SYSTEMATIC REVIEW

Narrative Review and Identification of Pharmacogenes Relevant to Adverse Drug Reaction of Aspirin Therapy Among East Asian Populations

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ABSTRACT

Introduction: Aspirin is drug that is widely used, but may cause adverse drug reactions (ADRs) in East Asian populations. ADRs are noxious and inadvertent reactions to drugs, occurring at doses usually utilised for therapy. Genetic polymorphism that causes variability in drug response may play a significant role in the development of ADRs. This study aims to identify and describe pharmacogenes that contribute to ADR of aspirin in Asian populations and determine its prevalence. **Methods:** The pharmacogenes implicated in ADR of aspirin were first identified using PharmGKB. Then, bioinformatics databases such as OMIM, dbSNP, ScienceDirect, EBSCO and PubMed were searched to investigate the pharmacogenes and determine their prevalence. Keyword-based search was conducted to obtain relevant literature. A narrative review of all extracted articles was executed by either summarizing or tabulating the reported data. The limitations for each study were considered and documented accordingly. **Results:** Thirty-six pharmacogenes were identified to be associated with aspirin toxicity and twenty-six genes were found to be important in the development of aspirin ADR such as bleeding, asthma, respiratory diseases and urticaria in East Asian populations. The evidence found was focused on East Asian populations, including Koreans, Japanese and Chinese. **Conclusion:** Gene polymorphisms are significantly associated with ADR occurrence alongside aspirin therapy among Asians. These genes provide a starting point to focus pharmacogenomics studies in Asian populations. However, more studies would need to be conducted to be more inclusive of all ethnics, and to further solidify the relevancy of pharmacogenes with the development of ADRs.

Keywords: Pharmacogenes, Aspirin, Adverse drug reaction, Asia, Database

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INTRODUCTION

Aspirin, a non-opioid and non-steroidal anti-inflammatory drug (NSAID) listed in the WHO Model List of Essential Medicines since 1977, was first indicated as an analgesic [1]. However, aspirin is currently and rampantly used as secondary prevention of cardiovascular events and also for cancer prevention [2]. Aspirin is generally considered as a well-tolerated drug when used short term, but it presents risks of adverse drug reactions (ADRs) when it is used chronically [2].

Side effects of aspirin include gastrointestinal maladies that include gastritis and bleeding, hypersensitivity reactions that range from rash to anaphylaxis, Reye syndrome and intracerebral haemorrhage [3]. Its use in primary prevention of cardiovascular disease (CVD) is debated because the increased risk of bleeding outweighs the benefit of protection against CVD, and this is evidenced in a study which revealed a higher risk of intracranial haemorrhage in patients of Asian descent [4].

ADRs are unintended responses to a drug, manifesting at standard doses and affecting up to 20% of inpatients and 25% of outpatients [5]. ADRs are categorized into type A and type B. Type A is considered as on-target reactions that occur in >1% of patients with effects that are usually dose dependent [5]. Type B reactions are unpredictable, off-target reactions that occur in <1% of patients [5]. Type A reactions are predictable, occurring in 80% of cases whereas type B reactions make up the rest, necessitating the need for more advanced

diagnostics [6]. ADRs occur among 1.6% of NSAID users, and it is a particular concern because most NSAIDs do not require medical prescription and thus, increase the risk of overuse [6]. The mechanisms on how ADRs manifest are largely unknown. However, there are several risk factors that may predispose individuals to ADR, such as age, liver, kidney functions and also genetics [7].

Patients with genetic polymorphisms may experience variable responses to aspirin, ranging from subtherapeutic response to hypersensitivity. Subtherapeutic response is termed as aspirin resistance (AR), and it may cause patients to take high drug doses that increase the risk of ADR. Laboratory AR was estimated to range from 5% to 65% of patients [8]. Patients who have laboratory AR are found to be more at risk of cardiovascular morbidity, such as death and acute coronary syndrome, and they do not respond to other antiplatelet therapies [9]. AR is associated with the genetic polymorphisms on COX-1, COX-2 and platelet glycoprotein receptors [8].

Patients may also experience aspirin hypersensitivity, which is the occurrence of side effects that include respiratory problems, urticaria/angioedema or anaphylaxis, thus necessitating the discontinuation of therapy [10]. Aspirin hypersensitivity has been reported in 1.5-2.6% of CVD patients taking aspirin. This is associated with COX-1 inhibition activity of aspirin, leading to increased release of histamine from mast cells and causing pruritus, urticaria, angioedema and hypotension in severe cases [11].

