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# Pharmacogenomics of the human $\mu$ -opioid receptor



The  $\mu$ -opioid receptor is a primary target for clinically important opioid analgesics, including morphine, fentanyl and methadone. Many genetic variations have been identified in the human  $\mu$ -opioid receptor MOP gene (*OPRM1*), and their implications have been reported in the effects of opioid drugs and susceptibility to drug dependence. Interestingly, agonistic and antagonistic opioid effects are inversely associated with the A118G polymorphism genotype. The A118G polymorphism may also be associated with substance dependence and susceptibility to other disorders, including epilepsy and schizophrenia. The IVS1+A21573G, IVS1-T17286C, and TAA+A5359G polymorphisms in the *OPRM1* gene may be associated with alcohol, opioid and tobacco dependence, respectively. However, some studies have failed to confirm the correlations between the polymorphisms and opioid effects and substance dependence. Further studies are needed to elucidate the molecular mechanisms underlying the effects of *OPRM1* polymorphisms.

**KEYWORDS:**  $\mu$ -opioid receptor analgesia drug addiction genetic polymorphism narcotic drugs

## Pharmacological importance of the $\mu$ -opioid receptor

The  $\mu$ -opioid receptor (MOP) is a subtype that belongs to the superfamily of 7-transmembrane-spanning G-protein-coupled receptors. Pharmacological studies with gene-knockout mice show that MOP is a major target for the clinically important opioid drugs, such as morphine and fentanyl, and it appears to play critical roles in the mediation of the major effects of these opioid drugs, including analgesia, tolerance, dependence and respiratory depression [1,2,201]. Homozygous MOP-deficient mice are insensitive to morphine [3-5]. In addition, heterozygous MOP-deficient mice, which possess approximately half of the amount of MOP protein in wild-type mice, exhibit haploinsufficiency in the analgesic effects of morphine [4,5]. The CXBK mouse strain, a recombinant inbred strain derived from an F2 intercross between BALB/c and C57BL/6 mice, exhibit reduced responses to opioid receptor agonists [6]. The CXBK strain expresses approximately half of the amount of MOP mRNA compared with progenitor strains and display phenotypes similar to those of heterozygous MOP-deficient mice [7]. In the CXBK strain, an intracisternal A-particle transposon is inserted in the 3'-UTR of the MOP gene, which would be expected to be the cause of the reduced response to opioids [8]. Among wild-derived inbred mouse strains, many genetic variations were identified in the

mouse MOP gene, and some of these variations were associated with interstrain differences in opioid sensitivity [9]. These results suggest that genetic variations in the MOP gene and MOP expression influence morphine sensitivity in a gene dosage-dependent manner.

In this brief article, we focus on and summarize the genetic variations in the human MOP gene, which are analyzed with regard to pain sensitivity, opioid drug sensitivity and susceptibility to drug dependence, and other disorders.

## ■ Structure of the human MOP gene

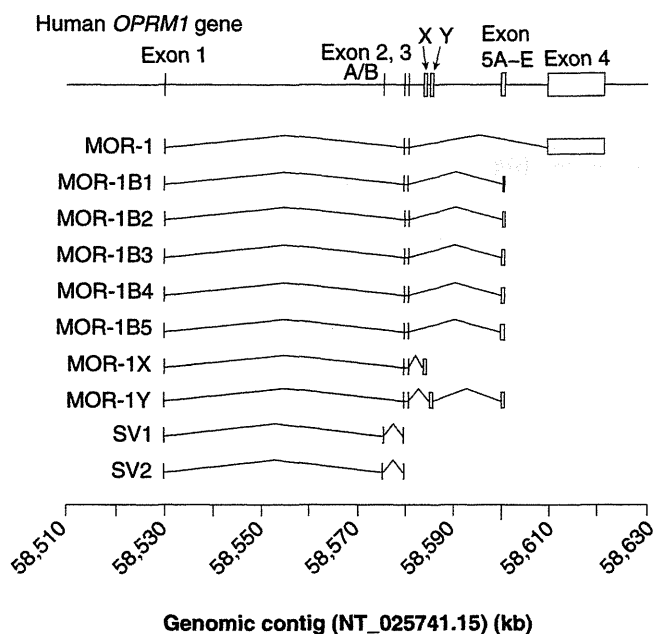
The cDNAs and genes encoding MOP have been cloned from mouse, rat, porcine, bovine, and human sources [10-17]. The human MOP gene (*OPRM1*) spans over 200 kb and consists of 11 exons that combine to yield 17 splice variants [18]. The exons A/B, X, Y and 5A-E in intron 1 or 3 of the *OPRM1* gene yield variants such as MOR-1B1-1B5, MOR-1X, MOR-1Y, SV1 and SV2 (FIGURE 1). Among the transcripts from the *OPRM1* gene, MOR-1, which consists of exons 1, 2, 3, and 4, is approximately 15 kb in length and the most abundant transcript [19]. The MOR-1 3'-UTR is continuously transcribed, beginning with the exon 4 coding region of MOR-1 mRNA. Human MOR-1 mRNA possesses a long 3'-UTR of over 13 kb. The other variants of the *OPRM1* gene, including MOR-1B5 and MOR-1Y, are also long transcripts defined as 15 kb, but the 3'-UTRs for these variants have not been identified [20].

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**Figure 1. Human  $\mu$ -opioid receptor gene (*OPRM1*) structure.** The human *OPRM1* gene spans over 200 kb and consists of multiple exons that combine to yield isoforms. Among these isoforms, MOR-1, which consists of exons 1, 2, 3 and 4 of the *OPRM1* gene, is approximately 15 kb in length and is the most abundant transcript. Exon A/B was identified in intron 1 as the first exon for the splice variants SV1 and SV2. In intron 3, exons X, Y and 5 were also identified as the last exons for the variants MOR-1X, MOR-1Y and MOR-1B1–1B5, respectively.

