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Original Research Paper

Impact of Genetic Variants on Drug Efficacy and Safety in Cardiovascular, Neurological, Pain Management, and Oncological Treatments: A Pharmacogenetic Analysis of Three Case Studies

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Abstract: Pharmacogenetics studies varying reactions to drugs at the individual level, which forms the basis for personalised medicine. We investigated the effects of single-nucleotide polymorphisms (SNPs) in important genes (HMGCR, SLCO1B1, VKORC1, CYP2C19, DPYD, MTHFR, and others) related to the efficacy, safety, and adverse effects of a series of cardiovascular, neurological, pain, and oncological drugs, including statins, anticoagulants, antidepressants, opioids, and chemotherapy. This study provides valuable information about their therapeutic approaches, refines dosing regimens, and minimises drug-related complications via pharmacogenetic markers. These results highlight an urgent need for clinical implementation of pharmacogenetic testing to take a step towards better precision medicine in patient care through improved efficacy and safety of medication and to prevent adverse drug reactions.

Keywords: Pharmacogenetics, Cardiovascular Medications, Neurological Medications, Pain Management, Oncology, Genetic Variants, Personalized Medicine

1. Introduction

According to the Food and Drug Administration definition (FDA), any active substance used for medical diagnosis, disease prevention, or treatment is referred to as a drug **[1].** Mainly, a drug is administered at a location away from its intended site of effect and undergoes four stages (ADME): absorption, distribution, metabolism, and excretion. The first stage of drug absorption happens after medication enters the body and moves from the administration site into blood circulation. During the second phase of distribution, the medication travels throughout the human body. The breakdown of a drug molecule occurs during the third stage, known as metabolism. The last stage of drug elimination is known as excretion **[2, 3].** These metabolic pathways need to be fully understood to evaluate drug safety and efficacy before public release or market availability, which helps reduce variations in drug response and adverse side effects **[3, 4].**

The relationship between the drug dose that is administered, its concentration level in the body, and pharmacological effects determines both clinical safety and efficacy. The one-size-fits-all traditional approach faces limitations because people exhibit different drug response variations between therapeutic success and toxicity. Precision dosing, which uses pharmacogenetics as a guide, has the ability to enhance treatment effectiveness by analysing genetic influences on drug metabolism and action **[5, 6].**

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The field of pharmacogenetics examines hereditary influences on drug responses to find optimal medications for individual patients. The effectiveness and safety of a drug dose depend on ADME processes, which might experience clinically important genetic variations as well as non-genetic elements that cause individual differences in drug response. A person's life includes numerous non-genetic elements that change frequently, such as age and sex, diet and disease type, and drug interactions. Genetic factors remain stable while showing conditioning properties because they determine gene expression variations, which produce different drug-processing genotypes in individuals. Different patients show unique drug responses because their genetic makeup determines both drug effectiveness and risk of adverse effects **[7-9].** This is why Different people show substantial variations in their drug response in terms of effectiveness, safety, and toxicity **[10].**

DNA genes pass on a genotype that determines an individual's susceptibility to drugs. The genetic variations known as single nucleotide polymorphisms (SNPs) appear in different genotypes. SNPs found in genes affect the functioning of proteins that process drugs **[11].** Population-based SNP profile variations lead to drug response variations between different groups of people **[12].**

The principle of "one size does not fit all" applies to drug response because it varies between individuals. This fundamental principle provides the basis for customised medical treatments. The metabolism of drugs depends heavily on genetic polymorphisms, which influence both treatment success and potential side effects of medication. Pharmacogenetic testing now appears in clinical guidelines to optimise drug prescriptions and improve treatment accuracy for specific patient populations **[13].** The process of drug prescription without knowing the patient-specific effects leads healthcare providers to use "trial and error" methods by testing various medications and dosages until they discover the right treatment, which results in delayed therapeutic effects, together with increased toxicity and higher healthcare costs **[14].** The examination of how personal genetic differences affect an individual's pharmacological response regarding treatment effectiveness and adverse effects is known as pharmacogenetics. The application of pharmacogenetic testing enables healthcare providers to predict optimal drug combinations and doses for individual patients, which reduces treatment failures and toxicities while minimising adverse reactions and enhancing treatment outcomes **[15, 16].**

This research investigates how genetic variations influence pharmacokinetics and pharmacodynamics to determine their impact on cardiovascular and neurological treatments, as well as pain management and oncological care. Healthcare providers who use genetic information during clinical decision-making can predict drug responses and reduce toxic effects while developing optimal dosing plans to enhance treatment effectiveness. The approach goes beyond traditional trial-and-error practices to decrease healthcare expenses while minimising drug-related adverse effects **[17-19].** The strategy serves an essential function in preventive medicine because it enables the identification of disease risks during their pre-development stage **[20].** Each medication underwent an analysis of genetic variants (SNPs), which affect drug metabolism and both efficacy and side effects. The analysis included clinical implications derived from peer-reviewed studies that documented genotype-related outcomes.

2. Methodology

Study design and participants

This study examined genetic variants associated with drug response in cardiovascular, neurological, pain management, and oncological medications. SNPs and their genotypes were analysed to assess their potential effect on drug metabolism and efficacy.

Three unrelated participants were included in the study, representing diverse ages, ethnic backgrounds, and genders (Table 1).

Table 1: Participant demographics

Participant No.	Gender	Age	Ethnicity
Participant 1	Female	28	European
Participant 2	Male	45	Middle Eastern descent
Participant 3	Male	62	Western Asian descent

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We selected participants based on the availability of high-quality DNA samples and their willingness to consent to the study. Inclusion criteria included being free of acute or chronic illnesses that could affect drug metabolism and adherence to the pre-collection protocol. We excluded participants who reported recent medication use that could potentially interfere with the study outcomes.

