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PharmGKB summary: very important pharmacogene information for PTGS2

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Very important pharmacogene: *PTGS2*

This PharmGKB summary briefly discusses the *PTGS2* gene and current understanding of its function, structure, regulation, and pharmacogenomic relevance. We also present three variants with pharmacogenomic significance and highlight the gaps in our knowledge of *PTGS2*-drug interactions.

Overview

The *PTGS2* gene codes for prostaglandin G/H synthase-2, which catalyses the first two steps in the metabolism of arachadonic acid. Prostaglandin G/H synthase-2 has two active sites, a hydroperoxidase and a cyclooxygenase (COX) site, and is colloquially termed COX-2. The bifunctional enzyme performs the bis-dioxygenation and reduction of arachadonic acid to form prostaglandin (PG)₂ and H₂. PGH₂ is then converted to other PGs that modulate inflammation, including PGD₂, PGE₂, PGF_{2α}, PGI₂, and thromboxane A₂ (This pathway is shown in the Lipid maps database at

<http://www.lipidmaps.org/data/IntegratedPathways/Data/SetupIntegratedPathways.pl?imgsize=730&Mode=RAW2647&DataType=FAEicosanoidsMedia>). COX-2 is the target for nonsteroidal anti-inflammatory drugs (NSAIDs) including those that were purposefully designed (pd) to be selective for COX-2 (pdNSAIDs or coxibs). *PTGS2* is a paralog of *PTGS1*, which codes for the COX-1 enzyme. Although both proteins perform the same endogenous reactions, there are dramatic differences in the pattern, regulation, location, and timing of their expression that suggest crucial differences in the function. COX-1 seems to be predominantly responsible for homeostatic functions including the protection of the gastric mucosa. COX-2, in contrast, is responsible for pathogenic and inflammatory responses. These differences led to the development of selective COX-2 inhibitors to treat

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Additional information, including detailed mapping information for PTGS2 variants, samples genotyped for these variants and lists of linked drugs and diseases are presented at <http://www.pharmgkb.org/search/annotatedGene/ptgs2/index.jsp>.

pain in individuals at risk for stomach ulcers with traditional NSAIDs. However, this simple designation of roles does not adequately capture the intricate balance between these two enzymes [1]. The market withdrawal of rofecoxib and valdecoxib, and limited marketing of etoricoxib and lumiracoxib, driven by increased risk for cardiovascular and hepatotoxic events [2], highlights the limitations of knowledge about PTGS2 biology and NSAID pharmacology.

The *PTGS2* gene encompasses approximately 8.6 kb on chromosome 1 and codes for a 4-kb mRNA [3]. *PTGS2* is an immediate early response gene not expressed constitutively in most of the cells [4]. However, constitutive *PTGS2* expression does occur in brain, kidney, blood vessels, and the female reproductive tract [5]. *PTGS2* can be induced in inflammation and noninflammatory processes such as in renal cells in response to salt exposure, vascular endothelium in response to laminar flow, or in the gastric mucosa in healing ulcers [1]. Depending on the cell type and stimulus, different PGs are produced (see Fig. 2 from [1] for an overview of the different PGs from different cell types and their downstream actions). *PTGS2* has been shown to be overexpressed in several cancer cell lines, animal models, and human cancers [6].

PTGS2 gene regulation occurs at both the transcriptional and posttranscriptional levels [4]. *PTGS2* expression is induced by tumor promoters, growth factors, oncogenes, and cytokines [7]. There are multiple signaling pathways that can lead to the activation of the *PTGS2* gene promoter (see [7] for a review). The *PTGS2* promoter contains transcription factor binding sites for C/EBP, $\text{Nf-}\kappa\text{-B}$, AP-1, Sp1 and, a TATA box [7]. *PTGS2* has AU-rich elements (AREs) in the 3' UTR, which control the degradation of the mRNA and its translation [4]. The AREs promote the degradation of the mRNA, but ARE-binding proteins such as CUGBP2 and HuR (ELAV1) can stabilize the message [8]. (Others have shown CUGBP2 inhibits *PTGS2* translation [9]). Inhibition of MAPK p38 (MAPK14) by dexamethasone destabilizes *PTGS2* mRNA, but the specific ARE-binding proteins involved in this action remain unknown [10]. MicroRNAs can regulate the *PTGS2* expression in mouse uterus during embryo implantation [11].