Identification of the genes that play a vital role in producing adverse reactions is crucial to avoid or reduce the occurrence of adverse drug reactions. This study will provide information on whether the usage of aspirin is related to genetic factors in causing adverse drug reaction amongst Asian populations. From the extracted information, patient's response towards aspirin would be able to be distinguished and genetic-guided drug therapeutic plans can be developed to prevent adverse drug reactions from developing in patients. This information plays a pivotal role, especially in reducing cost, enhancing patient's adherence to medication, promoting efficacy and improving patient's quality of life.

MATERIALS AND METHODS

Procedure used in this study is summarized in Figure 1. Multiple databases were used in this study, including Pharmacogenomic Knowledge Database (PharmGKB), Online Mendelian Inheritance in Man (OMIM), Ensembl Genebank and Single Nucleotide Polymorphism Database (dbSNP) for identification of genes; and Science Direct, EBSCO, and PubMed for literature search. The article search was focused on publications from year 2000 to 2021.

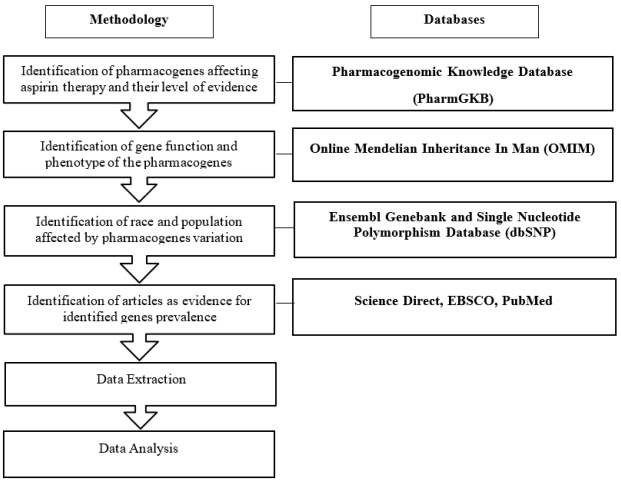

Figure 1 : Research procedure and the database used for study.

Identification of Pharmacogenes Related to Aspirin

PharmGKB was utilised to identify the pharmacogenes affecting aspirin therapy and their level of evidence (Table I). The keyword "Aspirin" was used as a search term. The information extracted was subsequently placed into spreadsheets.

Pharmacogene Function and Phenotype

OMIM was used to identify gene function and phenotype of the pharmacogenes after they were identified from PharmGKB.

Pharmacogenes Prevalence

Ensembl was used to identify the race and population affected by the pharmacogenes using the reference cluster ID of the genes or the name of the genes.

Collection and Screening of Journal Articles

Science Direct, EBSCO and PubMed were used to identify journals from year 2000 to 2021. Specific keywords in the English language were used to search the available articles in combination of the gene name in the format of "GENE + Southeast Asia", "GENE + Aspirin" and "GENE + Adverse Drug Reaction". The amount of hits for each keyword and number of journals that were able to be retrieved were then documented and screened for eligibility. Articles that were duplicates were excluded. Then, the articles were screened by their title, abstract and full text to ensure that they were a human-based primary study, were written in the English language, were not a conference abstract, had full text, and complied with the study's objectives.

Table I : PharmGKB Level of Evidence

Evidence level		Annotation
Variant Annotation		Reports the association between a variant for example, SNP, indel, repeat, haplotype and a drug phenotype from a single publication.
Clinical Annotation		Provides clinical relevance summary for each of the individual genotypes that may be distinguished for a certain gene variant and drug combination.
	1A	A variant-drug combination in a Clinical Pharmacogenetics Implementation Consortium (CPIC) or pharmacogenomics guideline endorsed by a medical society or performed at a PGRN site or in other vital health system.
	1B	A variant-drug combination in which the prevalence of evidence shows an association in more than one cohort with notable p-values and possibly strong effect size.
	2A	A variant-drug combination in which the variant is within a VIP that is eligible for level 2B.
	2B	A variant-drug combination with average evidence of an association that may not report statistical importance and/or the effect size may be small.
	3	A variant-drug combination investigated based on a single significant study or in multiple studies but lack substantial evidence of an association.
	4	It is derived from a case report, non-significant study or in vitro, molecular, or functional assay evidence only.