The human MOP gene structure and splicing sites are similar to those of mice [19,21]. Mouse MOR-1 mRNA is transcribed from exons 1, 2, 3 and 4 and possesses a long 3'-UTR of over 10 kb, which is continuously transcribed from exon 4, similar to human MOR-1 mRNA. Human MOR-1 (GenBank accession no. L25119) shares 87% cDNA and 94% amino acid sequence identities with mouse MOR-1 (GenBank accession no. U19380) [202]. The 3'-UTR of human MOR-1 mRNA shows high similarity to mouse MOR-1 mRNA in the regions of their 5' and 3' ends [19]. Many splice variants of MOR-1 mRNA have also been reported in mice. Studies with antibodies against splice variants of mouse MOR-1 mRNA and gene-modified mice for exon 11 were performed [22–25], but the functions of these splice variants of MOR-1 mRNA have been controversial.

### SNPs in the *OPRM1* gene

Over 700 SNPs have been identified in the *OPRM1* gene (refer to the dbSNP database, the NCBI database of genetic variations) [203]. Genetic variations in the *OPRM1* gene are quite different between different races and ethnicities. In the International HapMap project, genetic variations in the African population in Nigeria

(YRI), northern and western European ancestry in the USA (CEU), Japanese in Tokyo, Japan (JPT), and Han Chinese in Beijing, China (CHB) were analyzed, and variations in the SNPs in the *OPRM1* gene were the following: CEU > YRI > JPT and CHB [204]. These data suggest that the linkage disequilibrium (LD) blocks and minor allele frequencies (MAFs) of the SNPs in the *OPRM1* gene are different between different races and ethnicities.

In European populations (European Americans or Caucasians), the *OPRM1* gene is covered with two LD blocks whose boundary is located around the end of intron 1 between rs3778156 and rs2075572, rs1381376 and rs9479757, rs1381376 and rs563649, or rs3778151 and rs660756 [26–30]. In American Indians, the *OPRM1* gene also consists of two major LD blocks that are separated by the border between rs506247 and rs2075572 [31]. However, in the Japanese population, the *OPRM1* gene is covered with four LD blocks [32]. In the Uyghur population, the major LD blocks were not identified in the *OPRM1* gene, but a small LD block was identified at intron 3 containing rs3798683 and rs9397685 [33]. The MAFs of A118G (rs1799971), which is a well-studied nonsynonymous SNP leading to an Asn40Asp substitution in the *OPRM1* gene, are 0.047 in the African population, 0.154 in the European population, 0.485 in the Japanese population, 0.14 in the Hispanic population, 0.210 in the Ashkenazi population, 0.08 in the Bedouin population and 0.17 in the Ethiopian population, indicating a wide variety of MAFs of the A118G SNP in the *OPRM1* gene among different races and ethnicities [34]. These results suggest that genetic variations in the *OPRM1* gene need to be analyzed by the race/ethnicity of populations.

Numerous SNPs in the *OPRM1* gene have been analyzed with regard to clinical traits (SUPPLEMENTARY TABLE 1; [www.futuremedicine.com/doi/suppl/10.2217/pgs.11.68](http://www.futuremedicine.com/doi/suppl/10.2217/pgs.11.68)). SUPPLEMENTARY TABLE 1 lists the SNPs in the *OPRM1* gene that were previously reported in association studies, with the exception of haplotype analyses, pain sensitivity, opioid sensitivity, and susceptibility to drug dependence and other disorders. Almost all of the analyzed SNPs in the *OPRM1* gene are located at exons 1–4, corresponding to the genomic region for the MOR-1 mRNA.

### Association studies of SNPs in the *OPRM1* gene & pain sensitivity

Homozygous and heterozygous MOP-deficient mice exhibited higher sensitivity to thermal nociception compared with wild-type mice

in the tail-flick test at 50°C and 53°C [4]. These data suggest that hypomorphic SNPs in *OPRM1*, which reduce their expression or function, influence pain sensitivity.

Four SNPs in the *OPRM1* gene were analyzed in association studies with pain and related traits (TABLE 1) [35–43]. Among four SNPs, the IVS1-C2994T and IVS2+G31A SNPs were significantly associated with pain sensitivity scores and pressure pain thresholds, respectively [35,43]. However, no other reports have shown an association between these two SNPs and pain-related traits; therefore, the results of these association studies remain controversial. Significant associations with pain-related traits were also observed in studies of the A118G SNP. The G-allele carriers of the A118G SNP showed higher reactivity to social rejection compared with AA subjects in the dorsal anterior cingulate cortex and anterior insula, which are involved in processing social and physical pain [41]. However, G-allele carriers exhibited lower sensitivity to mechanical stimulation than AA subjects did [36]. Therefore, further studies are necessary to evaluate the results of these association studies between the A118G SNP and pain sensitivity.

### Association of *OPRM1* SNPs with opioid sensitivity

The MOP plays an integral role in the various effects of opioids. Morphine, fentanyl and methadone are agonists for the MOP, and the clinical effects of these analgesic opioids, such as analgesia and their side effects, including nausea, vomiting, pruritis and respiratory depression, are mainly produced through MOP [2]. The analgesic and side effects of analgesic opioids were abolished or reduced in homozygous or heterozygous MOP-deficient mice [4,5]. These results indicate that MOP gene dosage is related to the clinical efficacy of analgesic opioids. In addition, the opioid antagonist naltrexone is effective for the treatment of alcohol dependence [44]. Naltrexone is a nonspecific antagonist of opioid receptor subtypes, but it strongly interacts with MOP [45]. The effects of naltrexone on drinking outcome have been found to be greater in alcoholic individuals with a family history of alcoholism [46,47], suggesting that genetic factors highly contribute to the effects of naltrexone in alcoholic treatment. Furthermore, the endogenous opioidergic system via MOP plays a critical role in the regulation of hypothalamic–pituitary–adrenal (HPA) axis activation. Corticotropin-releasing factor neurons in the paraventricular nucleus of the hypothalamus,

which expresses MOP, initiates HPA axis activation [48,49]. Opioid blockade by naloxone has been found to show a greater cortisol response among individuals with a family history of alcoholism [50–52]. Thus, genetic variations in the *OPRM1* gene appear to affect the analgesic and side effects of opioids, efficacy of naltrexone for alcoholic treatment, and HPA axis activation by naloxone and exhibit interindividual differences in these effects of opioids.

