDlink LDpair tool (https://ldlink.nih.gov/?tab=ldpair; Machiela & Chanock, 2015), using 1000 Genomes GRCh38 high coverage data for all populations (1000 Genomes Project Consortium, 2015).

[e]Indicated associations are discussed in the review and detailed in Tables S3–S8. Non-significant associations not listed.

[f]Allele frequency ranges are for second most frequent allele (not necessarily alternative allele).

[g]These variants are 'rare' when assessed over aggregated populations (MAF < 1% in gnomAD v3.1.2) but reach >1% in specific ancestry sub-population(s) (Table S2).

[h]rs35761398 refers to the double base change produced by rs2501432 plus rs2502992.

Two studies have provided insight into the function of CB_2 63Q vs R in more physiological contexts by measuring responses of *ex vivo* cells from human donors. In the first, blood-derived T lymphocytes were genotyped for 63Q/R and homozygous donors arranged in pairs with matched demographics and clinical features (Sipe et al., 2005). 2-AG and N-arachidonoyl glycine (**NAGly**) inhibited T cell proliferation in cells from 63Q homozygous individuals, while about half the equivalent response was elicited in cells homozygous for CB_2 63R. Interpretation of this finding is somewhat challenging; a CB_2 receptor-selective inverse agonist blocked only ~15–20% of the response, and NAGly is not a widely accepted CB_2 receptor agonist. T cells also express GPR18, which can respond to both NAGly and 2-AG (Morales et al., 2020). Nonetheless, these findings were generally consistent with a later study, again in donor-derived T cells, that reported a modest reduction in potency of ERK phosphorylation in response to CP55,940 in cells homozygous for CB_2 63R, in comparison with those from heterozygous or homozygous 63Q individuals (Wang et al., 2018). However, the specificity of the CB_2 receptor in mediating this response was not verified.

Overall, *in vitro* studies of CB_2 63Q/R to date support the potential for at least subtle modulation of signalling due to this amino acid substitution, with 63R tending to produce lesser efficacy or lower potency responses. Given the high prevalence of 63Q/R in general populations it is unlikely that this variant alone is causative of disease, but it may still contribute to population variability in CB_2 receptor-mediated function with consequences for disease risk, progression, or drug action. However, it is important to keep in mind that this variant is in LD with many other non-coding and s-SNPs in *CNR2*, lower frequency ns-SNPs, and numerous SNPs in neighbouring genes (including some ns-SNPs), all of which may also be influential (see also Section 3).

4.2 | rs61996280, R66Q

rs61996280 refers to a base change encoding exchange of arginine for glutamine in ICL1 (R66Q; Figure 2). When evaluated over mixed populations this variant has ~0.9% MAF (Table 1), however, it has ~3% MAF in those of African or African American ancestry (Table S2). The minor allele, 66Q, tends to be co-inherited with 63Q (Tables 1 and S1). This ns-SNP has not yet been evaluated for molecular pharmacology or disease association.

4.3 | rs41311993, L133I

rs41311993 encodes a change from leucine (L) to isoleucine (I) at amino acid 133. This ns-SNP has low overall population prevalence (~0.3% MAF, Table 1) but is at ~1.5% MAF in those with Ashkenazi Jewish ancestry (Table S2) and tends to be co-inherited in the haplotype block with CB_2 63Q.

Residue 133 is located at the interface between TM3 and ICL2, immediately following the DRY motif (Figure 2), which is highly conserved in class A GPCRs and implicated in stabilisation of the active conformation and G protein coupling. In the CB_2 receptor specifically, ICL2 works in coordination with the C-terminus to determine G protein coupling selectivity (Zheng et al., 2013). Although leucine and isoleucine have similar chemical properties, they have distinct effects on the stability of alpha helices as well as different interactions with membrane lipids (Baumann & Zerbe, 2023; Deber & Stone, 2019) and CB_2 receptor structural homology model molecular dynamics simulations predicted movement of ICL2 towards the cytoplasm with the L133I substitution (Turu et al., 2021).

Just one study has investigated the molecular pharmacology of this SNP, overexpressing CB_2 variants in HEK293T cells (Turu et al., 2021). Stimulation of CB_2 63Q-133I with JWH-133 produced a subtle increase in maximum efficacy of $G\alpha_i$ activation in comparison with that for CB_2 63Q-133L, but there was no difference when stimulated with 2-AG, or for either agonist in a cAMP inhibition assay. However, more robust effects were observed on receptor regulation, with agonist stimulation of CB_2 63Q-133I eliciting lesser β-arrestin-2 recruitment (JWH-133 and 2-AG), lesser GRK2/3 recruitment (only JWH-133 tested), and slower internalisation (only JWH-133 tested) than CB_2 63Q-133L. Although bias was not formally analysed, the findings indicate that the L133I substitution may bias the receptor away from β-arrestin-2 coupling and consequent signalling, but potentially enable prolonged canonical G protein signalling via reduced desensitisation and internalisation.

4.4 | rs146922938, A280V

rs146922938, encoding substitution from alanine (A) to valine (V) at residue 280 (Figure 2), is a rare variant when assessed over mixed populations (MAF 0.04%), but present at ~1.7% in the Ashkenazi Jewish ancestry subpopulation (Tables 1 and S2). The substitution is chemically relatively conservative, both amino acids being somewhat hydrophobic, aliphatic and non-reactive, and generally having a neutral role in protein structure. Position 280 is at the interface between ECL3 and TM7, and is next to F281 which has been implicated in ligand binding to the CB_2 receptor (Feng et al., 2014). This variant has not been studied for molecular pharmacology or disease relevance.

4.5 | rs2229579, H316Y

rs2229579 encodes substitution of histidine (H) to tyrosine (Y) at position 316, which is in helix 8 in the cytoplasmic tail (Figure 2). Averaging across mixed populations, H316Y is found at ~7.7% allele prevalence, with 0.8% of individuals being homozygotes (Table 1). This SNP is enriched in East and South Asian ancestry sub-groups (~20% and ~13% allele prevalence respectively), and less frequent in those of African or African-American ancestry (~1.9% allele prevalence; Table S2). 1000 Genomes Project data indicates H316Y is in complete LD with 63Q (Tables 1 and S1). The amino acid exchange is relatively conservative, though both have unique properties, histidine

being polar but compatible with hydrophobic or hydrophilic environments, but tyrosine preferring hydrophobic environments and being able to be phosphorylated. Based on analogy to other GPCRs, helix 8 is likely involved in G protein coupling (Winfield et al., 2021).