Data Extraction

The articles were evaluated upon retrieval from Science Direct, EBSCO and PubMed databases. The information obtained from the articles was then documented into spreadsheets as follows:

1. Title of the Article
2. Name of the Author(s)
3. Year of Publication
4. Source of Article
5. Number of subjects in the study, allele, and genotype frequencies

Data Analysis

Data analyses were conducted based on the retrieved data that were documented into the spreadsheet. The interaction of the genes with aspirin, and the effects of their genetic variations were further investigated. Information of the alleles and phenotype frequencies was used to analyse the prevalence of each gene population and summarised accordingly.

RESULTS

PharmGKB was used to identify and select the pharmacogenes relevant in aspirin toxicity, the variant, and the level of evidence for this study. From PharmGKB, 73 pharmacogenes were discovered predominantly related to aspirin therapy. A total of 36 genes were found to be associated with aspirin toxicity and with clinical level of evidence (Level 3 and above) (Table II). Literature search using this 36-gene list is summarized in Table III. Initial search used keyword "Southeast Asian" but the results only showed East Asian populations, such as Korean, Japanese and Chinese population.

Reasons for excluding some studies included that the studies did not comply with this study's objectives, were not a primary human study, were not written in English and did not have full-text journal articles.

After searching for keywords on Science Direct, EBSCO and PubMed to look up journals from 2000-2021, only 26 gene variants were identified to have accessible journal articles related to ADR of aspirin therapy related to the population of interest.

DISCUSSION

Type A ADR for aspirin includes gastrointestinal bleedings and type B aspirin ADR includes aspirin-exacerbated respiratory disease, urticaria and/or angioedema [6].

Peptic ulcer

Angiotensinogen, AGT, is an a2-globulin that functions as a precursor molecule for angiotensin II and renin substrate. It is located in various tissues that express local renin-angiotensin-aldosterone system (RAAS) [12]. Studies have observed that the AGT -20C allele acts as the high-producer allele of AGT, and the plasma concentration of AGT increases linearly according to the genotype: CC > AC > AA [13]. AGT was significantly associated with peptic ulcer bleeding among the Japanese population with

Table II : Genes relevant in Aspirin toxicity based on PharmGKB

Symbol	Gene Name	Variant	Level of Evidence	Publication related to Asian
ACE	Angiotensin Converting Enzyme	rs4291	Level 3	YES
		rs4292	Level 3	YES
ADORA 1	Adenosine A1 receptor	rs16851030	Level 3	YES
		rs2228079	Level 3	
AGT	Angiotensinogen	rs5050	Level 3	YES
CEP68	Centrosomal protein 68	rs7572857	Level 3	YES
CHIA	Chitinase acidic	rs3818822	Level 3	YES
COL26A1	Collagen type XXVI alpha 1 chain	rs10279545	Level 3	
CYP2D6	Cytochrome P450 family 2 subfamily D member 6	rs28360521	Level 3	YES
FCER1G	Fc fragment of IgE receptor Ig	rs11587213	Level 3	YES
FSIP1	Fibrous sheath interacting protein 1	rs7179742	Level 3	YES
HLA-DPB1	Major histocompatibility complex, class II, DP beta 1	rs1042151	Level 3	YES
		rs1042136	Level 3	
		HLA-DPB1*04:01:01:01	Level 3	
		rs3097671	Level 3	YES
		HLA-DPB1*0301:01	Level 2B	YES
HLA-DPB2	Major histocompatibility complex, class II, DP beta 2 (pseudo gene)	rs3129294	Level 3	
HNMT	Histamine N-methyltransferase	rs1050891	Level 3	
IL4	Interleukin 4	rs2243250	Level 3	
IL1B	Interleukin 1 beta	rs1143627	Level 3	YES
LTC4S	Leukotriene C4 synthase	rs730012	Level 3	YES
NAT2	N-acetyltransferase 2	rs4271002	Level 3	YES
NOS3	Nitric oxide synthase 3	rs1799983	Level 3	
PEAR1	Platelet endothelial aggregation receptor 1	rs12041331	Level 3	
PLA2G4A	Phospholipase A2 group IVA	rs12746200	Level 3	
PLCG1	Phospholipase C gamma 1	rs2228246	Level 3	
PPARG	Peroxisome proliferator activated receptor gamma	rs3856806	Level 3	YES
PTGER2	Prostaglandin E receptor 2	rs1353411	Level 3	YES
		rs2075797	Level 3	YES
PTGER3	Prostaglandin E receptor 3	rs7551789	Level 3	YES
PTGIR	Prostaglandin I2 receptor	rs1126510	Level 3	YES
SLC30A9	Solute carrier family 30-member 9	rs1047626	Level 3	
SLC6A12	Solute carrier family 6-member 12	rs557881	Level 3	YES
TAPBP	Tab binding protein	rs1059288	Level 3	
		rs2071888	Level 3	YES
TBXA2R	Thromboxane A2 receptor	rs1131882	Level 3	YES
TBXAS1	Thromboxane A synthase 1	rs6962291	Level 3	YES
TGFB1	Transforming growth factor beta 1	rs1800469	Level 3	YES
THRA	Thyroid hormone receptor alpha	rs11819745	Level 3	
TLR3	Toll like receptor 3	rs3775291	Level 3	YES
TNFRSF11A	TNF receptor superfamily member 11a	rs1805034	Level 3	
TSC1	TSC complex subunit 1	rs7862221	Level 3	
ZBTB22	Zinc finger and BTB domain containing 22	rs3130100	Level 3	