Many SNPs in the *OPRM1* gene have been investigated in regard to opioid sensitivity, including the analgesic and side effects of analgesic opioids, efficacy of naltrexone for alcoholic treatment, and HPA axis activation by naloxone (TABLE 2) [37,40,42,53–96]. Among these studies, statistical significance was found in association studies between only three SNPs (A118G, IVS2+C691G and IVS3+A8449G) and opioid sensitivity.

The A118G SNP has been shown to be associated with the analgesic and side effects of opioids, including morphine, morphine-6-glucuronide (M6G) and fentanyl. In these studies, opioid dose [66,76], consumption [42,68], requirement [54,56,63,64,80], and 50% effective concentration ( $EC_{50}$ ) [58,62] were greater in G-allele carriers compared with AA subjects, regardless of the analgesic and analgesia type. Specifically, the analgesic effects were lower in

**Table 1. Association studies of *OPRM1* SNPs with pain sensitivity.**

Polymorphism	Result (MAF)	Ref.
G-172T	No (pressure pain threshold and tolerance) (0.174)	[35]
C17T	Not analyzed (0.000)	[35]
A118G	No (heat pain threshold) (0.112)	[36]
	G-allele carriers > AA subjects (pressure pain threshold, $p < 0.05$ )	
	No (ischemic pain threshold)	
	No (MPQ-sensory postoperative pain rating) (0.125)	[37]
	Association (MPQ-sensory and MPQ-affective pain ratings, $p < 0.05$ )	[38]
	No (pressure pain threshold and tolerance) (0.319)	[35]
	No (chronic widespread pain) (0.100) <sup>†</sup>	[39]
	No (cold pressor-induced pain threshold) (0.438)	[40]
	G-allele carriers > AA subjects (dispositional and neural sensitivity, $p < 0.05$ ) (0.208)	[41]
	G-allele carriers < AA patients (pain tolerance threshold, $p = 0.03$ and $0.001$ ) (0.313)	[42]
IVS1-C2994T	Association (pain-sensitivity score, $p = 0.0007$ )	[43]
	No (chronic widespread pain) (0.093) <sup>†</sup>	[39]
IVS2+G31A	GA subjects > GG subjects (pressure pain threshold, $p = 0.036$ ) (0.028)	[35]
	No (pressure pain tolerance)	
IVS2+C691G	Not analyzed (0.000)	[35]

<sup>†</sup>The number of subjects combined the control and chronic widespread pain groups. MAF: Minor allele frequency; MPQ: McGill Pain Questionnaire.

G-allele carriers than in AA subjects. G-allele carriers exhibited lower analgesic efficacy compared with AA subjects [40,67,70,73,75]. Similar to analgesic efficacy, the incidence of analgesic opioid side effects was lower in G-allele carriers than in AA subjects [56,60,68,73,75,77]. Numerous studies have also reported associations of the A118G SNP with the efficacy of naltrexone for alcoholic treatment. In contrast to the effects of analgesic opioids, the efficacy of naltrexone for alcoholic treatment (i.e., rate of relapse, time to relapse, craving for alcohol and clinical outcome) were higher in G-allele carriers than AA patients [57,84,86,88,89]. Similarly, HPA axis activation induced by naloxone was greater in G-allele carriers than AA subjects [93–96]. These results indicate that the G allele of the A118G SNP is hypomorphic and hypermorphic for the effects of analgesic opioids and opioid antagonists, respectively. The meta-analysis showed an association of the A118G SNP with less nausea (effect size, Cohen's  $d = -0.21$ ,  $p = 0.037$ ) and more dosage requirements ( $d = 0.56$ ,  $p = 0.018$ ) in GG subjects [97]. However, some reports showed no association between the A118G SNP and opioid sensitivity. Association studies of opioid sensitivity have been performed with various races and population ethnicities. As described above, the MAFs of the A118G SNP vary widely among race/ethnicity; therefore, the effect sizes of the A118G SNP in association studies are quite different between races and ethnicities. A possible explanation for the incidence of no association between the A118G SNP and effects of opioids is that the statistical power was inadequate and may be attributable to the different MAFs between races and ethnicities in the sample populations. The MAF in the studies of the association between the A118G SNP and analgesic effects of opioids is  $0.260 \pm 0.032$  ( $n = 16$ , average  $\pm$  standard error of the mean), which tends to be higher than the MAF in studies that found no association between the A118G SNP and analgesic effects of opioids ( $0.173 \pm 0.067$ ,  $n = 5$ ). However, the MAFs in the studies that found an association between the A118G SNP and side effects of analgesic opioids or efficacy of naltrexone for alcoholic treatment, are not different from the studies that found no associations. These opioid functions are dependent on metabolic enzymes, transporters and molecules involved in opioid signal transduction pathways. Specifically, the side effects of opioid analgesics are under the influence of drug-metabolizing enzymes and transporters, which facilitate the elimination of opioids from the body (e.g., CYP,

UDP-glucuronosyltransferase and ATP-binding cassette transporters). Therefore, genetic variations in the genes that encode these molecules might be involved in opioid sensitivity and affect the association between the A118G SNP in the *OPRM1* gene and the side effects of opioid analgesics. Naltrexone exerts its effect by interacting not only with MOP but also with  $\delta$ - and  $\kappa$ -opioid receptors. The A118G SNP in the *OPRM1* gene may be associated with the action of opioids, such as morphine and fentanyl, at the MOP rather than affect the action of nonspecific opioids, such as naltrexone, at other opioid receptor subtypes. The reasons as to why some studies did not confirm the association between the A118G SNP and side effects of analgesic opioids or treatment efficacy of naltrexone for alcoholism, remain to be clarified.

In an association study of the IVS2+C691G SNP, statistical significance was observed with the effects of naloxone [96], but another study did not show an association between the IVS2+C691G SNP and analgesic effects of morphine or fentanyl. Similar to the IVS2+C691G SNP, only one study reported an association between the IVS3+A8449G SNP and fentanyl analgesia [40]. Therefore, further work is needed to validate and determine the significance of the IVS2+C691G and IVS3+A8449G SNPs in the effects of naloxone and fentanyl analgesia, respectively.