Despite appreciable population prevalence, only one study has investigated the molecular pharmacology of CB_2 H316Y to date (Carrasquer et al., 2010). When expressed in HEK293 cells, CB_2 63Q-316Y had equivalent binding affinity to CB_2 63Q-316H for most ligands tested, except for 2-AG which bound with ~2.5-fold lower affinity to the 316Y variant. CB_2 63Q-316Y had enhanced constitutive activity in comparison with CB_2 63Q-316H, while agonist efficacy relative to baseline cAMP was reduced when stimulated with WIN55,212-2, subtly reduced with 2-AG, and not significantly different for CP55,940, HU-210 and anandamide.

5 | CB_2 SNP ASSOCIATIONS WITH DISEASES AND PHENOTYPES

Diseases and traits for which association with CB_2 SNPs has been studied are summarised in Table 1 (and Table S1), with the number of studies concluding a significant association indicated. Robust interpretation of genetic association studies relies on careful matching between study populations and/or correction for covariate factors to avoid spurious conclusions due to population stratification (e.g., differing ancestry-associated SNP prevalence). Details of the studies discussed here, including population characteristics, sizes, and specific findings regarding association with disease risk and/or clinical measures, are provided in Tables S3–S8.

5.1 | Osteoporosis and bone mineral density (BMD)

A role for the CB_2 receptor in bone physiology is well established, with CB_2 receptor agonism tending to promote bone formation and limit resorption (Rossi et al., 2019). It is in this context that potential genetic links between the CB_2 receptor and disease prevalence were first, and have been most comprehensively, investigated.

Osteoporosis is an age-related bone disease characterised by low BMD, disturbed micro-architecture of bone tissue, and increased fracture risk (Rossi et al., 2019). Several linkage studies have implicated genomic region 1p36, which includes *CNR2*, to osteoporosis and BMD (Huang et al., 2009). To date, eight reports have addressed association of *CNR2* SNPs with osteoporosis and/or measures of bone strength (Table S3).

The largest and most comprehensive study analysed the incidence of 39 SNPs from across an ~280 kilobase stretch of the 1p36.11 locus (incorporating the full *CNR2* gene) in 3121 Han Chinese postmenopausal non-obese females, 1032 of whom were osteoporosis patients (Zhang et al., 2015). Age, years since menopause, weight and height were equivalent between the case and control groups. Associations with osteoporosis for both genotype and allele were detected for rs2501431-A (exon 3 coding, s-SNP) and rs4237-A (~83 kb downstream of *CNR2*, in *PITHD1* 3′ UTR), with small but significant odds ratio (OR) 1.2 for both. These SNPs were also associated with reduced BMD in both the lumbar spine (LS) and femoral neck (FN). Two further *CNR2* SNPs were significantly associated with osteoporosis by nominal *p* values, but not after multiple comparisons correction (rs2229579 [H316Y], rs3003336 [exon 3 coding, s-SNP]).

LD analysis informed construction of six haplotype blocks across the gene region analysed, two of which were significantly associated with osteoporosis incidence; one in the exon 3 coding region from rs2501432 (Q63R) to rs3003336, the other spanning ~80–180 kb downstream of *CNR2*, incorporating rs4237 and genes *PITHD1*, *ELOA* and *RPL11* (Zhang et al., 2015). Of the three significantly associated haplotypes, two were common in the control population (35%–44%) and had ~4%–5% lesser prevalence in osteoporosis, suggesting a protective effect. The third, relatively rare, haplotype rs2501432-T (63Q)/rs2502992-T/ rs2501431-A/rs3003336-C increased from 2.0% in controls to 7.1% in osteoporosis cases.

Four other studies largely corroborate the main findings of Zhang et al. (2015). Allele rs2501431-A has emerged as a potential risk marker, with significant osteoporosis and/or reduced bone strength risk found in post-menopausal female Caucasian, Chinese and Korean populations (Huang et al., 2009; Karsak et al., 2005; Karsak et al., 2009; Woo et al., 2015; Zhang et al., 2015). Studies that surveyed multiple SNPs across *CNR2* also supported the prior-discussed linked haplotype block within exon 3 (Karsak et al., 2005; Karsak et al., 2009; Woo et al., 2015; Zheng et al., 2019). In contrast, two studies reported reference allele rs2501431-G (less frequent in general populations) to be associated with risk of low BMD in specific skeletal sites in both pre- and post-menopausal Japanese women (Yamada et al., 2007a) or with osteoporosis incidence in post-menopausal Chinese women (Zheng et al., 2019). The latter study additionally found an association of rs30033336-C with osteoporosis, with abdominal obesity being an interacting factor that further increased risk (Zheng et al., 2019). This allele association is also opposite to that in some other studies (Karsak et al., 2005; Woo et al., 2015), which is not surprising given that SNPs rs2501431 and rs30033336 are in high LD. It is not clear whether these opposing results to the other five studies relate to the populations under study, case–control matching, methods controlling for influence of covariates, and/or BMD measures and skeletal regions.

Implication in BMD of the region downstream of *CNR2* that includes rs4237 has also been inconsistent, with two studies finding significant association (Karsak et al., 2005; Karsak et al., 2009), one with lack of significance when analysed alone but contribution to a significantly associated haplotype (Woo et al., 2015), and one not finding association (Zheng et al., 2019). These discrepancies could relate to differential LD patterns in study populations, and the possibility that other genes in the region could be involved should be considered. However, it is notable that an analysis surveying 26 SNPs across the region found that *p* values tended to decrease, and ORs increase, for SNPs closer to *CNR2* (Karsak et al., 2005).

Contrasting findings have also been reported for ns-SNP rs2229579 (H316Y). The minor allele, encoding 316Y, was significantly associated with LS (but not FN) osteoporosis and BMD in Korean post-menopausal women (Woo et al., 2015). In contrast, 316Y has been reported to be a potentially protective allele in two studies, though these findings were tentative (barely significant, or only subset of measures implicated; Hu et al., 2012; Karsak et al., 2005). Four other studies found no significant association, though two were on the cusp of significance (Huang et al., 2009; Karsak et al., 2009; Zhang et al., 2015; Zheng et al., 2019). The low prevalence of this SNP in some ancestries (Section 4.5 and Table S2) implies that large cohort sizes would likely be required to reliably determine involvement of this SNP in some populations.

5.2 | Autoimmune disorders

The potential for therapeutic immunomodulation via CB_2 receptor activation is widely appreciated and has been demonstrated in preclinical autoimmune disease models (Turcotte et al., 2016). Despite this, investigation of *CNR2* SNPs in autoimmune disorders to date has been surprisingly limited. All studies have focused on just one SNP, rs2501432 (63Q/R), cohorts were typically small (~100 cases), and only limited replication has been undertaken (Table S4).