Table III : Results of literature search and screening

Gene	Total hits from databases	Titles screened after duplicates removed	Abstract screened	Full text screened	Number of accepted and reviewed studies
ACE	31098	25922	12222	12	2
ADORA 1	105	92	68	3	1
AGT	2926	2248	1718	5	1
CEP68	70	22	6	3	1
CHIA	4845	3630	2420	5	1
CYP2D6	7321	5161	1603	7	1
FCER1G	43	35	21	1	1
FSIP1	20	7	4	2	1
HLA-DPB1	431	347	118	12	4
HNMT	129	88	31	6	1
IL1B	985	944	571	3	1
LTC4S	492	304	191	6	4
NAT2	1314	1080	518	7	1
PPARG	754	730	332	2	1
PTGER2	107	91	55	5	1
PTGER3	117	89	52	3	1
PTG1R	51	43	26	2	1
SLC6A12	44	38	14	1	1
TAPBP	25	22	13	1	1
TBXA2R	229	155	91	13	4
TBXAS1	91	83	40	4	1
TGFB1	920	892	615	5	2
TLR3	1480	1404	466	2	1

$p < 0.05$, with the frequency of AGT -20CC genotype in the bleeding group being significantly higher compared to the AGT -20AA and -20AC genotype group [14].

CYP2D6 is a primary gene member of CYP450 superfamily. It partakes in about 25% of the presently available drugs' metabolism. The CYP2D6 gene belongs to chromosome 22q13.1 and consists of 12 exons. It is found to be highly polymorphic with more than 100 allele variants and various sub-variants of the CYP2D6 gene having been identified to date [15]. CYP2D6 was found to be associated with an increased risk for aspirin-induced small bowel bleeding among the Japanese population. CYP2D6 -2178GG polymorphism was significantly higher with a p-value of 0.02. This indicated that patients carrying the CYP2D6 -2178GG genotypes experienced small bowel bleeding more often when they were on aspirin therapy [16].

IL-1 family members influence all cells of the innate immune system, and play a vital role in the differentiation and function of polarised innate and adaptive cells. IL1B among the other seven molecules that possess agonist family belongs to the IL-1 family [17]. IL1B is also a cytokine that acts as a modulator in the inflammatory response in the gastrointestinal mucosa through the inhibition of gastric acid and pepsinogen secretion [18]. IL1B -581C >T was found to be significantly associated with aspirin-induced peptic ulcer disease in Korean patients. Patients who had IL1B -581C were notably more often associated with peptic ulcer, and the TT genotype was found to be less frequent among the peptic ulcer patients [19].

Aspirin-exacerbated Respiratory Disease (AERD)

AERD is also known as NSAID-exacerbated respiratory disease, and it has been referred to as aspirin-induced asthma, aspirin-intolerant asthma and aspirin-sensitive asthma with prevalence in the general population, ranging from 5.5% to 12.4% [20].

The MHC class I expression on the surface of cells is vital for the cytotoxic T lymphocytes recognition [21]. Multiple proteins aid in the assembly and

folding of MHC class I molecules that include antigen processing, TAP1 and TAP2, and TAP-binding protein binding or tapasin (TAPBP); and they are associated with the heterodimeric transporters [22]. Decreased expression of TAPBP gene decreases CD8 + T-cell responses against viral infections and other bodily processes that rely on the MHC class I molecules expression [23]. The presence of SNPs due to mutations on TAPBP gene could potentially increase the tendency of immune disorders to occur [24]. The rs 2071888 variant of TAPBP gene was significantly associated with AERD with p = 0.009. Patients who carried the rare allele rs 2071888 exhibited a notable decline in forced expiratory volume (FEV) provoked by aspirin exposure. Korean patients, who had aspirin-intolerant asthma (AIA) and were C allele carriers, were remarkably associated with AERD when compared with homozygous genotype GG carriers [25].