### Association of *OPRM1* SNPs with susceptibility to substance dependence

Pharmacological studies in animals implicate the endogenous opioid system in the reinforcing effects of a variety of drugs, including alcohol, cocaine, heroin, cannabinoids, nicotine and amphetamine. These drugs have been shown to release dopamine in the nucleus accumbens and ventral tegmental area, which are critical brain loci in the reinforcement pathway [98]. Dopamine release is a consequence of increased opioidergic activity, which inhibits GABA neurons, thereby disinhibiting dopaminergic neurons [99]. MOP-deficient mice exhibited decreased ethanol self-administration and decreased ethanol intake [100–102]. The rewarding effects of heroin, cannabinoids and nicotine, but not amphetamine, were also abolished or reduced in MOP-deficient mice [103–108]. Cocaine reward, measured by conditioned place preference, was reduced in both homozygous and heterozygous MOP-deficient mice [109], although cocaine produced comparable conditioned place preference in both wild-type and MOP-deficient mice

**Table 2. Association studies of *OPRM1* SNPs with the effects of opioid drugs.**

Polymorphism	Opioid	Opioid effect	Result	Number of subjects	Ref.	
G-1784A	Morphine	Cancer pain relief	GA carrier < GG carrier (pain relief)	GG, 1; GA, 1; AA, 0	[53]	
G-172T	Morphine	Cancer pain relief	No (morphine requirement)	GG, 90; GT, 8; TT, 1	[54]	
	Morphine	Cancer pain relief	No (opioid switching)	GG, 137; GT, 19; TT, 0 <sup>†</sup>	[55]	
	Morphine	Postoperative analgesia	No (morphine requirement)	GG, 819; GT, 156; TT, 8	[56]	
			Side effects	No (nausea, vomiting episodes and pruritis)		
C17T	Naltrexone	Alcoholic treatment	Not analyzed	CC, 6; CT, 5; TT, 0	[57]	
A118G	Morphine	Pupil constriction	No (EC <sub>50</sub> of morphine)	AA, 6; AG, 5; GG, 1	[58]	
	Morphine	Morphine tolerance	Morphine tolerance with high plasma M6G in GG subjects	AA, 1; AG, 0; GG, 1	[59]	
			Side effects	Dizziness, sleepiness and apathy in AA subjects		
	Morphine/M6G	Pupil constriction	G-allele carriers < AA subjects (miotic effects of morphine and M6G)	AA, 6; AG, 4; GG, 2	[60]	
			Side effects	G-allele carriers < AA subjects (nausea and vomiting, p < 0.05)		
	Morphine	Cancer pain relief	Less effective in AG patients	AA, 1; AG, 1; GG, 0	[53]	
	Morphine	Cancer pain relief	GG patients > AA patients (morphine requirement, p = 0.006)	AA, 78; AG, 17; GG, 4	[54]	
			Side effects	No (nausea, vomiting, dyspnea, sleepiness, loss of appetite and constipation)		
	Morphine	Cancer pain relief	No (opioid switching)	AA, 114; AG, 37; GG, 5 <sup>†</sup>	[55]	
	Morphine	Postoperative analgesia	No (morphine dose)	AA, 57; AG, 15; GG, 2	[61]	
			Side effects	No (PONV requiring ondansetron)		
	Morphine/M6G	Pupil constriction	GG subjects > AA subjects (EC <sub>50</sub> of opioids, p < 0.001)	AA, 23; AG, 6; GG, 2	[62]	
	Morphine	Cancer pain relief	GG patients > AA patients (morphine requirement, p = 0.024)	AA, 43; AG, 19; GG, 18	[63]	
			Side effects	No (nausea score, vomiting and sedation score)		
	Morphine	Postoperative analgesia	GG patients > AA patients (morphine requirement, p = 0.003)	AA, 74; AG, 33; GG, 13	[64]	
			Side effects	No (nausea, vomiting, and other adverse effects)		
Morphine/fentanyl	Postoperative analgesia	No (morphine dose)	AA, 70; AG, 30; GG, 1	[65]		
Morphine	Cancer pain relief	G-allele carriers > AA patients (morphine dose, p = 0.012)	AA, 166; AG, 36; GG, 5	[66]		
Morphine	Cancer pain relief	GG patients < AA patients (pain relief, p < 0.001)	AA, 106; AG, 22; GG, 10	[67]		
Morphine	Postoperative analgesia	G-allele carriers > AA subjects (morphine consumption, p < 0.05)	AA, 272; AG, 234; GG, 82	[68]		
		Side effects	G-allele carriers < AA subjects (nausea, p = 0.02)			
		Side effects	No (pruritus severity score)			
Morphine	Postoperative analgesia	Association (morphine requirement, p < 0.01)	AA, 389; AG, 435; GG, 170	[56]		
		Side effects	Association (nausea, p = 0.026; vomiting episodes, p = 0.022)			

<sup>†</sup>The number of subjects combined the control and switcher groups.

ACTH: Adrenocorticotrophic hormone; EC<sub>50</sub>: 50% effective concentration; ESWL: Extracorporeal shock wave lithotripsy; HPA: Hypothalamic-pituitary-adrenal; M6G: Morphine-6-glucuronide; MAP: Mean arterial pressure; PaCO<sub>2</sub>: CO<sub>2</sub> arterial pressure; PONV: Postoperative nausea or vomiting; VAS: Visual analogue scale.

Table 2. Association studies of *OPRM1* SNPs with the effects of opioid drugs (cont.).