5.2.1 | Childhood immune thrombocytopenia (ITP)

The autoimmune disorder with the most data replication in the literature for association with CB_2 receptor SNPs to date is childhood ITP (three studies, Table S4). ITP is an autoimmune bleeding disorder characterised by autoantibody-mediated platelet destruction and thrombocytopenia. B and T lymphocytes play crucial roles in pathogenesis, with both genetic and environmental factors thought to be important in aetiology (Zufferey et al., 2017).

In an Italian cohort of 190 juvenile ITP patients versus 600 healthy controls, the rs2501432 63R allele was associated with ITP prevalence, with the 63R/R genotype conferring a 3-fold increased risk for chronic but not acute ITP (Rossi, Mancusi, et al., 2011). These findings were corroborated in two Egyptian studies that also reported significantly higher prevalence of the rs2501432 63R/R genotype in chronic ITP patients (Ezzat et al., 2017; Gouda & Kamel, 2013).

5.2.2 | Inflammatory bowel disease (IBD)

IBD refers to chronic intestinal inflammatory conditions that can be subdivided into Crohn's disease and ulcerative colitis (UC). Genetic and environmental factors, the intestinal microbiome, and host immune responses contribute to the pathogenesis of IBD. The CB_2 receptor has been proposed as a drug target in IBD due to its anti-inflammatory potential, and an agonist has shown promise for alleviating abdominal pain associated with Crohn's disease in phase 2 clinical trials (Whiting et al., 2022). GWAS have identified more than 200 susceptibility loci associated with IBD, including the 1p36 locus (e.g., Asano et al., 2009).

Inconsistent findings have been reported from two investigations into potential association between CB_2 rs2501432 (63Q/R) and IBD incidence (Table S4). No association between the 63R allele and IBD was detected in an adult Turkish cohort stratified into 101 Crohn's disease and 101 UC versus 101 healthy controls (Yonal et al., 2014). In contrast, 63R was associated with incidence and severity of paediatric IBD in an Italian cohort of 112 Crohn's disease and 105 UC cases versus 600 healthy children and adolescents (Strisciuglio et al., 2018). In Crohn's disease, the greatest OR was found for the 63R/R or 63Q/R genotypes in comparison with 63Q/Q (OR 6.9), with these genotypes also associated with significant increase in scoring for disease severity. Effect sizes in UC were less striking, but the 63R/R homozygous genotype was associated with increased risk (OR 1.6), increased severity scores, and reduced time to clinical relapse. Among many potential reasons for the discrepancies between these studies, the earlier onset of disease (presumably enriched in the paediatric IBD study) might reflect a distinct genetic component in comparison with later onset IBD.

5.2.3 | Coeliac disease (CD)

CD is a chronic autoimmune disorder, triggered through exposure to dietary gluten in genetically susceptible individuals and characterised by lymphocyte infiltration across the gut barrier, production of autoantibodies, and chronic inflammation that damages the intestinal mucosa (Sciurti et al., 2018). CD patients possess genes encoding specific human leukocyte antigen (HLA) variants, but these alone are not sufficient for disease development, and many other genetic and environmental factors are implicated in CD susceptibility and pathogenesis.

An association study for CB_2 63Q/R (rs35761398) was carried out in a South Italian cohort of 317 CD children and adolescents versus 600 healthy controls (Rossi, Bellini, Tolone, et al., 2012). The 63R/R genotype was significantly associated with CD and conferred a six-fold increased risk of CD compared with the 63Q/Q genotype. However, the complexity of environmental and genetic risk factors in CD mean larger and more diverse studies will be required to robustly establish CB_2 rs35761398 as a useful risk marker for CD.

5.2.4 | Multiple sclerosis (MS)

MS is an autoimmune neurodegenerative disease of the CNS characterised by chronic inflammation and demyelination. A key aspect of MS pathology is the presence of autoreactive myelin-specific T cells in the CNS, which promote neuroinflammation and damage to CNS components. Genetic and environmental factors contribute to disease susceptibility and progression (Patsopoulos, 2018).

The first study to investigate a CB_2 SNP in immune function analysed rs35761398 (63Q/R) in a small cohort of Caucasian autoimmune disease patients (102 subjects), 70% of which were MS patients (Sipe et al., 2005). Both 63R allele frequency and homozygous genotype were significantly greater in the autoimmune cohort.

Only one study has since followed up a potential association with MS. In a cohort of 100 Iranian (predominantly Persian) MS patients and 100 healthy controls, the allele encoding 63R and the homozygous 63R genotype were significantly associated with MS, with 63R/R individuals having approximately three times the risk of developing MS in comparison with 63Q/Q individuals (Tahamtan et al., 2020).

5.2.5 | Arthritis

Arthritis is characterised by inflammation of the joints, causing considerable pain and limiting mobility. Several preclinical studies indicate that CB_2 receptor agonists have therapeutic potential in treating arthritis (Bryk & Starowicz, 2021).

Juvenile idiopathic arthritis is the most common chronic rheumatic disease in children (Ravelli et al., 2017). Potential association between CB_2 63Q/R (rs35761398) and incidence of juvenile idiopathic arthritis was investigated in an Italian cohort of 171 patients versus 600 healthy controls (Bellini, Olivieri, et al., 2015). Compared with the 63Q/Q genotype, 63R/R conferred a two-fold risk for developing juvenile idiopathic arthritis and, within the juvenile idiopathic arthritis cases, OR 5.3 for having polyarticular juvenile idiopathic arthritis as opposed to the less severe oligoarticular type. The 63R/R genotype was also associated with earlier disease onset and increased risk of disease relapse.

Rheumatoid arthritis is a chronic autoimmune disorder with aetiology likely involving genetic susceptibility and environmental factors (Scherer et al., 2020). A study of 105 Lebanese patients with rheumatoid arthritis versus 105 healthy controls found that CB_2 63R/R was significantly overrepresented in rheumatoid arthritis patients compared with healthy controls, with 63Q/R and 63R/R genotypes having a three-fold and ten-fold increased risk for developing rheumatoid arthritis respectively, compared with 63Q/Q (Ismail & Khawaja, 2018). There were no significant findings correlating disease-related blood biomarkers and genotype.