DNA sample collection and processing

We collected saliva samples from the participants according to strict pre-collection guidelines. Before sample collection, participants refrained from drinking, eating, smoking, brushing their teeth, and chewing gum for 60–120 minutes. We used swabs to firmly rub the inner cheeks of participants for one minute, ensuring sufficient DNA collection. The samples were then sealed in test tubes containing stabiliser capsules, labelled with barcode stickers, and sent to the 24Genetics DNA testing company in Spain for processing. DNA extraction and analysis were performed using high-throughput Illumina sequencing machines and chips, validated through internal quality controls (performed in a certified European laboratory to ensure precision and reliability). Approximately 0.7 million distinct genetic markers were analysed, focusing on a subset of genes relevant to drug response. Algorithms integrated genotypes into a detailed analysis of genetic variants, adhering to internationally recognised genetic research standards.

Genetic data analysis

Following the sequencing, the genetic data were examined to evaluate the impact of SNPs on drug efficacy and safety in cardiovascular, neurological, pain management, and oncological treatments.

The methodology complied with internationally accepted genetic research standards. We carried out the genetic analysis using scientifically validated studies and reliable public databases, such as PubMed and the National Centre for Biotechnology Information (NCBI). We also reviewed the results alongside established research to confirm their accuracy and reliability. According to 24Genetics, the interpretation of the test was based on established scientific consensus, further enhancing the robustness of the findings.

Ethical considerations

Ethical approval for this study was obtained from the [Ethics Committee in Sulaimani Polytechnic University], and informed consent was secured from all participants before sample collection.

Considerations for medication use

To avoid any confusion about how medications might affect the results, participants were asked to share what drugs they were taking at the time of sample collection. We noted the use of medicines for transparency and to aid in the interpretation of findings, even though they do not alter DNA sequences. This step helps ensure that any possible effects of medications on traits, such as enzyme induction or inhibition, are considered in the broader analysis of pharmacogenetic data. No participants were taking medications known to interfere with saliva quality or DNA collection.

3. Results

Table 2: Pharmacogenetic Variants in Cardiovascular Drug Response for Participants 1, 2, and 3.

Medications	**Genes**	**SNPs**	**Genotypes**		
			Participant 1	**Participant 2**	**Participant 3**
Pravastatin	HMGCR	rs17244841	A A	A A	A A
Simvastatin	SLCO1B1	rs4149056	TT	TT	TT
Warfarin	VKORC1	rs9923231	TT	TT	C C
Phenprocoumon	VKORC1	rs9923231	C T	TT	C C
Hydrochlorothiazide	YEATS4	rs7297610	C C	C C	C T

As shown in Table 2, all participants exhibited the AA genotype for HMGCR rs17244841 (pravastatin) and the TT genotype for SLCO1B1 rs4149056 (simvastatin). For VKORC1 rs9923231, Participant 1 demonstrated the TT genotype for warfarin, while Participants 2 and 3 exhibited the TT and CC genotypes, respectively. A similar trend was observed for phenprocoumon, except that Participant 1 exhibited the CT genotype instead of

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TT. Regarding hydrochlorothiazide, Participants 1 and 2 carried the CC genotype for YEATS4 rs7297610, whereas Participant 3 exhibited the CT genotype.

Table 3: Pharmacogenetic Variants in Neurological Drug Response for Participants 1, 2, and 3.

Medications	Genes	SNPs	Genotypes		
			Participant 1	Participant 2	Participant 3
Amitriptyline	CYP2C19	rs4244285	AG	AG	GG
Clomipramine	CYP2C19	rs4244285	AG	AG	GG
Citalopram/Escitalopram	CYP2C19	rs12248560	CC	CC	CC
Bupropion	ANKK1	rs1800497	GG	GG	GG
Clozapine	ANKK1	rs1800497	GG	GG	GG
Aripiprazole	MC4R	rs489693	AC	AC	AC
Amisulpride	MC4R	rs489693	AC	AC	AC
Carbamazepine	EPHX1	rs2234922	AG	AA	AA
Risperidone	DRD2	rs1799978	TT	TT	TT

The pharmacogenetic variants related to neurological drug responses for Participants 1, 2, and 3, as shown in Table 3, are summarized as follows. For CYP2C19 rs4244285, Participants 1 and 2 exhibited the AG genotype, while Participant 3 demonstrated the GG genotype, which was observed for both amitriptyline and clomipramine. Regarding CYP2C19 rs12248560, all participants showed the CC genotype for citalopram and escitalopram. For ANKK1 rs1800497, all participants carried the GG genotype, which was associated with bupropion and clozapine. Regarding the MC4R rs489693 variant, all participants exhibited the AC genotype for both aripiprazole and amisulpride. For EPHX1 rs2234922, Participant 1 had the AG genotype, while Participants 2 and 3 showed the AA genotype for carbamazepine. All participants showed the TT genotype for DRD2 rs1799978, indicating potential similarity in drug response profiles for risperidone.

Table 4: Pharmacogenetic Variants in Pain Management Drug Response for Participants 1, 2, and 3.

Medications	Genes	SNPs	Genotypes		
			Participant 1	Participant 2	Participant 3
Morphine	CREB1	rs2952768	TT	TT	TT
Meperidine	CREB1	rs2952768	TT	TT	TT
Fentanyl	CREB1	rs2952768	TT	TT	TT
Buprenorphine	CREB1	rs2952768	TT	TT	TT
Tramadol	OPRM1	rs1799971	AG	AG	AA
Aspirin	PTGS1	rs10306114	AA	AA	AA

As shown in Table 4, all participants exhibited the TT genotype for CREB1 rs2952768, associated with consistent responses to morphine, meperidine, fentanyl, and buprenorphine. For OPRM1 rs1799971 (tramadol), Participants 1 and 2 carried the AG genotype, while Participant 3 exhibited the AA genotype, indicating potential variability in tramadol response. Regarding PTGS1 rs10306114 (aspirin), all participants demonstrated the AA genotype, suggesting uniform efficacy and tolerability across the group.