Polymorphism	Opioid	Opioid effect	Result	Number of subjects	Ref.
A118G (cont.)	M6G	Pupil constriction	G-allele carriers > AA subjects (EC <sub>50</sub> of M6G, p < 0.05)	AA, 6; AG, 5; GG, 1	[58]
	M6G	Electrical pain relief	Low M6G analgesia in G-allele carriers	AA, 12; AG, 6; GG, 0	[69]
	M6G	Electrical pain relief	AG subjects < AA subjects (M6G analgesia, p < 0.01)	AA, 12; AG, 4; GG, 0	[70]
		Respiratory depression	No (E <sub>max</sub> and EC <sub>50</sub> of acute hypoxic response)		
	Fentanyl	Preoperative analgesia	No (gastric response to fentanyl)	AA, 15; AG, 2; GG, 1	[71]
	Fentanyl	Labor analgesia	G-allele carriers < AA subjects (EC <sub>50</sub> of fentanyl, p < 0.01)	AA, 150; AG, 62; GG, 11	[72]
	Fentanyl	Postoperative analgesia	G-allele carriers > AA patients (VAS score, p < 0.05)	AA, 99; AG, 66; GG, 24	[73]
		Side effects	G-allele carriers < AA patients (PaCO <sub>2</sub> , p < 0.05)		
			GG patients < AA patients (time to awakening and extubation, p < 0.05)		
			No (respiratory depression)		
	Fentanyl	Thermal pain relief	G-allele carriers < AA subjects (pain threshold decrease, p = 0.046)	AA, 86; AG, 143; GG, 51	[40]
	Fentanyl	Postoperative analgesia	GG patients > A-allele carriers (fentanyl consumption, p = 0.039 or 0.01)	AA, 86; AG, 67; GG, 21	[42]
	Fentanyl	Labor analgesia	No (duration of fentanyl analgesia)	AA, 144; AG, 34; GG, 12	[74]
	Fentanyl/morphine	Postoperative analgesia	No (morphine requirement and duration of morphine analgesia)	AA, 78; AG, 22; GG, 3	
	Alfentanyl	Electrical pain relief	G-allele carriers < AA subjects (alfentanyl analgesia, p < 0.05)	AA, 10; AG, 4; GG, 6	[75]
		Chemical pain relief	GG subjects < A-allele carriers (alfentanyl analgesia, p < 0.05)		
		Side effects	GG subjects < A-allele carriers (respiratory frequency, p < 0.01)		
	Alfentanyl	ESWL pain relief	G-allele carriers > AA subjects (alfentanyl dose, p < 0.01)	AA, 72; AG, 24; GG, 3	[76]
			G-allele carriers > AA subjects (frequency of boluses, p < 0.05)		
Levomethadone	Pupil constriction	G-allele carriers < AA subjects (miotic effect, p < 0.001)	AA, 40; AG, 8; GG, 3	[77]	
Buprenorphine	Heroin dependence treatment	G-allele carriers < AA patients (ACTH response, p = 0.03)	AA, 14; AG, 4; GG, 2	[78]	
Methadone	Opioid abuse treatment	No (methadone response)	AA, 177; AG, 57; GG, 4	[79]	
Some opioids	Postoperative analgesia	SNP × anger-out (analgesic consumption, p < 0.05)	AA, 37; AG, 10; GG, 1	[37]	
Some opioids	Chronic pain relief	G-allele carriers < AA patients (opioid dose, p < 0.005)	AA, 103; AG, 17; GG, 1	[65]	
Some opioids	Postoperative analgesia	GG patients > A-allele carriers (analgesic requirement, p < 0.05)	AA, 41; AG, 70; GG, 27	[80]	
Naltrexone	Alcoholic treatment	G-allele carriers < AA patients (rate of relapse, p = 0.044)	AA, 89; AG or GG, 41	[57]	
		G-allele carriers > AA patients (time to relapse, p = 0.040)			
Naltrexone	Alcoholic treatment	No (effects of naltrexone treatment)	AA, 59; AG or GG, 29	[81]	
		G-allele carriers > AA patients (decrease of MAP, p < 0.005)			

\*The number of subjects combined the control and switcher groups.

ACTH: Adrenocorticotropic hormone; EC<sub>50</sub>: 50% effective concentration; ESWL: Extracorporeal shock wave lithotripsy; HPA: Hypothalamic-pituitary-adrenal; M6G: Morphine-6-glucuronide; MAP: Mean arterial pressure; PaCO<sub>2</sub>: CO<sub>2</sub> arterial pressure; PONV: Postoperative nausea or vomiting; VAS: Visual analogue scale.

Table 2. Association studies of *OPRM1* SNPs with the effects of opioid drugs (cont.).