5.2.6 | Primary biliary cirrhosis

Primary biliary cirrhosis is an autoimmune disorder of the liver, characterised by inflammation and progressive autoantibody-mediated destruction of intrahepatic bile ducts (Carey et al., 2015). CB_2 mRNA and immunoreactivity has been detected in liver tissue taken from patients with primary biliary cirrhosis, but not healthy individuals (Floreani et al., 2010). Potential correlation between rs2501432 (63Q/R) and primary biliary cirrhosis incidence, clinical markers, and response to ursodeoxycholic acid (a primary biliary cirrhosis therapy) was investigated in small cohorts of Italian and American primary biliary cirrhosis patients (total 105 cases), but no significant associations were found (Floreani et al., 2010).

5.3 | Chronic liver disease

There is little CB_2 receptor expression in the healthy adult liver. However, in chronic liver disease, where fibrosis and persistent inflammatory responses are mediated by immune cells both originating in the liver and infiltrating from the circulation, CB_2 receptor activation may modulate disease mechanisms, including progression to cirrhosis and hepatocellular carcinoma. In animal models of cirrhosis, CB_2 receptor activation was found to counteract fibrosis and immune cell activation (Basu et al., 2014; Louvet et al., 2011). Conversely, CB_2 receptor activation can potentiate liver inflammation in obesity, and increase lipid accumulation (steatosis) in hepatocytes (De Gottardi et al., 2010; Deveaux et al., 2009).

5.3.1 | Non-alcoholic fatty liver disease (NAFLD)

NAFLD is characterised by elevated storage of fat in the liver (steatosis) independent of excessive alcohol use, viral hepatitis or steatogenic drugs, and is closely associated with metabolic disorders, particularly type 2 diabetes (DM-T2) and obesity and has high global prevalence in both adults and children (Le et al., 2022). Motivated by observations that CB_2 receptor activation has hepatoprotective and antifibrogenic properties, two studies have investigated *CNR2* rs2501432/rs35761398 (63Q/R) in childhood NAFLD (Table S5).

In 438 Italian obese children with steatosis, the 63R/R genotype was associated with elevated serum liver enzyme concentrations (indicating liver damage), with OR 2.7 for alanine transaminase (ALT) concentration >40 U/L (Rossi, Bellini, et al., 2011). No significant associations with BMI, size of abdominal fat, or insulin resistance were found. Conversely, in a cohort of 118 Italian children with NAFLD, including 53 with severe non-alcoholic steatohepatitis (NASH), CB_2 63R/R was *not* significantly associated with serum liver enzyme concentration (Rossi, Bellini, Alisi, et al., 2012). This difference was thought to relate to the latter cohort having overall more severe liver disease. There was no difference in severity of steatosis or degree of fibrosis between genotypes. However, CB_2 63R was associated with increased degree of histologically-graded inflammation, with 22% of both 63Q/R and 63R/R patients having grade 2 inflammation compared with none of the 63Q/Q individuals. Further, 43% of 63Q/R and 53% of 63R/R patients were diagnosed with definitive non-alcoholic steatohepatitis, compared with only 4% of 63Q/Q individuals (OR 5.2).

5.3.2 | Chronic hepatitis B (HBV) and C (HCV)

Some adults clear infections with HBV and HCV in the acute phases of infection, however, ~5% of those infected with HBV and

60%–80% with HCV will maintain chronic infection, with ~20% of these progressing to cirrhosis (Saraceni & Birk, 2021). Dysregulation of T lymphocyte responses are associated with development of chronic hepatitis, with various co-morbid, lifestyle and environmental factors implicated. Chronic hepatitis is also suspected be a trigger for autoimmune disorders (Sayiner et al., 2014).

Five studies, all of participants recruited in Italy, investigated association of *CNR2* rs2501432/rs35761398 (63Q/R) with clinical parameters of liver function and disease severity in hepatitis infection (Table S5). All reports found association of this SNP with at least one clinical parameter, but the specific parameters and directionality of findings have been somewhat inconsistent.

The first report studied 169 patients with chronic asymptomatic HCV (Coppola, Zampino, Bellini, et al., 2014). Clinical measures for the 63Q/Q genotype indicated more severe disease, with higher serum ALT, serum aspartate-aminotransferase (AST), and histological activity index (HAI) scores (but not gamma-glutamyltransferase, GGT) compared with 63R/R and 63Q/R. A similar study in a slightly larger cohort again found that 63Q/Q was associated with higher HAI (Coppola, Zampino, Sagnelli, et al., 2014). However, in contrast to the earlier study, 63Q/Q patients were more likely to have 'persistently normal' ALT levels, with 63R/R individuals and heterozygotes tending to have elevated ALT. These differing findings were hypothesised to relate to participants in the second study 'persistently normal ALT' group being older overall and potentially in a more 'terminal' phase of infection with liver damage (high HAI) but normalised ALT.

Chronic HCV patients with the 63R/R genotype were subsequently found to have an ~3-fold risk of having a concurrent 'immune-mediated disorder', correlating with various studies focusing on autoimmune disorders (Section 5.2) (Coppola et al., 2016). Independent of immune-mediated disorder diagnosis, 63R/R was associated with reduced serum enzyme levels (ALT, AST and GGT), with no significant difference in HAI. Uniquely in this study, 63R/R was associated with increased serum cholesterol, triglycerides, ferritin, transferrin and glucose; none of these were significantly associated with *CNR2* genotype in other hepatitis studies (Table S5).

Studying individuals with concurrent HCV and HIV infection, the 63R/R genotype was associated with elevated AST (though not ALT or GGT) and increased risk of high HAI (Sagnelli et al., 2017). This HAI finding contrasted with the earlier chronic HCV studies, though may have been a subtle effect as stratified analysis was required to detect this.

Correlation between markers for chronic HCV severity and CB_2 receptor genotype have therefore been very context-dependent. However, a common finding was that CB_2 63Q/R was not associated with degrees of fibrosis or steatosis (Coppola et al., 2016; Coppola, Zampino, Bellini, et al., 2014; Coppola, Zampino, Sagnelli, et al., 2014; Sagnelli et al., 2017).

Just one CB_2 SNP study has investigated chronic HBV infected patients (Coppola et al., 2015). Here, the 63R/R genotype was associated with more severe disease by HAI score, though there was no association with serum enzyme levels and 63R was also associated with reduced steatosis (but not fibrosis).

Overall, the studies on NAFLD and chronic HCV/HBV contribute additional evidence suggesting that the CB_2 receptor has potential to influence liver disease, most likely via immunomodulation rather than fibrosis or steatosis. However, it is also important to note that all the studies were relatively small, particularly once stratified to sub-groups of interest, and likely represented only a narrow ancestral background.