Posttranslational control regulates COX-2 protein degradation by two pathways: the first involves N-glycosylation of the C-terminus of the protein, and the second involves substrate-dependent suicide activation [12]. COX-2 protein contains a 27-amino acid instability motif (not found in COX-1) that regulates posttranslational N-glycosylation of Asn-594 [12]. COX-2 protein is abundantly located in the endoplasmic reticulum. When the N-glycosyl group is processed, the protein is translocated to the cytoplasm in which it undergoes proteasomal degradation [12].

COX-2 is a homodimeric integral membrane protein found in the endoplasmic reticulum lumen [12]. There are several crystal structures available of the mouse COX-2 protein alone (5COX) and bound to substrates arachadonic acid (1CVU), diclofenac (1PXX), flurbiprofen (3PGH), and indomethacin (4COX; see the Research Collaboratory for Structural Bioinformatics protein data bank, [13]). The COX-1 and COX-2 enzymes are 60% identical at the sequence level but differ in their affinity for NSAIDs; both traditional NSAIDs and those purposefully designed against COX-2 (pdNSAIDs). At high concentrations, even the COX-2 selective agents can have effects on COX-1 [3,14]. An estimate of the selectivity spectrum for COX-2 suggests that lumiracoxib = etoricoxib (most selective for COX-2) > rofecoxib > valdecoxib > celecoxib ~ diclofenac ~ meloxicam ~ etodolac. Ibuprofen and naproxen are nonisoform selective NSAIDs [14]. Timing and dosage of the NSAID and enzyme selectivity can modulate the relative inhibition of the two isoforms (see [14] for a graphical representation of this three-dimensional relationship).

Extensive studies in mice using deletions of *PTGS2* in the whole animal and targeted to particular tissues have identified many of the different roles and products of the gene under different conditions (reviewed in [15,16]). The double knockout of both *PTGS1* and *PTGS2* results in mice that die on day 1 after birth because of failure of the ductus arteriosus to close [17]. Persistence of the ductus arteriosus is thought to be COX-2 dependent as mice with deleted *PTGS2* but functional *PTGS1* still have high mortality because of this defect [17]. Deletion or inhibition of *PTGS2* results in severe kidney malformations [15], increases the vasoconstrictive response to angiotensin II [18], and elevates basal blood pressure in some mouse strains [19,20]. Deletion of *PTGS2* can also result in cardiomyopathy [21,22]. Although *PTGS2* knockout male mice are normal with respect to reproduction, *PTGS2* knockout female mice have reproductive defects [23]. The study of *PTGS2*-manipulated animal models has provided good supporting evidence to underpin the observations of NSAID action in humans.

There are over 100 putative variants reported for *PTGS2*, although to date there are no nonsynonymous amino acid substitutions with minor allele frequencies that would be considered common enough to be polymorphisms (dbSNP and Alfred accessed April/2010). There are some noncoding and synonymous variants that have been studied in several contexts, the most well studied is *PTGS2*: (-765)G > C (rs20417) [24] (see below).

The majority of studies of *PTGS2* variants have looked at epidemiological risk for cancer [25–27] or cardiovascular diseases [28–33] also with a few examining risk for Alzheimer's disease [34–36], asthma [37–40], lupus [41], rheumatoid arthritis [42,43], osteoarthritis [44], diabetes [45], and periodontitis [46,47]. A smaller number of studies have looked at *PTGS2* variation and drug [29,30,48–50] (summarized in Table 1) or diet interaction [51–55]. Variants in *PTGS2* have been shown to influence rofecoxib responses to pain after surgery [48]. Variants in *PTGS2* were shown to effect cardiovascular disease in aspirin users in the Atherosclerosis Risk in Communities study [30]. In a small study of variants impacting rofecoxib and celecoxib response in healthy volunteers, only one variant in *PTGS2* was polymorphic in the group studied (rs5273) and this was not associated with any phenotype [49]. A variant of *PTGS2* was shown not to modulate celecoxib effects on PG production [50]. These studies are discussed further with respect to the variants tested (see below).