Polymorphism	Opioid	Opioid effect	Result	Number of subjects	Ref.
A118G (cont.)	Naltrexone	Alcoholic treatment	No (effects of naltrexone treatment)	AA, 16; AG, 6; GG, 3	[82]
	Naltrexone	Alcoholic treatment	No (rate and time to relapse)	AA, 148; AG or GG, 42	[83]
	Naltrexone	Alcoholic treatment	G-allele carriers < AA patients (craving for alcohol, $p < 0.05$ ) No (alcohol-induced stimulation, sedation or mood changes)	AA, 25; AG, 14; GG, 1	[84]
	Naltrexone	Alcoholic treatment	No (effects of naltrexone treatment)	AA, 119; AG or GG, 54	[85]
	Naltrexone	Alcoholic treatment	G-allele carriers > AA patients (% of days abstinent, $p < 0.05$ ) G-allele carriers < AA patients (% of heavy drinking days, $p < 0.05$ ) G-allele carriers > AA patients (rate of good clinical outcome, $p = 0.005$ )	AA, 469; AG or GG, 135	[86]
	Naltrexone	Alcoholic treatment	No (effects of naltrexone treatment)	AA, 75; AG or GG, 17	[87]
	Naltrexone	Alcoholic treatment	G-allele carriers > AA patients (time to relapse, $p = 0.014$ )	AA, 25; AG or GG, 38	[88]
	Naltrexone	Alcoholic treatment	Haplotype (including A118G) $\times$ medication ( $p = 0.03$ ) G-allele carriers > AA patients (rate of good clinical outcome, $p = 0.006$ )	Unknown	[89]
	Naltrexone	Alcoholic treatment	No (effects of naltrexone treatment)	AA, 89; AG, 16; GG, 3	[90]
	Naltrexone	Alcoholic treatment	No (naltrexone effects on impulsive choice ratio)	AA, -; AG, -; GG, -	[91]
	Nalmefene	Alcoholic treatment	No (effects of nalmefene treatment)	AA, 167; AG, 96; GG, 29	[92]
	Naloxone	HPA axis activation	G-allele carriers > AA subjects (cortisol response, $p < 0.05$ ) AG subjects > AA subjects (plasma ACTH response, $p < 0.05$ )	AA, 29; AG, 9; GG, 1	[93]
	Naloxone	HPA axis activation	G-allele carriers > AA subjects (cortisol response, $p < 0.05$ ) No (plasma ACTH response)	AA, 24; AG, 5; GG, 1	[94]
	Naloxone	HPA axis activation	G-allele carriers > AA subjects (cortisol response, $p = 0.046$ ) No (plasma ACTH response)	AA, 59; AG, 14; GG, 1	[95]
	Naloxone	HPA axis activation	G-allele carriers > AA subjects (cortisol response, $p < 0.05$ ) No (cortisol response) G-allele carriers < AA subjects (plasma ACTH, $p = 0.04$ )	AA, 6; AG, 5; GG, 1 AA, 7; AG, 8; GG, 2 AA, 13; AG, 13; GG, 3	[96]
IVS1+C5143T	Morphine	Cancer pain relief	No (opioid switching)	CC, 100; CT, 55; TT, 1 <sup>†</sup>	[55]
IVS1-C17823T	Morphine	Cancer pain relief	No (opioid switching)	CC, 80; CT, 70; TT, 6 <sup>†</sup>	[55]
IVS2+G31A	Morphine	Cancer pain relief	No (morphine requirement)	GG, 83; GA, 16; AA, 0	[54]
	Morphine	Cancer pain relief	No (opioid switching)	GG, 129; GA, 27; AA, 0 <sup>†</sup>	[55]
	Morphine/M6G	Pupil constriction	No ( $EC_{50}$ of opioids)	GG, 26; GA, 5; AA, 0	[62]
IVS2+C691G	Morphine	Cancer pain relief	No (morphine requirement)	CC, 39; CG, 46; GG, 14	[54]
	Morphine	Cancer pain relief	No (opioid switching)	CC, 34; CG, 72; GG, 50 <sup>†</sup>	[55]
	Morphine/M6G	Pupil constriction	No ( $EC_{50}$ of opioids)	CC, 11; CG, 16; GG, 4	[62]
	Fentanyl	Preoperative analgesia	No (gastric response to fentanyl)	CC, 4; CG, 14; GG, 0	[71]

<sup>†</sup>The number of subjects combined the control and switcher groups.

ACTH: Adrenocorticotropic hormone;  $EC_{50}$ : 50% effective concentration; ESWL: Extracorporeal shock wave lithotripsy; HPA: Hypothalamic-pituitary-adrenal; M6G: Morphine-6-glucuronide; MAP: Mean arterial pressure;  $PaCO_2$ :  $CO_2$  arterial pressure; PONV: Postoperative nausea or vomiting; VAS: Visual analogue scale.



Table 2. Association studies of OPRM1 SNPs with the effects of opioid drugs (cont.).

Polymorphism	Opioid	Opioid effect	Result	Number of subjects	Ref.
IVS2+C691G (cont.)	Some opioids	Postoperative analgesia	No (analgesic requirement)	CC, 87; CG, 45; GG, 6	[80]
	Naloxone	HPA axis activation	G-allele carriers > CC subjects (plasma ACTH response, p = 0.04)	CC, 13; CG or GG, 16	[96]
IVS3+G5953A	Some opioids	Postoperative analgesia	No (analgesic requirement)	GG, 112; GA, 25; AA, 1	[80]
IVS3+A8449G	Fentanyl	Postoperative analgesia	G-allele carriers > AA subjects (fentanyl requirement, p = 0.01)	AA, 219; AG, 60; GG, 1	[40]
	Some opioids	Postoperative analgesia	No (analgesic requirement)	AA, 116; AG, 21; GG, 1	[80]
IVS3-A1188G	Naltrexone	Alcoholic treatment	No (rate and time to relapse)	AA, 152; AG or GG, 50	[83]
	Nalmefene	Alcoholic treatment	No (nalmefene effects of treatment)	AA, 169; AG, 95; GG, 8	[92]
TAA+T1371C	Morphine	Cancer pain relief	No (opioid switching)	TT, 91; TC, 55; CC, 10*	[55]
TAA+A2109G	Some opioids	Postoperative analgesia	No (analgesic requirement)	AA, 116; AG, 21; GG, 1	[80]

\*The number of subjects combined the control and switcher groups.

ACTH: Adrenocorticotropic hormone; EC<sub>50</sub>: 50% effective concentration; ESWL: Extracorporeal shock wave lithotripsy; HPA: Hypothalamic-pituitary-adrenal; M6G: Morphine-6-glucuronide; MAP: Mean arterial pressure; PaCO<sub>2</sub>: CO<sub>2</sub> arterial pressure; POMV: Postoperative nausea or vomiting; VAS: Visual analogue scale.

when they were conditioned for a long period of time (two sessions per day for 4–5 days) [103,104]. SNPs in the *OPRM1* gene might be expected to affect the susceptibility to substance dependence in humans. To date, numerous SNPs in the *OPRM1* gene have been analyzed for their involvement in the susceptibility to substance dependence (SUPPLEMENTARY TABLE 2) [26–31,34,110–150]. In studies of substance dependence or related traits, SNPs in exon 1 and intron 1 correlated with clinical traits with high frequency (number of analyses with positive correlation/total analyses: 0/7 [5' flanking region], 0/5 [5' UTR], 25/66 [exon 1], 26/47 [intron 1], 5/17 [intron 2], 0/1 [exon 3], 10/37 [intron 3], 3/11 [3'-UTR]). In the European and Japanese populations, a large LD block covers the region from exon 1 to intron 1, indicating that the LD block covering exon 1 and intron 1 in the *OPRM1* gene is critically involved in substance dependence and related traits.