5.4 | Other immune-related responses and phenotypes

5.4.1 | Response to viral infection

Cannabis use has long been recognised to influence the course of viral infections, which has been ascribed in part to immunosuppressive effects via CB_2 receptor activation (Maggirwar & Khalsa, 2021). Further evidence towards CB_2 receptor involvement in responses to viral infections has been gained from genetic studies (Table S6). In a follow-up study to the work on Italian HCV-infected patients discussed earlier (Section 5.3.2), the 63R/R genotype conferred an approximately two-fold increased risk of being co-infected with HIV (Sagnelli et al., 2018). CB_2 receptor genotype was also implicated in the course of SARS-CoV-2 (COVID) infection, with CB_2 63R associated with increased severity in an Iranian population (Rastegar et al., 2021), and intronic *CNR2* SNPs (rs250144 and rs6658703) associated with severity in a Polish GWAS (along with ~18,000 other SNPs of ~15.5 million studied; Slomian et al., 2023). Conversely, the 63Q/Q genotype was associated with increased risk of hospitalisation in a small study of Iranian children with acute respiratory tract infection (ARTI) (Tahamtan et al., 2018).

5.4.2 | Respiratory distress syndrome

Respiratory distress syndrome is a breathing disorder that is prevalent in pre-term newborns and thought to be caused primarily by deficiency of lung surfactant, with inflammatory cascades likely influencing fetal lung maturation. In a study of 300 preterm Caucasian infants, no association was found between incidence or severity of respiratory distress syndrome with allele or genotype frequency for rs35761398 (63Q/R) (Binaafar et al., 2018).

5.4.3 | Haematological traits

The CB_2 receptor has been suggested to play roles in haematopoiesis and immune cell differentiation (Danner et al., 2019; Simard et al., 2022). Five GWAS on haematological phenotypes have identified *CNR2* SNPs to be among those associated with traits (Astle et al., 2016; Chen et al., 2020; Höglund et al., 2022; Kichaev et al., 2019; Vuckovic et al., 2020; Table S6). All five studies detected one or more CB_2 SNPs in the 3′ UTR as significantly associated with

eosinophil abundance (rs2229586, rs3003334, rs2501426, rs2502994 and rs2502995). Two studies found intronic *CNR2* SNPs to be associated with lymphocyte count (rs61778217 and rs35675064) (Chen et al., 2020; Vuckovic et al., 2020), and two found association of 3′ UTR *CNR2* SNPs with corpuscular volume (red blood cell size/volume; rs2502994 and rs2229586) (Kichaev et al., 2019; Vuckovic et al., 2020). Although CB_2 receptor variants were not highlighted as having particularly striking significance or effect sizes, repeated implication of the CB_2 receptor lends support to these being robust associations. However, there was very limited ancestral diversity in the cohorts (predominantly European; two studies included ≤25% non-European participants), and there was likely a degree of resampling of participants between studies as all included UK Biobank data.

5.5 | Cardiovascular and metabolic health and disease

Cardiovascular disease is one of the leading causes of death globally. Risk factors for and aetiology of cardiovascular disease are intertwined with multiple other physiological systems and disorders relating to metabolism, including control of body weight and insulin response, all of which are influenced by genetic, behavioural, environmental, social and economic factors.

5.5.1 | Blood pressure and myocardial infarction

The CB_2 receptor is expressed in cells of the cardiovascular system, is up-regulated under inflammatory conditions, and activation is generally found to be cardioprotective in animal models of atherosclerosis and ischaemia/reperfusion injury (Steffens & Pacher, 2012). Two studies directly addressing cardiovascular health have investigated potential links to CB_2 receptor genetics (Table S7). In a Japanese cohort aged 40–79 years without cardiovascular disease or disorders associated with secondary hypertension, males homozygous for the rs2501431-G reference (minor) allele had slightly higher systolic and diastolic BP, but not greater frequency of hypertension (Yamada et al., 2007b). There was no association for females. Two other genes included in the study had greater effects, with significant association to hypertension. In a German cohort of 928 people, 13 *CNR2* SNPs (including rs2501431 and rs2229579 [H316Y]) were investigated for association with myocardial infarction and cardiovascular risk factors (such as arterial hypertension, obesity, hypercholesterolemia, and diabetes). No significant associations were detected (Reinhard et al., 2008).

5.5.2 | Obesity

Obesity is defined as a disproportionate body weight for height with excessive accumulation of adipose tissue that is usually accompanied by systemic inflammation. CB_2 receptor knock-out animal models have increased food intake and body weight, whereas overexpression produces a lean phenotype (Agudo et al., 2010; Romero-Zerbo et al., 2012). Stimulation of *ex vivo* adipocytes with a CB_2 receptor agonist also counteracts obesity-related changes in adipokine and cytokine release (Rossi et al., 2016).

Analysis of European subjects in a large dataset collated from multiple GWAS found that seven SNPs downstream of, but linked to, *CNR2* (including rs4237) were not significantly associated with body mass index (BMI) (Ketterer et al., 2014). However, subsequent studies of more specific patient groups have revealed potential associations of *CNR2* with body weight and related characteristics (Table S7).

In Italian children with obesity, one study found a slight increase in *z*-score BMI with the CB_2 63R/R genotype but no change in other measures (including waist-to-hip ratio, cholesterol and triglyceride levels, insulin, insulin resistance) (Rossi et al., 2016), whereas another (smaller) study on female children did not find a significant association with BMI (Bellini, Grandone, et al., 2015). CB_2 63Q was, however, associated with a two-fold increased risk of early menarche which was hypothesised to relate to altered endocannabinoid and oestrogen tone in obese individuals.

A set of five studies in Caucasian Spanish individuals with obesity (∼150 to ∼1,000 participants in each) investigated association of SNP rs3123554 with various clinical measures (Aller et al., 2019; de Luis et al., 2017; de Luis et al., 2018; de Luis et al., 2019; Primo et al., 2020). This SNP is ∼0.6 kb downstream of the *CNR2* coding region, in the intergenic region upstream of *FUCA1*, and is in LD with *CNR2* exon 3 (Ketterer et al., 2014; Zhang et al., 2015). All found the G/G genotype (G being the major allele in general populations, ∼63.4%) to be significantly associated with reduced BMI (mean difference between homozygotes 0.4–1.2 kg/m^2), weight, total body fat and waist circumference. The largest study also detected association with reduced insulin, insulin resistance, triglyceride levels and leptin. No studies found association with baseline glucose levels, cholesterol or BP. As well as these baseline findings, the G/G genotype for this SNP also correlated with more positive outcomes (e.g., greater reduction in BMI and/or insulin levels) in obesity interventions such as hypocaloric diet and bariatric surgery.