Table 5: Pharmacogenetic Variants in Oncological Drug Response for Participants 1, 2, and 3.

Medications	Genes	SNPs	Genotypes		
			Participant 1	Participant 2	Participant 3
Cisplatin	XPC	rs2228001	GG	GG	GT
Fluorouracil	DPYD	rs67376798	TT	TT	TT
Methotrexate	MTHFR	rs1801133	GG	GG	GG
Mercaptopurine	NUDT15	rs116855232	CC	CT	TT

As illustrated in Table 5, the pharmacogenetic analysis of oncological drug response revealed that Participants 1 and 2 exhibited the GG genotype for XPC rs2228001, while Participant 3 demonstrated the GT genotype, indicating potential variability in cisplatin response. All participants shared the TT genotype for DPYD rs67376798 (fluorouracil) and the GG genotype for MTHFR rs1801133 (methotrexate). Additionally, All participants exhibited different genotypes (CC, CT, and

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TT) for NUDT15 rs116855232 (mercaptopurine), indicating genetic variability among them regarding this medication.

4-Discussion:

Some drugs have the desired effect on some people but not on others, and some drugs may even be highly toxic (adverse reaction) to certain patients. There can be many causes for these differences, which may be due to exogenous factors, such as diet or other medicines. However, endogenous factors such as age, gender, and, importantly, genetics are undoubtedly some of the most important [21-23].

Currently, adverse drug reactions lead to significant morbidity and mortality in patients, often resulting in increased healthcare costs. Although drug compatibility has been known and studied for many decades, and any package leaflet specifies the incompatibility of a drug with many others, genetics also has much to contribute to the pharmacogenetics tests. The idea that patients are a homogeneous group of individuals and that medicines and treatments that are usually effective in one group will work for the rest is almost certainly wrong. Clinical experience shows that medicines that work very well in some patients can have many side effects, be ineffective, or cause adverse, even fatal, consequences in others. Pharmacogenetics tests are needed to find out [24].

In this study, the DNA pharmacogenetics tests analyse a list of drugs and rely on recognised scientific studies that match the genetic data and are obtained through algorithms that show participants' predisposition to these drugs. We selected three unrelated individuals of different ages and ethnic backgrounds to ensure that we could observe a range of genetic variations and their potential impact on drug response. This approach enabled us to investigate the potential impact of genetic differences on the pharmacogenetic response to the medication. This study divides the pharmacogenetics DNA analysis into four medical specialities: cardiology, neurology, pain, and oncology, and analyses predispositions to dozens of drugs.

The pharmacogenetics analysis of three participants showed different reactions to cardiovascular drugs like warfarin, phenprocoumon, and hydrochlorothiazide. Previous studies on warfarin underscore its role as a prime example of pharmacogenetics in clinical practice. Genetic testing is often recommended for individuals requiring warfarin to predict drug effects based on their genetic profiles, enabling dose optimisation and reducing adverse effects [25]. Similarly, studies on phenprocoumon and hydrochlorothiazide have highlighted the importance of pharmacogenetics in improving treatment outcomes [26]. Expanding the sample size in future studies may help uncover a broader range of genetic variations and their implications for other cardiovascular drugs. The rs17244841 SNP in the HMGCR gene affects the efficacy of pravastatin, which is a statin medication and used to lower cholesterol [27, 28].

Patients possessing the AA genotype typically exhibit superior responses to pravastatin, experiencing more effective liver targeting and fewer side effects compared to those with AT or TT genotypes, leading to greater drops in LDL and total cholesterol levels; they often hit their target LDL levels with regular doses without needing any changes. Individuals with the AT genotype show a reduced response, which might result in smaller decreases in cholesterol levels; while standard doses can still be effective, they may require higher doses if the desired reduction is not achieved, along with careful monitoring for side effects.. The TT genotype is associated with the lowest response to pravastatin [27], often necessitating increased doses or the use of alternative therapies, such as more potent statins (rosuvastatin) or combination treatments (rosuvastatin/ezetimibe), to achieve cholesterol goals [29]. These differences highlight the need to factor in genetic variations when personalising Pravastatin therapy, along with other clinical factors that may influence outcomes. In the present study, all participants showed AA genotypes that experienced a better response to pravastatin compared to other genotypes. Simvastatin is a lipid-lowering agent. Genetic studies have indicated that SLCO1B1 polymorphisms are associated with varied responses to simvastatin. Patients with the rs4149056 TT genotype generally show a better response (this means they may achieve a greater reduction in LDL cholesterol at standard doses) and a lower risk of myopathy, which makes these patients more suitable for higher doses of Simvastatin. Meanwhile, CT and CC genotypes may have a reduced response (a smaller reduction in LDL cholesterol) and a higher risk of muscle side effects, particularly with higher doses, because the SLCO1B1 gene variant affects the transport

of Simvastatin, leading to higher blood levels of the drug and therefore a greater chance of muscle toxicity, requiring closer monitoring or dose adjustments [27, 30, 31]. Genotyping for SLCO1B1 can prevent myopathy, especially in high-risk populations. However, other genetic factors (like variations in other transporters or enzymes) and clinical factors (such as age, sex, liver function, and concurrent medications) can also influence the response to simvastatin. These variables may lead to variability in the significance of rs4149056's impact across individuals [30]. In the present study, all participants showed TT genotypes.