Among the SNPs that have been analyzed with regard to substance dependence and related clinical traits, numerous studies showed that the A118G and IVS1+A21573G SNPs were associated with alcohol dependence or related traits. The G-allele frequency of the A118G SNP in alcohol dependence is higher or tends to be higher compared with nonalcoholic controls [111–113,121,124,125,130]. In contrast, some studies showed lower G-allele frequencies of the A118G SNP in alcohol dependence than non-alcoholic controls [119,120,128]. These controversial results in the A118G SNP for alcoholism might result from the various MAFs in different races/ethnicities, but this remains to be elucidated. The minor allele (G) frequency of the IVS+A21573G SNP in alcohol dependence was higher than in nonalcoholic controls [26].

In the case of opioid dependence, many studies have reported that the A118G and IVS1-T17286C SNPs were associated with opioid dependence. Similar to alcohol dependence, the G-allele frequency of the A118G SNP in opioid dependence was higher than in controls [114,133,137]. The minor allele (C) frequency of the IVS1-T17286C SNP in heroin dependence was higher than in controls [138].

The A118G and TAA+A5359G SNPs were also associated with tobacco dependence. In contrast to alcohol and opioid dependence, abstinence rates in G-allele smokers were higher than in AA smokers [139,141,142], and the number of cigarettes smoked in G-allele female smokers was smaller than in AA allele smokers [140], suggesting that the G-allele of the A118G SNP

is protective against smoking. In smokers, the minor allele (G) frequency of the TAA+A5359G SNP was smaller than in control subjects [27].

In these three types of substance dependence, previous studies have reported no significant association with the A118G SNP. A meta-analysis of 22 case-control studies failed to detect a significant association between A118G and substance dependence (odds ratio = 1.01, 95% CI: 0.86–1.19) [151]. The case-control studies examined by this meta-analysis examined dependence on several substances, including alcohol and opioids. Therefore, this meta-analysis did not strictly include specific substances. In another meta-analysis of case-control studies that examined the association between the A118G SNP and opioid dependence, no significant evidence was found for either dominant ( $p = 0.810$ ) or additive ( $p = 0.406$ ) effects of the A118G SNP on the risk for opioid dependence [152]. The pooled odds ratios and 95% CI derived from the eight European, six Asian, four African, two Hispanic, and one Native American samples were 1.20 (0.91–1.58), 0.93 (0.66–1.31), 0.99 (0.44–2.21), 2.60 (0.54–12.47) and 2.34 (0.68–8.03), respectively. The association with opioid dependence was not significant for any of these specific ancestral groups. However, the meta-analysis was designed to maintain statistical power greater than 97% for detecting additive effects and greater than 70% for detecting dominant or recessive effects with an odds ratio as small as 2.0. Therefore, if the odds ratio for the actual effect of the A118G SNP on the risk for opioid dependence was smaller than 2.0, then the meta-analysis would not have sufficient power for detecting the effects of the A118G SNP, indicating that further analyses are needed with specific ancestral samples.

### Association of SNPs in the *OPRM1* gene with other disorders

SNPs in the *OPRM1* gene have been investigated for their involvement in various other disorders (SUPPLEMENTARY TABLE 3) [33,153–170]. The A118G SNP is the only variation that has been associated with susceptibility to disorders and related traits in numerous studies. Patients with idiopathic absence epilepsy showed high G-allele frequencies of the A118G SNP compared to control subjects [154,157]. The G-allele frequency in patients with schizophrenia was also higher than in control subjects [160]. By contrast, G-allele carriers, including normal subjects, with glucose tolerance and patients with impaired fasting glucose or Type 2 diabetes mellitus exhibited

better glucose tolerance compared with AA-homozygotes [161]. Furthermore, G-allele carriers in patients with painless diabetic foot ulcer were higher than in patients with painful diabetic foot ulcer [162]. In addition, a positive association was found between BMI and copy number of G-allele of the A118G SNP, and the G-allele frequency in the obesity groups was lower than in control groups in the Uyghur population [33]. The obese controls showed a lower G-allele frequency of the A118G SNP than patients with binge eating disorder [167]. These results indicate that the G-allele of the A118G SNP is a risk allele for epilepsy and schizophrenia, but it is protective for diabetes and obesity.

### Effects of A118G SNP on MOP expression & function

Some *in vitro* and *in vivo* studies have reported the effects of the A118G SNP on opioid functions, including receptor binding and expression. One report found that the ligand-binding affinities of  $\beta$ -endorphin, morphine and naloxone for the MOP were not significantly different between wild-type and knockin mice (*Oprm1* A112G) [171]. Mice have four putative *N*-glycosylation sites in the MOP, and the number of these *N*-glycosylation sites is purportedly reduced to three in *Oprm1* A112G knockin mice. The human MOP has putatively five *N*-glycosylation sites, and the number of these *N*-glycosylation sites is reduced to four in 118G/G subjects. For this reason, the *Oprm1* A112G knockin mouse strain is not a suitable model for analyzing the effects of the A118G SNP in the human *OPRM1* gene. The effects of opioid antagonists have not been analyzed with regard to differences between G-allele and common allele homozygous carriers of the A118G SNP *in vitro*.

The binding affinity of  $\beta$ -endorphin, but not endomorphin-1, to the 118G variant of the MOP was higher than the common allelic form of the MOP in AV-12 cells [172]. No differences were observed, however, in morphine and [D-Ala(2),N-Me-Phe(4),Gly(5)-ol]-enkephalin (DAMGO) agonist binding between the 118G and common form of the MOP in COS cells [173]. Similarly, in HEK cells, no differences were observed in morphine, M6G, and  $\beta$ -endorphin agonist binding between the 118G and common form of the MOP [174]. A subsequent study, however, did not confirm these binding affinity results [175]. Krosiak *et al.* reported that the binding activity of morphine, DAMGO, and methadone but not  $\beta$ -endorphin were lower in

the 118G variant than in the common form of the MOP in both AV-12 and HEK cells. *In vivo*, in the somatosensory region of homo- and heterozygous carriers of the 118G variant, the efficacy of DAMGO was lower compared with homozygous carriers of the common allele, whereas the number of DAMGO binding sites was unaffected [176]. These discrepancies in the binding affinities of MOP agonists remain to be resolved. In heterozygous samples, the mRNA from the common allele was 1.5–2.5-fold more abundant than from the 118G variant allele [177]. A possible explanation for the reduced efficacy of opioid antagonists in 118G allele carriers may be the attenuation of MOP expression.