5.5.3 | Diabetes type 2 (DM-T2)

DM-T2 is a chronic metabolic disorder closely linked with obesity and characterised by insulin resistance and hyperglycemia. Diabetic kidney disease (DKD) is one of the most serious arising potential complications of DM-T2. CB_2 receptor agonism has been found to modulate insulin secretion and reduce inflammation in diabetes animal models, and be protective in various kidney disease models (Kumawat & Kaur, 2019).

CNR2 SNP rs3123554 was correlated with body weight in ∼2000 individuals at high risk of DM-T2 from Germany (Ketterer et al., 2014; Table S7). The A/A genotype was associated with smaller changes in BMI and insulin sensitivity than G allele carriers with lifestyle

intervention. While this finding correlated with the findings in Spanish obesity cohorts summarised above (Section 5.4.2), the opposite correlation to BMI was detected, with the A/A genotype significantly associated with reduced BMI in females but not males (female homozygote mean difference 2.3 kg/m^2). Four other *CNR2* SNPs, three in the intron between exons 2 and 3 (rs2501392, rs9424398 and rs4625225) and one in exon 3 (rs2229579 [H316Y]), were also included in this study; none were significantly associated with baseline measures or response to lifestyle intervention.

The *CNR2* locus has also been associated with increased risk of DKD in a GWAS analysing ~7.9 million SNPs in Emirati DM-T2 patients (Osman et al., 2023). In gene set analysis, *CNR2* had the smallest genome-wide *p* value (individually identified SNPs were rs542405361 and rs2501391 in the intron between exons 2 and 3, OR 1.7–1.8), with 11 other genes also identified as having significant association with DKD risk. In a follow-up replication study on different large datasets, rs2501391 was also associated with kidney disease in a DM-T2 Japanese cohort (OR 1.4), but no significant links with *CNR2* SNPs and kidney disease were found in datasets of predominantly Caucasian individuals with DM-T2 and DM-T1.

5.6 | Neurological disorders and characteristics

The CB_2 receptor is an attractive therapeutic target for diseases involving neuroinflammation and blood–brain-barrier compromise such as neurodegeneration (Grabon et al., 2023). Dysregulated immune function in the CNS is also implicated in affective disorders and psychosis, with a probable role for peripheral circulating inflammatory factors also recognised (Millett et al., 2022). The potential association of *CNR2* SNPs has been investigated for a range of neurological disorders (Table S8).

5.6.1 | Affective disorders—Depression, anxiety and bipolar disorder (BD)

Affective disorders, also referred to as mood disorders, involve abnormality of emotional state that negatively influence quality of life. A range of evidence has suggested a bidirectional relationship between cannabis use and mood disorder risk, and that the endocannabinoid system plays a role in pathophysiology (Lucatch et al., 2018). CB_2 receptor agonists have varying effects on anxiety- and depressive-like traits in animal models (Grabon et al., 2023).

Three studies have investigated links between CB_2 SNPs and incidence of major depression or severity of depressive phenotypes (Table S8). In a Japanese study of 166 major depressive patients and 487 age-matched healthy controls, the rs2501432-C (63R) allele was overrepresented in individuals with major depression (OR 1.4) (Onaivi et al., 2008). This finding was corroborated in a later study of 921 Caucasian (Hungarian) volunteers without history or diagnosis of psychiatric disorder, in which the 63R/R genotype was associated with a higher depression score on the Zung Self-related Depression Scale (ZSDS) (Lazary et al., 2019). This effect was enhanced in individuals with history of childhood trauma, with increases in both depressive and anxious phenotypes. A larger study of 3121 Caucasian (Spanish) major depression patients also observed an increase in severity of symptomology for carriers of rs2501431-A, which is in LD with rs2501432-C (Mitjans et al., 2012). This SNP was not associated with responsiveness to citalopram treatment. Also relating to treatment for affective disorders, rs2501432 and a range of other *CNR2* SNPs were not significantly associated with response to cognitive behavioural therapy (CBT) or relapse in a study of childhood anxiety disorder (Lester et al., 2017).

A study of 80 BD patients (and 160 controls) investigated incidence of ns-SNPs rs2501432 (Q63R) and rs2229579 (H316Y), as well as rare variant rs41311993 (L133I) (Minocci et al., 2011). A significant association with BD was found for L133I, but not 63Q/R or H316Y. The increase in allele frequency for 133I was substantial, from 4% in controls to 19% in BD cases (OR 4.7). No control cases were homozygous for 133I, versus 6% of BD cases. It is unclear why allele frequencies in this study's control group for both L133I (4%) and H316Y (21%) were considerably higher than expectations from consolidated databases (Table 1 and S2); the study was undertaken in Italy but participant ancestry is not stated. Nonetheless, this striking result would certainly be interesting to follow up, particularly given the recent *in vitro* finding that L133I influences CB_2 receptor arrestin recruitment and internalisation (Section 4.3).

Specifically studying panic disorder, a type of anxiety disorder, rs2501432-C (63R) and rs2501431-A were risk factors for males (OR 2.2) but not females in a Caucasian (Spanish) cohort (Peiro et al., 2020). *CNR2* variants rs41311993 (L133I), rs2229579 (H316Y), and rs28655469 (intron between exons 2–3) were not significantly associated. However, small group sizes resulted in very few detections of the minor allele for rs41311993 (L133I) (<10 in entire study), limiting interpretability of data for this rare variant.

5.6.2 | Schizophrenia and psychosis

Schizophrenia is a psychiatric disorder characterised by positive (hallucinations, delusions, paranoia), negative (affective blunting, social withdrawal and anhedonia), and cognitive symptoms (loss of memory, attention, verbal learning/problem-solving). Heritable factors are thought to explain up to 80% of the risk of schizophrenia, with many candidate genes identified in GWAS being associated with the immune system. A link between cannabis use and schizophrenia onset and symptoms is recognised, though causality has not been definitively established (Marder & Cannon, 2019). Alteration of the peripheral endocannabinoid system in schizophrenia has been reported, including reduced CB_2 receptor expression in peripheral immune cells (Cortez et al., 2020). Four studies have investigated the association between CB_2 SNPs and schizophrenia (Table S8).

Two studies, in Japanese and Han Chinese schizophrenia patients, detected overrepresentation of the rs2501432-C (63R) variant in cases (OR 1.2–1.3) (Ishiguro, Horiuchi, et al., 2010; Tong et al., 2013).