Warfarin is an anticoagulant drug that is commonly used to prevent blood clot formation and migration. Warfarin has several properties that should be noted when used medicinally, including its ability to cross the placental barrier during pregnancy, which can result in foetal bleeding, spontaneous abortion, preterm birth, and neonatal death. Other side effects of warfarin use include necrosis, vascular calcification, and drug interactions. Warfarin does not directly change the viscosity of blood. It works by blocking the vitamin K-dependent synthesis of biologically active forms of various clotting factors, as well as several regulatory factors. Warfarin does not directly alter blood viscosity. Instead, it stops the production of certain active forms of clotting factors that depend on vitamin K, along with some regulatory factors. [32]. People with the rs9923231 CC genotype of the VKORC1 gene may require a higher dose of warfarin to effectively work as an anticoagulant, which reduces the risk of bleeding compared to those with the CT (medium dose) and TT (low dose) genotypes [33]. VKORC1 genotyping helps personalise dosing and minimises the risks of over- or under-anticoagulation. Other genetic and clinical factors can influence warfarin dose requirements [27]. In the present study, both participants 1 and 2 showed the TT genotype, while participant 3 presented the CC genotype.

Phenprocoumon is a long-acting oral anticoagulant drug extracted from coumarin and sold under the brand names Marcumar and Falithrom. It is a vitamin K antagonist and can inhibit coagulation by blocking the synthesis of several coagulation factors, such as II, VII, IX, and X [34, 35]. People with the CC genotype of the rs9923231 SNP in the VKORC1 gene may need higher doses of phenprocoumon than those with the CT or TT genotypes because they respond differently to vitamin K antagonists. Those with the CT genotype typically require an intermediate dosage; those with the TT genotype have reduced drug sensitivity and therefore are at an increased risk of clotting if underdosed. The CT and TT genotypes are associated with increased sensitivity and therefore have a higher risk of bleeding if overdosed. VKORC1 rs9923231 genetic testing is important for guiding phenprocoumon dosing to ensure that the patient receives the right dose for treatment with minimal side effects. However, other genetic factors, such as CYP2C9 variants, age and weight, also affect dosing. Hence, it is important to monitor the patient closely and make adjustments to the dose for effective and safe anticoagulation therapy [27, 36]. In the present study, participants 1, 2, and 3 exhibited CT, TT, and CC genotypes, respectively.

Hydrochlorothiazide (HCTZ) is a diuretic medication often recommended as a first choice to treat high blood pressure and oedema. Beyond these uses, HCTZ is also used to treat diabetes insipidus and renal tubular acidosis and prevent kidney stones in individuals with high calcium levels in their urine. The rs7297610 genotype can lead to differences in response to HCTZ because of changes in the expression of the YEATS4 gene [37].

Patients with the rs7297610 CC genotype and high blood pressure might respond better to standard doses of HCTZ, leading to greater drops in blood pressure than those with the CT or TT genotypes. In contrast, people with the CT or TT genotypes may not respond as well to the same dose, resulting in less effective blood pressure management. In contrast, those with the CT or TT genotypes may have a reduced response to the same dosage, which could lead to less effective blood pressure control. Patients with the CC genotype are likely to experience better therapeutic outcomes, whereas those with the CT or TT genotypes may require adjusted or higher doses. Genetic testing for rs7297610 assists clinicians in personalising HCTZ therapy, optimising dosing strategies, and enhancing hypertension management according to the patient's genetic profile [27, 37]. In the present study, both participants 1 and 2 showed the CC genotype, while participant 3 presented the CT genotype.

The pharmacogenetics analyses of three participants' responses to neurological drug treatments revealed varying responses to amitriptyline, clomipramine and carbamazepine, as shown in Table 3. The

pharmacogenetics analysis of these drugs aligns with our result [38]. Earlier research indicated how carbamazepine [39], amitriptyline, clomipramine [40], citalopram [40] and amisulpride [41] respond to various genetic differences.

Amitriptyline hydrochloride is a tricyclic antidepressant (TCA) derived from dibenzocycloheptene. In non-depressed individuals, amitriptyline does not affect mood but may cause sedation, while it improves mood in people who are depressed [42]. TCAs' action is blocking the histamine-H1 receptor, α1-adrenergic receptors, and muscarinic receptors, which accounts for their calming effect, lowers blood pressure, and anticholinergic effects, such as blurred vision, dry mouth, constipation, and urinary retention [43]. Genetic variations, particularly the rs4244285 polymorphism, influence the CYP2C19 enzyme, which metabolises amitriptyline [44]. The common genotypes related to this polymorphism are GG, AG, and AA. Individuals with the GG genotype usually have normal enzyme activity, leading to a standard metabolism of amitriptyline that typically requires conventional dosages to achieve therapeutic effects. Patients with the AG genotype may begin with a lower starting dose, with careful monitoring. This genotype may have decreased amitriptyline metabolism, leading to higher plasma concentrations. Adjustments can be made based on clinical response and side effects. This increased concentration could enhance therapeutic effects but also raises the risk of side effects. It is recommended that a further reduction in the starting dose be made for individuals with the AA genotype, as this genotype is likely to show further reduced metabolic activity. Such an outcome can lead to even higher plasma levels of amitriptyline and lower levels of its active metabolite. The increased plasma levels of amitriptyline could enhance therapeutic effects but also raise the risk of side effects. Genotyping for CYP2C19 helps adjust dosing to prevent excess therapeutic effects [27].

In the present study, participants 1, 2, and 3 showed AG, AG, and GG genotypes, respectively.