The haplotype structure of *PTGS2* differs between populations. Studies of the promoter region observed only two haplotypes in European Americans ($n=184$) but there were six haplotypes present in African American ($n=288$) and Bini Nigerian ($n=264$) populations [56]. A depiction of the haplotype structure across the full *PTGS2* gene was reported in German Caucasians ($n=350$) [24]. This diversity of haplotypes may explain some of the contradictory results seen so far with single variant association studies.

Important variants

***PTGS2*: (-765)G > C (rs20417)**—The -765G > C promoter SNP (rs20417) is the best-studied variant in *PTGS2*. It modulates the acute phase inflammatory response [57]. The C variant is associated with lower promoter activity compared with the G variant [57]. The SNP seems to affect transcription factor binding to the promoter with the G > C transition eliminating an Sp1 site and creating an E2F site [40,58,59]. This variant has also been referred to as -899G > C and ss5112606 in the literature [24,56].

The C variant occurs at a frequency of 0.145 in Caucasians, 0.219 in Native American/Hispanic and 0.364 in African/African American sample sets from the CEPH Human Diversity Panel and was not significantly different in the SNP500 cancer control sample set from the Coriell collection [60] (see Table 2). The -765G > C variant is found in a haplotype with -1195G > A (rs689466) in Pima Indians [45], Chinese Asians [58] and Australian

Caucasians [37] (see below for more on this variant) and with -1290A > G (rs689465) in a Caucasian Australian population [37].

The epidemiological relevance of rs20417 is unclear despite several studies (see Table 1 of [24] for summary up to 2007). The C variant was initially found to be protective against myocardial infarction and stroke in a European Caucasian population [61], but this was not replicated [62]. Other studies have found that the C variant is associated with increased risk of stroke in African Americans but not White individuals [30,31]. Diabetics homozygous for the C allele of rs20417 had increased carotid-calcified plaque [63]. Other studies have shown no impact on secondary cardiovascular events [62] and aortic aneurysm [64]. The CC genotype was associated with asthma in Polish women [40]. In Australian Caucasians the rs20417 polymorphism was not associated with asthma alone [39], but the G variant was associated with a reduced incidence of asthma as part of a haplotype (-1290A/-1195G/-765G) [37].

There are also conflicting results of cancer: metaanalyses showed no effect on prostate cancer [26], or for breast cancer [65], no effect on colorectal cancer [66] but the C variant has been associated with oral premalignant lesions (as part of a haplotype) [67], risk for gastric cancer [68], and was protective for skin cancer [69]. To try and further clarify the role of rs20417 in disease etiology some studies have looked at dietary interaction [51,55]. In individuals consuming higher than average n-6 polyunsaturated fatty acids, the C allele was associated with risk for colon cancer [51]. In a study of Mediterranean-style dietary intervention for reduction of inflammation, *PTGS2*-765G > C was associated with inflammatory markers but all genotypes responded favorably to diet [55].

A small number of studies have looked at drug interaction with rs20417. In the Atherosclerosis Risk in Communities Study, -765C showed a small nonsignificant association with higher risk of coronary heart disease in aspirin nonusers and lower risk of coronary heart disease in those reporting aspirin use [30]. Lemaitre *et al.* [29] replicated this observation of the interaction of rs20417 with aspirin use on myocardial infarction risk. The -765C variant was associated with a higher reduction of 11 dehydrothromboxane B2 (11dTxB2) after aspirin treatment [70]. However, Takahashi *et al.* [71] suggest that individual differences in platelet thromboxane production and aspirin resistance cannot be explained by COX protein levels or variants although they did not test -765G > C in their study. In a study of rofecoxib versus ibuprofen for pain relief after dental surgery, individuals with GG genotype were more likely to report lower pain intensity with rofecoxib whereas CC individuals were more likely to report lower pain intensity with ibuprofen [48]. This variant was also examined in a study of rofecoxib and celecoxib in healthy individuals; however, all patients in the study were GG homozygotes [49]. In an ex-vivo study of celecoxib on monocyte PGE₂ production, no effect was attributable to rs20417 [50]. It is interesting to note that the studies in which an interaction of rs20417 was observed with drugs [29,30,48], the drugs were often more nonisoform selective (aspirin, ibuprofen). Thus variant *PTGS2* may be more relevant when COX-1 function is disrupted, at least under some circumstances.

PTGS2: 8473T > C (rs5275)—The 8473T > C variant is located in the 3'UTR in which it may stabilize the mRNA [52]. CC individuals were shown to have lower *PTGS2* expression than TT individuals, with CT individuals having intermediate expression [48]. It has also been discussed in the literature as '6498T > C' [48].