The latter study performed stratified analysis and found a greater effect in males (OR 1.5). Ns-SNP rs2229579 (H316Y) was also included in both studies; no significant association was found in the first, but a tentative association was noted in the 2013 study (OR 1.3; nominally significant but no correction for multiple comparisons). Haplotypes combining three SNPs (adding rs2501401, in the intron between exons 2–3, not significantly associated alone) indicated protection from schizophrenia (rs2501401-G / rs2501432-T / rs2229579-G, OR 0.6) versus elevated risk (rs2501401-A / rs2501432-T / rs2229579-A, OR 3.3). Further evidence for rs2229579-A (316Y) as a risk allele for schizophrenia was obtained in a small Brazilian study, with allele frequency encoding 316Y increasing from 7% in controls to 17% in cases (OR 2.8) (Ferretjans et al., 2022).

Aside from intronic SNP rs2501401 noted above, findings for SNPs in *CNR2* introns or linked downstream regions have been mixed. A study of Korean individuals found no association of rs6689530 (intron between exons 2–3) or rs34570472 (∼5 kb downstream of *CNR2*, in *FUCA1* intron) with incidence of schizophrenia (Bae et al., 2014). However, another downstream SNP rs12744386 (∼29 kb from *CNR2*, intergenic between *FUCA1* and *HMGCL*) was associated with schizophrenia in the 2010 Japanese study, with slightly greater risk when considered in a haplotype with rs2501432 (OR 1.3) than when either SNP was considered alone (Ishiguro, Horiuchi, et al., 2010).

Finally, a GWAS on UK Biobank data studying the phenomenon of psychotic experience in individuals without neurological diagnosis identified *CNR2* as one of four loci (from >7.5 million SNPs analysed) that were significantly associated with having distressing psychotic experiences (Legge et al., 2019). While psychotic experience is a hallmark of schizophrenia, it is unclear whether psychotic experience in the general population represents a mild phenotype on the same spectrum as schizophrenia and/or relates to liability for developing schizophrenia or other mental illness, or is unrelated to schizophrenia and other mental disorders. The risk SNP was rs75459873-A, in the intron between *CNR2* exons 1b and 2 (not in proximity of putative promoter regions or splice sites, and not in LD with exon 3; Cunningham et al., 2022; Machiela & Chanock, 2015). This association was specific to distressing psychotic experiences, as incidence of any psychotic experience was not significantly associated, nor was having multiple psychotic experience episodes. There was no interaction of cannabis use with the SNP-psychotic experience association.

5.6.3 | Substance use disorders

Substance use disorders are chronic conditions involving compulsive drug seeking and use, despite deleterious consequences. Susceptibility to development of addiction is thought to include a strong genetic component, and although there are likely commonalities in the neuroadaptive pathways leading to addiction, genetic factors appear to be fairly divergent between different substances of abuse and consumption measures (Deak & Johnson, 2021; Poisson et al., 2021). There is also high co-occurrence of substance use disorder with other mental illnesses. The CB_1 receptor, and the enzymes regulating endocannabinoid synthesis and degradation, have received particular attention with relation to modulation of reward (Navarrete et al., 2022). Preclinical evidence suggests that the CB_2 receptor may also play a role in reward and addiction, potentially in concert with regulation of affective traits (Navarrete et al., 2021).

The potential for a role of *CNR2* in genetic susceptibility to substance use disorder has been investigated in five studies to date (Table S8). These were disparate in terms of the populations and substances of interest, and findings have likewise been inconsistent. Of four studies including rs2501432 (63Q/R), one identified 63R as a risk allele for alcohol dependence in a Japanese population (OR 1.5; Ishiguro et al., 2007), one found 63R to correlate with reduced incidence of cannabis use disorder in Caucasian schizophrenia patients (OR 0.5; Horcajadas et al., 2023), and two found no significant association with methamphetamine dependence (Japanese population) (Japanese population; Okahisa et al., 2011) or synthetic cannabinoid use disorder (Turkish population; Pehlivan et al., 2020). A further study of 'moderate to heavy' (but not necessarily dependent) cannabis use found no association of rs2501431, which is typically found to be in LD with rs2501432; however, this was a particularly small study with fewer than 50 individuals in the cannabis use group (Gerra et al., 2018). The study of synthetic cannabinoid use disorder, although also fairly small (∼100 participants per group), detected a significant and striking association for rs2229579-A (316Y), with incidence of the homozygous genotype increasing from 2% in controls to 29% in cases (OR 18.7; Pehlivan et al., 2020).

5.6.4 | Autism

Autism is characterised by heterogeneous childhood-onset symptoms relating to social interaction and communication, and other verbal and non-verbal behaviours, with various frequent co-occurring symptoms such as epilepsy and immune dysfunction. Alterations of the endocannabinoid system, including CB_2 receptor expression, have been detected in peripheral immune cells from children with autism, with experiments in animal models suggesting potential for CB_2 receptor agonism to alleviate some autism-related symptoms (De Pol & Kolla, 2021).

Four studies investigating rare variants and post-zygotic (somatic, non-germline) mutations in autism have reported data regarding *CNR2* (Table S8). These studies employed whole exome sequencing-based approaches to compare autistic individuals with parent or ancestry-matched controls (De Rubeis et al., 2014; Lim et al., 2017;Ruzzo et al., 2019; Wu et al., 2020). One or more rare variants in *CNR2* were detected in all studies, but rates of occurrence did not indicate increased risk of autism.

In a cohort with various neurological phenotypes, 11 rare missense mutations in *CNR2* were found, with seven of these being in individuals with autism and/or developmental delay (Smith et al., 2017). The rate of *CNR2* mutation was not significantly different from the control population. However, given the small number of

individuals with *CNR2* mutations, the power to detect associations with specific disorders was likely low. Interestingly, one of the mutations produced a truncation (R131*, rs150233022) and another resulted in loss of the native stop codon with a consequent extension of 50 amino acids (Ter361Asp-fsTer50, rs758031503). These were each detected once in later autism rare variant studies (Ruzzo et al., 2019; Wu et al., 2020). The consequence of *CNR2* mutation to these individuals is unknown.

5.6.5 | Eating disorders

Eating disorders are characterised by abnormal eating or weight-control behaviours and include anorexia nervosa, bulimia nervosa, and binge-eating disorder (Treasure et al., 2020). Genetic and environmental factors are implicated in development, as well as psychiatric comorbidities in which the endocannabinoid system also plays a role (Gonzalez et al., 2021; Treasure et al., 2020). Due to roles in regulating food intake and energy metabolism, the CB_2 receptor is a potential drug target for modulating feeding behaviour (see also Section 5.5.2).