Clomipramine is classified as a TCA, which is commonly used in the treatment of depression. The metabolism and clinical response of clomipramine are influenced by genetic variations in the CYP2C19 gene, specifically the rs4244285 SNP. Individuals with the GG genotype (extensive metabolisers) show normal CYP2C19 activity, achieving balanced therapeutic outcomes with standard doses and a minimal risk of side effects. In contrast, those with the AG genotype (intermediate metabolisers) have reduced CYP2C19 activity, leading to moderately elevated levels of clomipramine and its metabolites, which may enhance therapeutic effects but also increase the risk of side effects such as sedation or anticholinergic symptoms. Individuals with the AA genotype (poor metabolisers) exhibit markedly reduced or absent CYP2C19 activity, resulting in impaired drug clearance and substantially higher blood concentrations of clomipramine. This condition increases the risk of adverse effects, such as excessive sedation and orthostatic hypotension, and often necessitates dose reductions or alternative treatments to minimise these risks [27, 45]. Genotyping of the CYP2C19 rs4244285 variant is therefore recommended to personalise clomipramine therapy, optimise dosing, and minimise adverse effects, with therapeutic drug monitoring advised for intermediate and poor metabolisers [45]. In the present study, both participants 1 and 2 showed AG genotypes, while participant 3 showed GG genotypes.

Citalopram (brand names Celexa, Cipramil, and others) is an antidepressant in the selective serotonin reuptake inhibitor (SSRI) class [40], while escitalopram, known by brand names such as Lexapro and Cipralex, is also an SSRI antidepressant [46]. The CYP2C19 gene (rs12248560 SNP) commonly directs the metabolism and dosing requirements of citalopram and escitalopram. Individuals with the CC genotype are normal metabolisers and commonly respond well to standard doses because their enzyme activity balances drug clearance and therapeutic levels. Individuals with the TC genotype (intermediate metaboliser) need lower starting doses (dose adjustments) to avoid side effects from elevated drug levels because their metabolism is moderately reduced. On the other hand, the TT genotype (ultrarapid metaboliser) results in faster drug metabolism, which produces lower drug concentrations that could make effective treatment less. Individuals who require a higher dose within the therapeutic range need careful monitoring to prevent adverse effects. In such cases, a higher dose within the therapeutic range may be

necessary, but close monitoring is required to avoid adverse effects. Other genetic variants, like 2 (rs4244285) and 3 (rs4986893), and clinical factors can also direct citalopram or escitalopram metabolism [27, 47]. This relationship between genetic variation and the SSRI response supports the utility of pharmacogenetic testing in optimising treatment, particularly for modifying doses or choosing an alternative medication if necessary to minimise side effects while maintaining efficacy or maximising therapeutic benefit. Further clinical adjustments and monitoring would be necessary to optimise treatment outcomes based on the patient's CYP2C19 genotype[48]. In the present study, all participants 1, 2, and 3 showed CC genotypes.

Bupropion hydrochloride is a noradrenergic/dopaminergic antidepressant; it is also used for smoking cessation. Patients treated with bupropion for smoking cessation show varying success rates based on their rs6265 genotype of the ANKK1 gene. Individuals with the GG genotype are generally more likely to achieve abstinence (are more likely to benefit from bupropion therapy), while those with the AA or AG genotypes tend to have a lower likelihood of quitting smoking successfully. However, research findings can be mixed, with some studies indicating that other genetic and clinical factors may influence the outcomes [27]. Genetic testing for the ANKK1 rs6265 SNP could help tailor bupropion treatment plans, enabling clinicians to identify patients who might require alternative or additional support for smoking cessation to improve success rates. In the present study, all participants 1, 2, and 3 showed GG genotypes.

Clozapine, sold under the brand name clozaril, among others, is a non-traditional antipsychotic medication. It is usually used for treatment-resistant schizophrenia (schizophrenia that does not respond to common treatments). In those with schizophrenia and schizoaffective disorder, it may decrease the rate of suicidal behavior [49]. The ANKK1 gene rs1800497 SNP is associated with dopamine activity in the brain and may influence how individuals respond to clozapine. Different genotypes of the rs1800497 SNP might impact clozapine responses. Patients with the AA genotype might have altered dopamine D2 receptor function, which could affect how they respond to clozapine. These patients may require standard or lower doses due to their potentially heightened sensitivity to the dopaminergic effects of clozapine to avoid side effects such as high prolactin levels, sedation, weight gain, or metabolic problems. Those with the AG genotype are considered intermediate responders. They might show a more balanced response to clozapine, typically using standard doses; however, they may still be at moderate risk for side effects, including weight gain, sedation, and metabolic disturbances, requiring monitoring and dose adjustments based on clinical factors and therapeutic effects. While the GG genotype is associated with a variant that may alter dopamine receptor binding and function, potentially leading to a higher dose requirement for achieving therapeutic effects. These patients might also have a lower risk of side effects like weight gain compared to those with the AA or AG genotypes. But they may be at greater risk for tardive dyskinesia and other motor-related side effects. Understanding a patient's ANKK1 rs1800497 genotype may help clinicians personalise clozapine therapy, optimising dosing strategies and reducing adverse effects. However, individual treatment responses are also influenced by other genetic and clinical factors, so comprehensive monitoring remains essential [50, 51]. In the present study, all participants 1, 2, and 3 showed GG genotypes.

Aripiprazole and amisulpride are antipsychotic drugs used to treat schizophrenia and bipolar disorders. The effectiveness and side effects (like changes in appetite, weight gain, and metabolism) of these two drugs might be affected by variations in the MC4R gene and the rs489693 SNP.[27, 41, 52]. The AA genotype carrier may need standard dosing of aripiprazole and amisulpride, but may be at a higher risk of weight and hypertriglyceridemia adverse events, which may require adjustments to minimize the impact on metabolism. Furthermore, the AC genotype patients usually receive standard doses with careful monitoring due to a moderate risk of weight gain. In contrast, those with the CC genotype are likely to have fewer side effects concerning weight gain and metabolic changes compared to those with AA or AC genotypes. However, the effectiveness of aripiprazole and amisulpride is mostly the same for all these genotypes; the main concern is managing side effects, so standard doses can be given without much worry about metabolic issues. In patients with higher genetic risk of weight gain (AC or CC genotypes), close monitoring of body weight, diet, and

physical activity should be recommended, as well as possible dose adjustments. Genetic testing and knowledge of the patient's MC4R rs489693 genotype could help providers identify potential side effects and improve patient compliance and overall treatment effectiveness [27, 41, 52]. In the current study, all participants 1, 2, and 3 had AC genotypes.