The variant TBXA2R +795T>C was implicated in the development of AERD among Japanese females with p = 0.025. C allele carriers were found to be linked with increased tendency of AERD development [26]. The rs1131882 CC genotype was associated with increased platelet aggregation and subsequently, elevated level of platelet TXB2 synthesis which were risk factors for aspirin resistance in Chinese ischemic stroke patients [27].

CHIA gene secretes protein that degrades chitin, a glycopolymer found as a structural component in most fungi cell wall, arthropods' exoskeleton and parasitic nematodes microfilarial sheath [28]. CHIA protects the airway endothelial cells from apoptosis, and thus plays a role in susceptibility to asthma and other respiratory diseases [29]. The rs3818822 variant of the CHIA gene was implicated notably with the increased risk of aspirin-exacerbated respiratory disease (AERD) with a p value of <0.01. Upon exposure to aspirin, it was shown that A allele contributed significantly to the development of AIA compared to G allele [30].

HLA-DPBI gene belongs to the family of genes called the human leukocyte antigen (HLA) complex. The gene produces instructions on the production of protein that plays a pivotal role in the immune system. It helps the immune system to differ between the body's own proteins from proteins produced by foreign materials, such as those of bacteria and viruses [31]. Genome-wide association study in Koreans revealed that HLA-DPB1 gene polymorphisms were mostly significantly with risk of AERD [32]. The rs1042151 gene polymorphism of HLA-DPB1 exhibited the highest tendency to AERD development (mean decline of 6.8% of FEV after aspirin exposure) with a p-value of less than 0.00001 in a gene-dose dependent relationship [32].

Toll-like receptors (TLRs) are a family of type I transmembrane receptors. This family could recognise various conserved pathogen-associated molecular patterns commonly found in microbes like viruses, fungi, and parasites. This recognition will subsequently lead to the initiation of intracellular signalling pathways that trigger the expression of inflammatory genes such as cytokines [33]. TLR3 is a member of the TLRs family and when TLR3 is activated, there will be an expression of multiple kinds of cytokines and type 1 interferon (IFN), leading to the development of asthma and allergy [34]. Genetic polymorphism of TLR3 293391G>A was associated with the development of AERD (p = 0.025 in co-dominant model, and p = 0.036 in dominant model). The A allele carriers were more susceptible to AERD compared to G allele carriers [35]. Angiotensin-converting enzyme (ACE) is found at elevated levels in the lungs, and it demonstrates an anti-inflammatory effect that induces smooth muscle airway constriction, bronchial oedema, mucus hyper-secretion and neurogenic inflammation [36]. However, the ACE conversion of angiotensin I into angiotensin II contributes to the proliferation and contractility of smooth muscle airway which ultimately causes excessive airway obstruction [36]. ACE insertion/deletion of intron 16 was shown to not be significantly associated with peptic ulcer and ulcer bleeding [14]. However, the polymorphisms ACE -262A>T (rs 4291) and ACE -115T>C (rs 4292) were significantly associated with aspirin-intolerant asthma (AIA) in the Japanese population with p = 0.015 and p = 0.050, respectively. The minor allele frequencies of the SNPs were higher in AIA than in aspirin-tolerant asthma (ATA). This indicates that asthmatics who carry the minor alleles of both SNPs are prone to the development of aspirin hypersensitivity [37].

Adenosine receptors are G-protein coupled 7-transmembrane receptors with several subtypes, including ADORA 1 known as A1 adenosine receptor [38]. Adenosine promotes bronchoconstriction, inflammation and airway plasma exudation, leading to airway obstruction [39]. The genetic variants of ADORA 1 contribute to the more rapid bronchoconstriction amongst the patients. The presence of the TT homozygotes in 1405C>T of ADORA 1 posed an elevated risk for the development of AIA in the Korean population with p = 0.001. This subsequently implies that patients carrying the TT genotype are prone to significant clinical outcomes on bronchoconstriction alteration [40].

The centrosome is known as a vital microtubule-organising centre of animals, and involved in the shape of cell, polarity and motility by acting on the cytoskeleton [41]. Centrosomal protein 68 (CEP68) gene is significantly associated with aspirin-intolerant

asthma. Several polymorphisms of CEP68 gene were associated with the decline of forced expiratory volume (FEV) with aspirin provocation. Variant rs7572857G>A demonstrated a four-fold increase in the mean decline of FEV. This implied that the rs7572857 of CEP68 gene had a profound influence on the development of aspirin-intolerant asthma upon aspirin provocation with p = 0.003 [42].