A Japanese study of 204 patients diagnosed with anorexia nervosa or bulimia nervosa and 1876 healthy controls found that the rs2501432-C (63R) allele was significantly overrepresented in the eating disorder group compared with healthy controls (Ishiguro, Carpio, et al., 2010). The homozygous 63R/R genotype was significantly associated with incidence of anorexia nervosa (OR 1.3), but not bulimia nervosa. Three SNPs from *CNR2* introns and UTRs were subsequently found not to be significantly associated with anorexia in a Caucasian cohort (Gonzalez et al., 2021). However, two of these three SNPs (rs6658703-G [intron between exons 2–3], rs3003335-A [exon 3, 3′ UTR]), which were also in complete LD with each other in cases, were associated with higher global positive symptom distress index (PSD), and increased hostility, interpersonal distrust, and interoceptive awareness dimension scores. Interoceptive awareness relates to ability to discriminate between feelings and sensations, including satiety and hunger, suggesting a potential role in feeding behaviour.

6 | CONCLUDING REMARKS

In vitro and *in vivo* evidence supporting a role for the CB_2 receptor in various physiological processes and pathologies, and in some cases association of the 1p36.11 chromosomal locus with disease risk, has prompted a variety of investigations into CB_2 SNP associations with disease. Understanding such associations is hoped to be beneficial in identifying risk biomarkers to facilitate screening and intervention, elucidating biological pathways to inform therapeutic design, and enabling personalised treatment through knowledge of genetically-mediated response discrepancy.

The majority of studies addressing potential disease risk association for CB_2 receptor genetic factors to date have analysed SNPs that are highly prevalent in general human populations (36 SNPs in *CNR2* exon 3 with ~37% MAF). Interestingly, most studies reporting a significant disease association implicate the *more* frequent alleles as increasing risk (~52%–81% ancestry-dependent allele frequency, mean homozygote prevalence ~41%). These SNPs are therefore unlikely to be pragmatically useful as risk markers alone, nor solely responsible for associated pathology or traits with rare to moderate prevalence. However, it is feasible that these high frequency *CNR2* SNPs could be risk markers for and/or contribute to phenotypes in multifactorial disorders and traits (Astle et al., 2016; Bush & Moore, 2012). These include ns-SNP rs2501432/rs35761398 (63Q/R), for which the amino acid change can context-dependently modify CB_2 receptor function. Although many studies discuss the consequent likelihood that the 63Q/R ns-SNP modulates disease, this remains to be established directly. However, the potential for ligand-specific signalling at CB_2 63Q vs 63R may be important to consider in therapeutic drug development and clinical trial design. Strong LD between 63Q/R and ~35 other SNPs in *CNR2* exon 3 implies the full co-inherited haplotype block may contribute to functional differences, with non-coding and s-SNPs potentially influencing CB_2 receptor expression via effects on DNA structure and/or mRNA. If these high frequency SNPs do modify CB_2 receptor expression and/or function (including, potentially, biased agonism), it is plausible that clinical trial participants possessing differing genotypes for these common SNPs may have differing responses to therapies, thereby increasing variability of outcomes. Conversely, stratification of patients by CB_2 SNP genotype could reveal genotypes for which a drug is 'successful' versus 'unsuccessful'.

Lower frequency *CNR2* variants (~ < 8% MAF), particularly non-synonymous variants, may be better candidates for direct disease relevance (Astle et al., 2016; Gorlov et al., 2011). Larger association studies with more in-depth genetic coverage will likely be required to elucidate potential disease links. Ancestry-related diversity of variant prevalence must also be considered carefully in study design. To date there are only a few studies addressing the functional impact of CB_2 H316Y and L133I, and none for any of the other non-synonymous variants. Knowledge of changes in molecular pharmacology may well be important for predicting and interpreting disease relevance and drug responses.

The current CB_2 receptor genetic-disease association literature relies considerably on small case–control gene-of-interest studies, often monitoring association of only one SNP to the disease/trait in a specific population/ancestry, with variable quality of statistical design and control group matching. These studies might best be considered 'hypothesis-forming', with more in-depth studies required to cement the suggested disease associations. An important but rarely acknowledged point is that *CNR2* exon 3 is in strong LD with neighbouring genes and SNPs harboured therein (e.g., *FUCA1*, including at least three ns-SNPs). Therefore, disease association of a single exon 3 *CNR2* SNP could implicate linked genes. There is also potential for interaction effects between SNPs on different genes that are in LD, which is so far unexplored.

Of the various conditions and phenotypes studied for association to CB_2 receptor genetics so far, osteoporosis and immune cell phenotypes have some of the more robust findings. Osteoporosis

has been addressed the most thoroughly, via eight studies. Three of these consider LD structure and/or haplotypes with indication of convergence of SNP association at the *CNR2* locus. However, ORs and clinical measure effects were small, which might reflect the CB_2 receptor having a role as a contributing factor to a polygenic/multifactorial pathology. As well, findings have not always been consistent between studies, perhaps due to population or ancestry-related differences. Association of CB_2 SNPs to immune cell counts in multiple GWAS supports the underlying potential of CB_2 receptor genetics to impact immune-related conditions. Many other disease links are tentatively established, and have logical precedence based on what is known of CB_2 receptor biology. Further investigation into disorders suggested to have larger CB_2 SNP ORs seems particularly warranted; these include childhood CD, Crohn's disease and NAFLD, rheumatoid arthritis, BD, and substance use disorder.

With the broadly suggested potential for genetic factors in *CNR2* to be associated with disease, this will be an interesting space to watch. We anticipate that increasing utilisation of deep sequencing and availability of large datasets with improved diversity of population sampling, potentially with techniques useful for deciphering contributors to polygenic diseases such as eQTL and network analysis (e.g., Escala-Garcia et al., 2020; Vosa et al., 2021), will enable further clarification and more robust determination of the involvement of CB_2 genetics in disease risk and mechanisms. Meanwhile, the impact of SNPs on responses to CB_2 receptor-targeted drugs may be pertinent in clinical trial design and interpretation, and eventually personalised medicine.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/23 (Alexander, Christopoulos et al., 2023; Alexander, Fabbro et al., 2023).

AUTHOR CONTRIBUTIONS

Tahira Foyzun: Conceptualization (lead); data curation (equal); investigation (lead); visualization (equal); writing—original draft (lead). **Maddie Whiting:** Data curation (equal); investigation (equal); writing—review and editing (lead). **Kate K Velasco:** Data curation (lead); investigation (supporting). **Jessie C Jacobsen:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); writing—review and editing (supporting). **Mark Connor:** Conceptualization (equal); funding acquisition (supporting); investigation (supporting); supervision (lead); visualization (supporting); writing—original draft (supporting); writing—review and editing (equal). **Natasha L Grimsey:** Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); supervision (lead); visualization (lead); writing—original draft (equal); writing—review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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