The anticonvulsant carbamazepine (CBZ) is used to treat epilepsy and bipolar disorders, and it is partially metabolised by the enzyme epoxide hydrolase, which is produced by the EPHX1 gene. The SNP rs2234922 within the EPHX1 gene affects the enzyme's activity and, consequently, CBZ metabolism and potential toxicity, such as drug hypersensitivity reactions. Individuals with the GG genotype exhibit higher enzyme activity, leading to faster drug clearance and requiring a higher dose to maintain a balance between efficacy and side effects. Individuals with the AG genotype have intermediate enzyme activity, leading to moderate drug clearance and requiring a moderate dose for therapeutic balance. Conversely, those with the AA genotype typically have reduced enzyme activity, leading to slower drug metabolism and an increased risk of CBZ-induced toxicity. So genotyping the EPHX1 gene and the rs2234922 polymorphisms can guide and help healthcare by monitoring plasma levels and adjusting the dose to ensure therapeutic effectiveness while minimising adverse effects [27, 39, 53]. In the present study, Participant 1 had the AG genotype, while both Participants 2 and 3 had the AA genotype.

Risperidone (Risperdal brand name) is an antipsychotic for schizophrenia, bipolar disorder, and irritability in autistic people. It may exhibit a varying response to the rs1799978 variant of the DRD2 gene [54]. Patients with schizophrenia with the TT genotype are more likely to improve symptoms with risperidone at standard doses and have a lower, though not absent, risk of hyperprolactinaemia compared to CT or CC genotype carriers. CT genotype patients, who often receive similar standard doses, may have a moderate response to risperidone and an intermediate risk of hyperprolactinaemia, while CC genotype patients may show the least symptom improvement with standard risperidone doses and have the highest risk of developing hyperprolactinaemia, potentially necessitating lower dosages or closer monitoring for side effects. Despite these trends, evidence remains mixed, and genetic factors as well as other clinical considerations influence the therapeutic response and risk of side effects, requiring a tailored approach to risperidone dosing and monitoring for each patient [27, 50]. In the present study, all participants 1, 2, and 3 showed TT genotypes.

The pharmacogenetic analysis of drug responses to pain management in Participants 1, 2, and 3 revealed similar responses to morphine, meperidine, fentanyl, buprenorphine, and aspirin, with variation observed only for tramadol. Previous studies have highlighted the importance of genetic analysis in understanding variability in response to tramadol and emphasised the role of pharmacogenetics in personalised medicine [55]. In our study, a larger sample size might have revealed genetic variations in response to other pain management drugs, as genetic variability has been reported in studies on morphine and fentanyl [56] and aspirin [57]. Sex differences, DNA methylation [58], and ethnicity[59] can influence analgesic or opioid pain responses and serve as critical factors in advancing precision and personalised medicine in pain management.

Opioids such as morphine and meperidine are the most commonly used narcotic analgesics for the relief of pain (including postoperative pain) in hospitalised patients [60]. The choice is often based on perceived differences in efficacy and side effects, like analgesia quality and nausea and vomiting [61]. Meperidine is less commonly used in the United States and Canada but remains in use for pain management in emergency departments in countries like Iran [62].

For both meperidine and morphine, the CREB1 gene's (rs2952768 polymorphism) greatly affects drug metabolism and dosing requirements. Patients with the CC genotype may have a decreased analgesic response to opioids, possibly requiring dosage adjustments or higher doses to achieve effective pain relief and minimise the risk of inadequate analgesia or potential side effects compared to those with the CT or TT genotypes. In contrast, individuals with the CT and TT genotypes tend to experience an enhanced analgesic response, potentially benefiting from standard or even lower doses of opioids. Despite these trends, other genetic factors and clinical considerations can also influence the overall response to opioid therapy [27, 56,

63]. In the present study, for both meperidine and morphine, all participants 1, 2, and 3 showed TT genotypes.

Fentanyl and buprenorphine are opioids that are among the most commonly used analgesics for postoperative pain, and their transdermal patches provide sustained blood levels of the drug for a sufficient period [64]. Buprenorphine has been approved by the FDA for managing acute and chronic pain, along with treating opioid dependence [65]. Fentanyl is a synthetic opioid analgesic 50 times more potent than morphine, with a more rapid onset and shorter duration of effect [66].
The effectiveness of treatment and dosing requirements, along with the risk of side effects of buprenorphine and fentanyl, depends on the rs2952768 polymorphisms in the CREB1 gene. Patients with the TT genotype might exhibit a better response to buprenorphine and fentanyl, potentially experiencing greater efficacy in pain relief or opioid dependence treatment compared to the CT and TT genotypes. The TT genotype could be started on standard dosing regimens with adjustments based on clinical response. Individuals with the CT genotype may have a moderate response, potentially showing a balance between pain relief and the risk of side effects. Standard doses are typically effective, but clinical monitoring is important to examine efficacy and adjust doses as needed, while patients with the CC genotype may have a less strong response, possibly requiring higher doses to achieve therapeutic effects. The standard dosing range can still be used initially, but clinicians may need to consider higher doses within safe limits or additional interventions for effective management of pain or opioid use disorder [27, 56, 67]. For this reason, constructing prediction formulas for analgesic requirements of individual opioids, such as buprenorphine and fentanyl, based on genetic polymorphisms is crucial [67]. In the present study, all participants 1, 2, and 3 showed TT genotypes for both fentanyl and buprenorphine.