High affinity immunoglobulin epsilon receptor (FCER1) is found on tissue mast cells and blood basophils in the form as tetrameric complex of three chains encoded by three genes known as FCER1A, FCER1B and FCER1G [15]. FCER1G gene variants are associated with the risk of developing allergic rhinitis [43]. FCER1G -237A>G polymorphisms might promote the development of AIA in the Korean population. The frequency of FCERIG -273A>G genotype was significantly different between AIA and ATA patients with $p < 0.05$. The AIA patients with homozygous AA genotype were predisposed to AIA with higher levels of serum IgE in comparison to those with AG and GG genotype [44].

Fibrous Sheath Interacting Protein 1 (FSIP1) gene is found in the epithelial lining of airway and it is regulated by amyloid beta (AB) precursor protein (APP). In Asian samples, FSIP1 was discovered to be in linkage disequilibrium with thrombospondin-1 (THBS1 or TSP-1) gene, having roles in pulmonary response to oxidative stress in asthma [45]. This indicated that there was a significant association between the variants in FSIP1 and AIA development among Korean asthmatics [46]. The rs7179742 of FSIP1 gene had notably higher minor allele frequency for AIA than that of ATA, and an increased decline rate of FEV upon aspirin provocation, contributing to an increased susceptibility of AIA with p = 0.03 [46].

Leukotriene (LT) C4 synthase is an important microsomal membrane protein. It predominantly conjugates LTA4, an epoxide intermediate, into reduced glutathione to form a pro-inflammatory mediator, LTC4. LTC4 synthase (LTC4S) can be found in human eosinophils, basophils, and mast cells [47]. Levels of LTC4S have found to be remarkably increased in eosinophils in the airways of aspirin-intolerant asthmatics [48]. However, there was no significant relationship between LTC4S gene polymorphism, and the activity of the gene in eosinophils even though LTC4S actions were significantly elevated in patients with AIA among Japanese patients [49]. No significant differences were noted between AIA and ATA patients among Korean population as well [50].

N-acetyltransferase 2 gene (NAT2) codes for a xenobiotic metabolising enzyme that belongs to the phase II [51]. NAT2 is required in several drugs and arylamine xenobiotics detoxification. Some studies reported that acetylation could affect the inactivation process of excess biogenic amines such as histamine, thus being accountable for the rise of allergic reactions' symptoms [52]. SNPs of the gene are indicators of asthma, elevated levels of serum IgE and high blood eosinophil counts [53]. Genetic polymorphisms of NAT2 were discovered to be associated to a risk of aspirin hypersensitivity among asthmatics. The -9246G>C was related to enhanced response to provocation of aspirin with p = 0.007. The C allele carriers were more frequently associated with aspirin intolerance compared to G allele [54].

PPARG is a nuclear receptor that plays a principal role in pathways regulating chronic inflammation in several diseases including asthma. Upregulation of the tumour necrosis factor alpha (TNF-α) which plays a role in airway reactivity in asthma, indicates inflammation. It was found that variants of PPARG modulated the actions associated with the gene activity [55]. It was discovered that the rare allele of +82466C>T was significantly associated with an increased risk of AIA with p = 0.04. The homozygous CC genotype showed greater decline in FEV upon aspirin provocation compared to the other alleles [56].

Prostaglandin E receptor 2 (PTGER2) is pleotropic and found highly expressed in the lungs. PTGER2 helps to mediate anti-inflammatory, anti-fibrotic and immune restrictive actions in the lungs. It is also involved in the relaxation process such as bronchodilation by increasing cyclic adenosine monophosphate (cAMP) through the activation of adenyl cyclase [57]. Polymorphisms in PTGER2 would reduce its expression in the lungs. Positive associations were observed between some SNPs in PTGER2 and AIA in Japanese population [58]. A study done among Korean population showed that PTGER2 gene polymorphism found in the promoter area of PTGER2, -616C>G (rs 2075797, p = 0.038) and 166G>A (rs 1353411, p = 0.023) caused exacerbation of aspirin sensitivity [58].

PTGER3 is also one of the four different G-coupled receptors that encode PTGE2 [59]. The inhibition of PTGER3 production by NSAIDs is linked with the development of allergic reactions. The coupling of PGE2 and PTGER3 exacerbates degranulation of mast cells, eventually enhancing inflammatory responses which could also be a factor of AIA development [60]. The -1709T>A genotype of PTGER3 was associated with an increased risk of AIA among Koreans with p = 0.043. The SNP is positioned in the promoter region of PTGER3 which could alter transcriptional activities. The T allele carriers were observed to be significantly associated with AIA in comparison to other alleles [58].