The C variant occurs at a frequency of 0.355 in Caucasians, 0.435 in Native American/Hispanic and 0.667 in African/African American sample sets in the SNP500 cancer control

sample set from the coriell collection [60]. The C variant was also observed at a frequency of 0.291 in German Caucasians [24] (see Table 2).

Several studies have associated this variant with risk for cancer (see Table 2 in Skarke *et al.* [24]) including basal cell carcinoma, breast cancer, lung cancer, bile duct cancer, and colorectal cancer although there are contradictory reports for lung cancer and breast cancer and no association was reported for cervical cancer. One study has reported an association between diet and this variant and disease risk. High salmon-type fish consumers with the C-allele had a 72% lower risk of prostate cancer compared with those eating low or no fish [54]. In a study of Chinese children, carriers of the C allele had a higher risk of developing asthma than those homozygous for the T allele [38]. There are conflicting reports concerning the impact of this variant for cardiovascular disease. The 8743T allele was associated with decreased risk ratio of acute coronary syndrome in Polish coronary artery disease patients (in combination with rs708494 in *PTGER2*) [72]. Danish male C variant carriers of 8473T > C were at lower risk of acute coronary syndrome than TT homo-zygotes, and this was independent of NSAID use [28].

Homozygous TT genotype was associated with better progression-free survival and overall survival in patients with advanced colorectal cancer treated with XELOX (capecitabine and oxaliplatin) chemotherapy [73]. In addition, the TT genotype was associated with lower risk for severe pain in lung cancer patients [74]. This may have relevance for pain response to NSAIDs although literature searches did not find data to support this. Lee *et al.* [48] measured this SNP in a study of rofecoxib versus ibuprofen pain relief. However, no interaction was discussed for this particular variant.

PTGS2: (-1195)G > A (rs689466)—The rs689466 variant is found in the promoter of *PTGS2*. The A variant creates a myb-binding site in the promoter that increases transcription [58]. This variant has also been described as ‘-1329A > G’ in the literature [24].

The A variant had a frequency of 0.65 in Pima Indians [45], 0.51 in Chinese Asians [58], 0.84 in German Caucasians [24], and 0.79 in Australian Caucasians [37] (see Table 2). This variant has been shown to be part of a haplotype with rs20417 in Pima Indians [45], Chinese Asians [58] and, Australian Caucasians [37].

The A variant was associated with asthma in Australian Caucasians [37], (note: the abstract of [37] has a typographical error in which the rs for -1195G > A and -1290A > G are switched). The A variant has been associated with esophageal cancer [58] and pancreatic cancer [75].

The minor allele (likely G but not described) was associated with risk for hypertension in Japanese Asian men [76]. Given the side effects of some NSAIDs include elevation of blood pressure, this could be an interesting variant to study in that context. No report of such a study was found to date.

Conclusion

PTGS2 is a well-characterized gene and drug target with a critical role in multiple important biological pathways including NSAID response. Although many variants of *PTGS2* have been reported and several have been studied for disease risk, only a handful have been examined in PGx studies (see Table 1). These studies so far have totaled only a few hundred patients and not all of the potentially relevant variants were examined in most studies or the variants were at too low frequencies to be observed in the populations studied. With recent advances in technologies for measuring genetic variations, new studies will be able to

examine all of the relevant variants and haplotypes in *PTGS2* and the other genes in the NSAID response.

Studies of *PTGS2* variants and their modulation of risk for cancer, asthma, and cardiovascular diseases may hint at how these variants may influence NSAID pharmacodynamics. Variants that are associated with increased COX-2 expression or activity, increased risk for cancer or other inflammatory diseases (such as asthma or cardiovascular disease), may alter responses to pNSAIDs rather than NSAIDs that preferentially inhibit COX-1. This is supported by the study by Lee *et al.* [48] in the context pain relief and may explain the mixed results in the use of coxibs in cancer prevention [77,78]. The effect of preexisting disease is postulated to play an important role in the development of cardiovascular side effects of NSAIDs [1,79], thus knowledge of the interplay of variants, drugs and disease may also be used to prevent adverse drug reactions.