Tramadol, also known by the trade name ULTRAM, is widely used worldwide. Physicians prescribe this opioid medication to relieve moderate to severe pain [68]. Genetic variations in the OPRM1 gene (rs1799971 polymorphisms) can influence tramadol's effectiveness, but other genetic and clinical factors also contribute to overall response. Individuals with the AA genotype may have a decreased analgesic response to tramadol, potentially requiring higher doses to achieve pain relief compared to those with the AG or GG genotypes. This increased need for higher doses could raise the risk of adverse effects compared to those with the AG or GG genotypes, who respond better to standard doses. In contrast, individuals with the AG or GG genotypes may respond better to standard doses, while GG carriers possibly show the highest response. Tailoring tramadol doses based solely on this genotype is not currently recommended, so clinicians should continue to rely on patient-reported pain levels and clinical judgement when adjusting dosages [27, 69]. In the present study, both participants 1 and 2 showed the AG genotype, while participant 3 showed the AA genotype.

Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to treat pain, fever, and inflammation. Specific inflammatory conditions for which aspirin is used include Kawasaki disease, pericarditis, and rheumatic fever. Aspirin is a non-steroidal anti-inflammatory drug (NSAID) and works similarly to other NSAIDs but also suppresses the normal functioning of platelets [70]. Variability in response to the rs10306114 polymorphism in the PTGS1 gene can impact the effectiveness of aspirin in reducing the risk of cardiovascular events or managing inflammation. Those with the AA genotype tend to have a lower risk of non-response to aspirin, suggesting a more consistent antiplatelet effect, but the risk is not absent. The typical dosage for these patients remains standard, depending on the clinical need. AG genotype patients may face a higher risk of reduced response to aspirin, indicating a potentially less effective inhibition of platelet aggregation. For this group, standard doses are often used, but additional clinical monitoring may be required to ensure efficacy. Patients with the GG genotype are at the highest risk of non-response, potentially reducing the antithrombotic benefits of aspirin. Standard dosages apply, yet alternative or adjunct therapies might be considered if platelet inhibition is insufficient. Other genetic and clinical factors may also influence a patient's response to aspirin [27]. Genetic testing for the rs10306114 polymorphism in the PTGS1 gene may guide personalised aspirin therapy, helping optimise dosage or consider alternatives for those with higher

risks of non-response [71]. In the present study, all participants 1, 2, and 3 showed AA genotypes.

The pharmacogenetic analysis of oncological drug response in this study identified potential variability in cisplatin response among the participants. However, consistent genetic profiles were observed for the remaining medications, likely due to the study's limited sample size. Previous studies have demonstrated the role of personalised treatment based on pharmacogenetic analysis for medications such as fluorouracil, mercaptopurine, methotrexate, and cisplatin [72]. A chemotherapeutic drug, cisplatin, is used for the treatment of numerous human cancers, including bladder, head and neck, lung, ovarian, and testicular cancers, as well as carcinomas, lymphomas, and sarcomas [73]. The XPC gene rs228001 genotype polymorphism may affect risk intensity for cisplatin-induced ototoxicity [74]. Individuals with the GG or GT genotypes may have an elevated risk of developing ototoxicity, including hearing loss and neutropenia, when undergoing cisplatin treatment, compared to those with the TT genotype. This increased susceptibility means that individuals with GG or GT genotypes might experience ototoxicity even at lower doses of cisplatin, whereas patients with the TT genotype generally have a lower risk of cisplatin-induced hearing loss. However, TT carriers are not entirely protected and may still develop ototoxicity under certain conditions [72, 75]. Other genetic and clinical factors may also influence a patient's risk for ototoxicity when treated with cisplatin [27]. In the present study, both participants 1 and 2 showed GG genotypes, while participant 3 showed GT genotypes.

An antimetabolite drug, fluorouracil, is widely used in the treatment of solid tumours, including cancers of the colorectum, breast, and aerodigestive tract [76]. For individuals receiving fluorouracil treatment or fluoropyrimidine chemotherapy, variations in the DPYD gene rs67376798 impact the metabolism of the drug and influence toxicity levels. The DPYD gene encodes dihydropyrimidine dehydrogenase, an enzyme crucial for breaking down fluorouracil. The rs67376798 variant, specifically, has been associated with decreased enzyme function, and this effect varies by genotype [77]. Those with the AA genotype have the highest risk due to decreased enzymatic activity, which allows fluorouracil to accumulate and increases the severity of toxicity. The AT genotype carriers also show increased toxicity compared to the TT carriers, but typically with less severity than AA. Conversely, patients with the TT genotype generally tolerate the drug better, presenting a lower toxicity risk. Even the TT carriers, though, might become toxic at higher dosages or for other clinical reasons [27, 78]. Despite these genotype-related trends, studies provide conflicting evidence, suggesting other genetic and environmental factors also modulate toxicity [27]. Across all genotypes, cumulative dosage remains a key factor, with AA and AT patients often requiring dosage adjustments to reduce toxicity, while TT carriers generally tolerate standard dosing more effectively. This relationship between genotype and dosage emphasises the need for personalised approaches to fluorouracil therapy to optimise safety and efficacy. In the present study, all participants 1, 2, and 3 showed TT genotypes.