Prostaglandin I2 (PGI2) belongs to the eicosanoid family that is constituted of lipid mediators produced by endothelial cells. It plays a pivotal role in primary homeostasis through platelet activation and inactivation. Protein kinase A in smooth muscles is activated to produce smooth muscle relaxation, occurring through the binding of PGI2 to platelet G protein-coupled receptor that subsequently activates the receptor [61]. It was reported that seven genetic variations were found in PTGIR gene in Japanese population [62]. The 1915T>C showed a significant association with AIA among the Korean patients. It could be due to the influence of the genetic variation on the stability of the PTGIR mRNA and consequently, the PTGIR-mediated response to PG12. The T allele carriers were found to be more prone to the development of AIA ($p = 0.015$ in the dominant model; $p = 0.020$ in the codominant model) in comparison to homozygous genotype CC [58].

Solute carrier family 6 (neurotransmitter transporter, betaine/ GABA) member 12 (SLC6A12) belongs to the SLC family [63]. SLC6A12 gene is involved in the airway remodelling, including the enhancement of mucous hypersecretion of airway epithelial cells that lead to the development of AERD through its relationship with GABAnergic system. The SNP of the SLC6A12 gene, rs557881 was associated significantly with AIA with $p = 0.007$ in Korean population. It showed remarkable decline in FEV upon aspirin provocation in AIA patients. This implicates that rs557881 of SLC6A12 could be the cause for the reversibility of lung function abnormalities among AIA patients [64].

TBXAS1 gene produces thromboxane A synthase 1 that plays a critical role in the arachidonic acid cascade. Thromboxane A synthase 1 converts prostaglandin H2 into another molecule, TXA2 [65]. TXA2 causes constrictions and hyper-responsiveness in the airway, leading to asthma. The presence of SNPs in the TBXAS1 gene is associated with the risk of AIA among Koreans with $p = 0.003$, and the TBXAS1 rs6962291 variant is linked to aspirin hypersensitivity. Commonly, T allele carriers had increased tendency of AIA development with a significant decline in FEV. Homozygous AA genotype carriers were the least prone to get AIA [66].

Tpα receptor is an eicosanoid receptor and a rhodopsin-like G protein-coupled receptor (GPCR) with sequence variants in TBXA2R. TBXA2R gene encodes the Tpα involved in several diseases including asthma and atopic dermatitis [67]. The +795T>C of TBXA2R gene was significantly associated with the risk of AIA in Korean population with $p = 0.03$. AIA patients who carried either homozygous CC genotype or heterozygous CT genotype showed a notable association with AIA. This implies that TBXA2R with genetic polymorphism is capable to modulate bronchoconstriction response to aspirin, thus increasing the tendency for AIA development [68]. TBXA2R with variant rs1131882 ($p = 0.028$) was linked with AIA development among Chinese patients [27].

DPB1*0301 allele potentially presents as an aspirin-intolerant asthma phenotype in the Korean population ($p < 0.0124$), and exhibits a tendency to have a higher serum total IgE levels among the younger Koreans [9]. However, another study has reported a persistent decreasing of FEV upon lysine aspirin inhalation with prevalence of rhinosinusitis with chronic bronchial responses, implying that HLA-DPB1*0301 was significantly associated with AIA [69].

Transforming growth factor encoded by TGFB1 is involved in embryogenesis, development and tissue homeostasis, and investigated for its effects in cancer and inflammation [70]. It was found that TGFB1 -509C>T was associated with the occurrence of rhinosinusitis with the AIA patients. However, while TGFB1 promoter polymorphism was not related with the AIA development in the Korean population, it could cause AIA development with rhinosinusitis [71].

Aspirin-intolerant chronic urticaria

Apart from AIA, TGFB1 gene with -509C>T polymorphism may also be associated with risk of aspirin-intolerant chronic urticaria (AICU) development among Korean patients. Homozygous TT genotype or heterozygous CT genotype carriers were found to have lower levels of serum TGFB1 in comparison to CC genotype carriers [72].

The HLA-DRB1*1302 was overrepresented in patients with aspirin-induced urticaria (18.1%) compared to aspirin-intolerant asthma patients (5.3%, $p = 0.0004$; 2.0%, $p = 0.0024$) and controls (8.1%, $p = 0.0005$; 3.2%, $p = 0.0008$), and this observation remained significant even after adjustments [73]. This study conducted in Korean population may highlight the potential of HLA-DRB1*1302 to be used for predicting aspirin-induced urticaria [73].