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Table 1

Summary of PGx studies examining *PTGS2*

Reference (PMID)	<i>PTGS2</i> rs# tested	Other genes studied	Population	Drugs studied	Phenotypes
Fries <i>et al.</i> [49] (16401468)	rs20417, rs20426, rs4987011, rs3218622, rs4648279, rs5272, rs5273, rs3218625	<i>PTGS1</i>	Healthy volunteers, American (58% Caucasian, 24% Black, 18% Asian; <i>n</i> = 50)	Celecoxib, rofecoxib	No effects of <i>PTGS2</i> variants
Lee <i>et al.</i> [48] (16678543)	rs689465, rs20417, rs2745557, rs2066826, rs4648276, rs5275, rs689470	<i>PTGS1</i>	Volunteers for elective surgery for third molar extraction, American (95.3% European American, 2.1% African American, 1.2% Asian American, 1.2% Hispanic, and 0.2% mixed race; <i>n</i> = 135)	Ibuprofen, rofecoxib	rs20417 GG genotype associated with significantly decreased pain intensity after surgery and rofecoxib administration but not ibuprofen administration rs20417 C allele associated with significantly decreased pain intensity after surgery and ibuprofen administration but not rofecoxib administration rs20417 was associated with <i>PTGS2</i> expression levels (CC genotype lowest, CG intermediate, GG genotype highest expression) rs5275 was associated with <i>PTGS2</i> expression levels (CC genotype lowest, CT intermediate, TT genotype highest expression)
Skarke <i>et al.</i> [50] (17178263)	rs20417	<i>CYP2C9</i>	Healthy volunteers, German (<i>n</i> =20)	Celecoxib	No effects of <i>PTGS2</i> variants
Lee <i>et al.</i> [30] (17495879)	rs20417, rs5273	<i>PTGS1</i>	Case-control cohort study, ARIC (1023 CHD cases, 270 stroke cases, 919 controls), Americans (Caucasians: 56% of stroke cases, 77% CHD cases, African American 44% of stroke cases, 23% CHD cases), approximately 25% aspirin users (<i>n</i> = 2212)	Aspirin	rs20417 C allele associated with lower risk of CHD in aspirin users
Lemaitre <i>et al.</i> [29] (19046748)	rs689466, rs20417, rs2745557, rs5277, rs5275, rs2206593, rs4648310	<i>PTGS1</i> , <i>TBXAS1</i> , <i>PTGS1</i> , <i>PTGES</i> , <i>ALOX5AP</i> , <i>ALOX12</i> , <i>ALOX15</i>	Case-control cohort study, Group Health HMO, (1063 CHD cases, 469 stroke cases, 3462 controls), American (91% White) approximately 50% aspirin users (<i>n</i> =)	Aspirin	rs20417 C allele associated with lower risk of CHD in aspirin users

ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; HMO, Health Management Organisation; PGx, Pharmacogenomics; PMID, PubMed Identifiers.

Table 2

Summary of reported frequencies of PTGS2 variants in different ethnic groups

rs#	Common names	Variant	Frequency and ethnicity
rs689466	-1195G>A (-1329A>G)	G	16.6% in German Caucasians (<i>n</i> = 328) [24], 21% in Australian Caucasians [37], 35% in Pima Indians (<i>n</i> = 1000) [45], 49% in Chinese Asians [58]
rs20417	-765G>C	C	0% in European Americans (<i>n</i> =92) [56], 0% in Americans (<i>n</i> =50) [49], 14.5% in Caucasians (<i>n</i> =62) [60] 16.8% in German Caucasians (<i>n</i> = 348) [24], 17% in European Americans (<i>n</i> =295) [48], 3% in African Americans (<i>n</i> =147) [56], 14% in Bini Nigerians (<i>n</i> = 110) [56], 12% in Pima Indians (<i>n</i> = 1000) [45], 21.9% in Native American/Hispanic (<i>n</i> =48) [60] 36.4% in African/African American (<i>n</i> =70) [60]
rs5275	8473T>C	C	29.1% in German Caucasians (<i>n</i> =342) [24], 33% in European Americans (<i>n</i> =295) [48], 35.5% in Caucasians (<i>n</i> = 31) [60], 23% in Pima Indians (<i>n</i> = 1000) [45], 43.5% in Hispanic (<i>n</i> =23) [60], 66.7% in African/African American (<i>n</i> =24) [60]