Methotrexate (MTX) is an antineoplastic antimetabolite with immunosuppressive properties. Dermatology, rheumatology, and pulmonology are among the fields that use it. By slowing down the growth of cancer cells, it can also serve as an antimetabolite for cancer therapy [27, 79, 80]. The MTHFR rs1801133 genotype variant influences MTX concentrations differently based on genotypes, impacting pharmacokinetics without conclusive clinical outcome associations [81]. Patients with the AA genotype often have higher MTX levels than those with AG or GG genotypes, which may be due to reduced enzymatic breakdown, potentially affecting drug metabolism and increasing toxicity risks. This could theoretically increase the risk of toxicity. AG carriers exhibit intermediate concentrations (partial decrease in metabolism), while GG carriers generally have lower levels, suggesting more efficient metabolism. However, studies provide conflicting evidence on the clinical relevance of these pharmacokinetic differences [27, 82]. The Dutch Pharmacogenetics Working Group has therefore assigned this drug-variant pair a "no recommendation" status, deeming it not clinically actionable for dosing adjustments. Despite this, genetic and clinical factors beyond RS1801133 may influence MTX responses, highlighting the importance of individualised monitoring, especially at higher doses, to avoid potential toxicity [27, 72]. In the present study, all participants 1, 2, and 3 showed GG genotypes.

Mercaptopurine (6-MP), sold under the brand names Purinethol or Purixan, among others, is an immunosuppressant and antineoplastic agent. It is a medication used for cancer and autoimmune diseases. Specifically, it is used to treat acute lymphocytic leukaemia, chronic myeloid leukaemia, Crohn's disease, and ulcerative colitis [44]. The rs116855232 variant in the NUDT15 gene influences the required dosing of 6-MP across different genotypes, impacting pharmacokinetics and potentially affecting treatment efficacy and safety. Patients with the CC genotype may require increased doses of 6-MP, likely due to more efficient drug metabolism. In contrast, those with the CT or TT genotypes generally need lower doses, as they may have reduced enzymatic function, leading to slower drug clearance and a higher risk of toxicity [72, 83, 84]. These dose adjustments are essential for achieving therapeutic effectiveness while minimising adverse effects. Nonetheless, other genetic factors, such as TPMT or NUDT15 variants, along with clinical factors like age, body weight, and liver function, can also affect 6-MP dosing. This genotype-based approach emphasises the need for personalised dosing strategies to optimise therapeutic outcomes and reduce toxicity risks [27, 44]. In the present study, all participants exhibited different genotypes (CC, CT, and TT). In a study by Yang et al. (2015) on the treatment of acute lymphoblastic leukaemia in children of diverse racial and ethnic backgrounds with mercaptopurine (MP), patients with CT and TT genotypes exhibited increased susceptibility to the drug, resulting in higher toxicity and adverse effects. Conversely, those with the CC genotype had a lower risk of such complications. The study adjusted doses based on genotype, reducing dose intensities for CT and TT carriers to minimise toxicity. These findings highlight the importance of considering genotype, as well as racial and ethnic differences, when optimising MP dosing and treatment outcomes [83].

The integration of pharmacogenetics data into clinical practice has the potential to enhance drug safety and efficacy, particularly for cardiovascular and neurological medications and pain and oncology treatments. The Estonian Biobank contains genetic and health data for a large cohort of participants and is regularly updated through national registries and hospital databases. Estonia uses this data to support personalised medicine initiatives with the goal of integrating genetic research into routine healthcare practices [85]. Furthermore, Finland's healthcare system is advancing in using genetic information for tailored treatments, including medication adjustments [86].

Pharmacogenetic testing enables personalised medicine through genetic variation analysis to find alternative treatments, reduce adverse drug effects, maximise treatment effectiveness, and adjust medication amounts. Pharmacogenetics reduces healthcare expenses by reducing the risk of adverse drug reactions, shortening drug trial durations and eliminating the requirement for multiple trials to discover effective treatments [87, 88]. However, alongside genetic factors, other clinical variables such as coexisting conditions and drug interactions must also be considered when tailoring therapy. Additional research needs to validate pharmacogenetic testing through large-scale clinical trials. Healthcare providers, including physicians and pharmacists, can obtain pharmacogenetic data from patients who have consented to this information to improve medication prescription and dispensing accuracy. Treatment strategies become more effective through genetic information, which leads to better patient outcomes, reduced adverse drug reactions and increased precision and efficiency in patient care [89, 90] The drug misuse results in thousands of annual deaths worldwide while creating billions of dollars in healthcare costs [91]. A major contributor to this issue is adverse drug reactions, often resulting from a failure to consider individual genetic variations [92]. Over the past few decades, research has strengthened our knowledge about how drugs interact with human genes. Pharmacogenetics, the field dedicated to analysing these interactions, uses genetic knowledge to optimise drug efficacy and safety. In addition to its significant health benefits for patients, pharmacogenetics also has economic implications. However, a considerable portion of medical expenditures remains wasted on treatments that fail to produce the desired effects or, in some cases, lead to fatal outcomes. This variability in drug response is largely due to genetic differences, as each individual possesses a unique genetic profile [92, 93].

5-Conclusion

Pharmacogenetic research reveals how genetic variations influence drug metabolism, efficacy, and the

risk of adverse effects in cardiovascular, neurological, pain management, and oncological treatments. By analysing SNPs, this study identifies key genetic markers that can inform clinical decisions, enhancing drug effectiveness while lowering the likelihood of side effects. Genetic markers associated with specific genetic polymorphisms refine dosing strategies and improve treatment outcomes. Evaluating a patient's genetic profile before starting therapy enables healthcare providers to predict drug responses, customise treatments, and make better-informed prescribing choices. Integrating pharmacogenetic data into clinical practice represents a crucial step toward more precise and safer medication use. By connecting genetics with pharmacology, this approach strengthens the role of precision medicine in personalising treatments, minimising adverse reactions, and enhancing patient care.

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Ethics

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