Histamine N-methyltransferase (HNMT) is the key enzyme for histamine degradation in the airway [74]. A single nucleotide polymorphism (SNP) in HNMT gene will lead to the build-up of histamine. The polymorphism will hinder HNMT from breaking down histamine, in turn predisposing the people who carry the polymorphism in the gene to hypersensitivity reactions [43]. HNMT enzymatic activity levels were found to be low when coupled with elevated levels of histamine in aspirin-intolerant

chronic urticaria (AICU) patients [75]. The SNP in HNMT gene found to be associated with the development of AICU among Korean population was 939A>G polymorphism. This evidently suggests that 939A>G alters the HNMT enzymatic activity and influences the cellular histamine levels in AICU patients [75].

Prospects of Aspirin Pharmacogenomics Studies in Asia

A study compared the risks and use of aspirin between Asian and Western populations, and discovered that aspirin was underutilized for cardiovascular risk prevention in both regions [76]. The reasons behind the underutilization among Asians may be the overestimation of ADR risks attributed to genetic differences inherent in Asian populations [76]. A strategy to tackle this issue is to use genetic polymorphism to identify and assess ADR risks prior to aspirin therapy [8].

Undoubtedly, pharmacogenomic study activities are rapidly growing. However, from the 36 genes identified to be implicated in aspirin toxicity, only 26 genes were investigated in Asians. This highlight a gap in knowledge of aspirin pharmacogenomics in Asians. Moving forward, people of Asian descent should be served better clinically by running more pharmacogenomic studies on ethnically diverse cohorts. There are three primary areas in which pharmacogenomic research in Asia could contribute to the field globally: to increase research in underrepresented populations, to focus research on diseases and drugs that are regionally important, and to encourage discovery-by-design studies in Asian populations [77].

Evidently, there are multiple populations in Asia that are underrepresented in the studies especially the Vietnamese, Burmese, Cambodians, Indonesians, Filipinos as well as Laotians. According to Pan-Asian SNP Consortium, the whole genome analyses have reported that there are subtle differences between those groups [78]. The Malays and Indians of various parts of countries in Asia have shown genetic variations. More studies would need to be conducted on these populations as the consequence of these differences is undetermined [77]. The HLA-DPB1 gene which had level 2B of evidence was found to be associated with several adverse effects, especially among the Koreans. However, there is significant research insufficiency among the Southeast Asians [79].

Next, pharmacogenomic studies in Asia would need to shift focus on medications implicated for diseases which are more prevalent or causing a significant burden in terms of healthcare in Asian regions. Communicable diseases like HIV infection, tuberculosis and malaria are known to be the foremost cause of mortality and morbidity in the less developed countries. Thailand has been very progressive in researches regarding HIV disease and has made noteworthy progress in the pharmacogenomics of antiretroviral drugs [77]. Japan and Korea have reported several studies on non-communicable diseases of high burden, such as lung and gastrointestinal cancers as well as diabetes mellitus. However, there is clear need of more pharmacogenomics research on the pertinent anti-cancer and hypoglycaemic agents. There are limited research of aspirin intolerance in Asia even though it is more prevalent in Asian population compared to Caucasians [80]. Moreover, there are significantly insufficient studies in specific populations, for example the paediatrics [81].

Lastly, encouraging more discovery-by-design studies would be beneficial in the field of pharmacogenomics in Asia. The greater number of Asian pharmacogenomic studies were replication studies. Therefore, an uptake of the next-generation sequencing technologies together with genome-wide association study would be favourable to make way for more novel and/or population specific markers to be recognised [77].

CONCLUSION

Our review reveals that AGT, IL1B and CYP2D6 are significantly associated with peptic ulcer development and intestinal bleeding. Aspirin-intolerant asthma (AIA) development is associated with genes such as ACE, ADORA 1, CEP68, FCER1G, FSIP1, HLA-DPB1, NAT2, PPARG, PTGER2, PTGER3, PTGIR, SLC6A12, TBXA2R, TBXAS1 and TGFB1. Aspirin-exacerbated airway disease (AERD) is associated with polymorphisms in CHIA, HLA-DPB1, TAPBP, TBXA2R, and TLR3 genes. Genetic polymorphisms of HLA-DPB1, HNMT and TGFB1 are linked to the prevalence of aspirin-induced urticaria. These show that gene polymorphisms are associated with ADR occurrence during aspirin therapy among East Asian populations, but are undetermined in other Asian populations due to the lack of studies. Therefore, more efforts should be directed to pharmacogenomic studies in Asians by including more populations in order to holistically represent Asia.

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