The expression of endogenous opioid peptides, including preproenkephalin and preprodynorphin, was reduced in numerous regions of heterozygous carriers of the 118G allele [178]. Alterations of endogenous opioid systems might underlie the enhanced susceptibility to alcohol and opioid dependence in 118G allele carriers.

### Conclusion & future perspective

We have reviewed many *OPRM1* gene variations that have been identified and analyzed for their associations with pain sensitivity, opioid sensitivity and susceptibility to substance dependence and other disorders. These studies revealed significant associations between

genetic variations, including the A118G SNP, with opioid sensitivity and susceptibility to substance dependence and other disorders (FIGURE 2). However, associations between variations in the *OPRM1* gene were not found in every analysis. Therefore, the pharmacogenetic significance of variations in the *OPRM1* gene is still being discussed. One explanation why statistical significance was not found in some analyses is that the MAFs of the variations are different among different races and ethnicities and lead to different effect sizes in the analyses. The MAFs of the A118G SNP vary among different races/ethnicities, which would be expected to affect the results of association studies. To further elucidate the genetic variability in the *OPRM1* gene that contributes to opioid efficacy and susceptibility to substance dependence, replication studies will be required in different races/ethnicities with sufficient samples for each effect size. In addition, although some functional analyses of the A118G SNP have been performed, the results of these studies are also controversial similarly to those of association studies. Molecular mechanisms underlying the relationships between genetic variations in the *OPRM1* gene and MOP expression and function should be elucidated for underlying and supporting the associations of these variations with clinical traits.

Human <i>OPRM1</i> gene polymorphisms	
<b>Pain</b> .....	A118G (G; risk or protective?)
<b>Opioid effects</b>	
– Analgesia .....	A118G (G; low)
– Side effect .....	A118G (G; low)
– Alcoholic treatment .....	A118G (G; high)
– HPA axis activation .....	A118G (G; high)
<b>Substance dependencies</b>	
– Alcohol .....	A118G (G; risk), IVS1+A21573G (G; risk)
– Opioid .....	A118G (G; risk), IVS1-T17286C (C; risk)
– Tobacco .....	A118G (G; protective), TAA+A5359G (G; protective)
<b>Susceptibility to disorders</b>	
– Epilepsy .....	A118G (G; risk)
– Schizophrenia .....	A118G (G; risk)
– Diabetes .....	A118G (G; protective)
– Obesity .....	A118G (G; protective)

**Figure 2. SNPs in the *OPRM1* gene associated with disorders and clinical conditions.**

Numerous SNPs in the human *OPRM1* gene have been reported to be associated or not associated with pain sensitivity, opioid effects, drug dependence and susceptibility to other disorders. Only the SNPs that have been reported to be associated with disorders and clinical conditions in numerous studies are listed for each disorder and clinical condition. HPA: Hypothalamic–pituitary–adrenal.

As written in this article, a great number of genetic variations in the *OPRM1* gene have been analyzed for the opioid sensitivity, susceptibility to substance dependences and other disorders. Technologies for genetic analyses are developing remarkably in recent years and therefore genetic studies will be carried out more generally and inexpensively in the future. The pharmacogenetic information of the *OPRM1* gene including the associations with individual opioid sensitivity and susceptibility to substance dependences will be accumulated (see PharmGKB [205]), and these data will be

absolutely essential for the establishment of personalized medicine for pain and drug abuse in the future.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Executive summary

#### SNPs in the *OPRM1* gene

- Over 700 polymorphisms have been identified from exon 1 to exon 4 of the *OPRM1* gene.
- Numerous studies have shown associations between these polymorphisms and opioid effects, substance dependence and susceptibility to other disorders, including epilepsy and schizophrenia.

#### Association of *OPRM1* SNPs with opioid sensitivity

- The analgesic and side effects of opioid agonists may be lower in G-allele carriers of the A118G polymorphism (rs1799971) compared with AA patients.
- The effects of opioid antagonists for alcoholic treatment may be higher in G-allele carriers than in AA patients.

#### Association of *OPRM1* SNPs with susceptibility to substance dependence & other disorders

- The G-allele of the A118G polymorphism may be a risk allele for alcoholism, opioid dependence, epilepsy and schizophrenia, but it may also be a protective allele for tobacco dependence, diabetes and obesity.
- The G-allele of the IVS1+A21573G polymorphism and C-allele of the IVS1-T17286C polymorphism may be risk alleles for alcohol and opioid dependence, respectively.
- By contrast, the G-allele of the TAA+A5359G polymorphism may be a protective allele for tobacco dependence.

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平成 23 年度 代表・分担研究者氏名一覧

「乱用薬物による薬物依存の発症メカニズム・予防・診断及び治療法に関する研究」

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The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that every entry, no matter how small, should be recorded to ensure the integrity of the financial statements. This includes not only sales and purchases but also expenses and income. The document also highlights the need for regular reconciliation of bank statements and the company's records to identify any discrepancies early on.

In addition, the document provides a detailed breakdown of the accounting cycle, from identifying the accounting entity to preparing financial statements. It explains how each step contributes to the overall accuracy and reliability of the financial data. The document also includes a section on the importance of internal controls, which are designed to prevent errors and fraud, and to ensure that the company's assets are protected.

The second part of the document focuses on the practical application of these principles. It provides a series of examples and exercises that illustrate how to record and classify transactions, and how to prepare a trial balance. The document also includes a section on the preparation of financial statements, including the income statement, balance sheet, and statement of cash flows. Each section is accompanied by a detailed explanation of the underlying accounting principles and the specific steps involved in the process.

Finally, the document concludes with a summary of the key points discussed throughout the document. It reiterates the importance of accuracy, regular reconciliation, and the use of internal controls to ensure the reliability of the financial statements. The document also includes a list of references and a glossary of key terms to help readers understand the terminology used throughout the document.