

## Bridging the genetic gulf: a deep dive into neurotransmission, pharmacogenomics, and genetic variations for optimal pain management

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**ABSTRACT:** Pain embodies a complex sensory experience influenced by a medley of biological, psychological, and genetic. Pain perception can be classed into four main categories: nociceptive pain, neuropathic pain, acute pain, and chronic pain. Genetic polymorphisms, which are basically genetic variations in DNA sequences, have a part to play in the neurotransmission pathways associated with pain perception and the ultimate effectiveness of pain management interventions. Learning about the effects of genetics on neurotransmission in pain management offers a fresh viewpoint on individual variations in pain sensitivity, response to treatment, and the development of personalised approaches to pain management. A closer look at the relationship between genetic polymorphisms and neurotransmission provides a better understanding deep down at the genetic level. These chemical messengers, neurotransmitters, help pass signals between nerve cells; they are essential for pain processing and modulation. Differences in genetic makeup in neurotransmitter-related genes could change how these genes express, function, and regulate, thus changing how humans perceive pain and respond to pain management interventions. The conjunction of neurotransmission and pharmacogenomics forms a unique convergence, composing a narrative that discloses the perceptive influence of individual genetic differences on neural communication and responses to pharmaceuticals. These genetic variations elaborately construct the molecular architecture supervising neurotransmitter release, receptor interactions, and enzymatic processes within the nervous system. In this review, the convergence of neurotransmission, pharmacogenomics, and genetic variations illuminates a pivotal realm in healthcare. Genetic variations intricately influence neurotransmission pathways, moulding individual responses to pharmacological interventions. This intersection not only underscores the complexity of human biology but also holds the promise of personalised healthcare solutions. Recognising subtle genetic variations in neurotransmission and pharmacogenomics opens the door to precision medicine, tailoring treatments to individual genetic codes and revolutionising our approach to medical care.

**Keywords:** Neurotransmission; Pharmacogenomics; Genetic Variations; Pain Management

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## 1.0 INTRODUCTION

In 2020, a research endeavour harnessing data from the National Health Interview Survey 2019-2020 Longitudinal Cohort publicised that chronic and high-impact chronic pain were registered at a rate of 52.4 cases per 1000 person-years ([Nahin et al., 2023](#)). Unfortunately, the availability of pain information in Malaysia remains obscure. A recent study carried out at a pain clinic in a Malaysian tertiary hospital, involving 180 patients, found that 65% of them followed their prescribed regimens ([Kerpagam et al., 2023](#)), which suggests the promising prospect of improved well-being for individuals managing pain through habitual conformity to their treatment plans.

At the forefront of genetic research lies the complex interrelation between genetic polymorphisms and neurotransmission, a union at the heart of advanced genetic discoveries ([Gilbert et al., 2009](#); [Ma et al., 2016](#)). Functioning as quintessential biochemical communicators, neurotransmitters send signals from one nerve cell to another, a process fundamental for pain perception and modulation. Variations within genes responsible for neurotransmitter functions could significantly alter their expression, operation, and regulation. These alterations, in turn, profoundly impact shaping individual pain experiences and the efficacy of various pain management interventions ([Teleanu et al., 2022](#); [Yam et al., 2018](#)).

One illustrative example is the serotonin system, known for its role in mood regulation and pain modulation. Variations in genes that encode for serotonin receptors and serotonin transporter are linked to differences in pain receptivity and the efficacy of antidepressants that modulate serotonin levels. Genetic polymorphisms within the catecholamine neurotransmitter system, encompassing genes involved in dopamine and norepinephrine pathways, are implicated in pain modulation ([Hao et al., 2023](#)). A further instance is opioid neurotransmission, which relies on receptors like the mu-opioid receptor and plays a critical role in pain relief. Genetic variations in opioid receptor genes can affect how an individual responds to opioid drugs, manipulating their pain-relieving efficacy and possible side effects. Polymorphisms in genes related to endogenous opioid peptides, which control pain perception and stress responses, have also been

identified as potential determinants of individual differences in pain sensitivity and treatment response ([Herman et al., 2022](#); [Pathan et al., 2012](#)).

Undoubtedly, the study of genetic polymorphisms in neurotransmission pathways is necessary for advancing individualised pain management. By observing genetic variations that affect neurotransmitter systems fundamental to pain perception and control, this testing can guide the selection of the most effective medications, determine appropriate dosages, and devise custom-fit treatment strategies. It allows healthcare professionals to customise pain management to each individual's unique genetic profile ([Kaye et al., 2019](#); [Tanguay-Sabourin et al., 2023](#)).

To illustrate, knowledge about the genetic variations in opioid receptors can assist in determining the most appropriate opioid medication and the correct dosage for one's specific needs. This can lower the likelihood of experiencing unwanted side effects or inconsistencies in pain suppression. Genetic information related to neurotransmission pathways is extremely useful for choosing the right non-opioid analgesics, adjuvant medications, or even behavioural interventions that might work better for someone based on their specific genetic profiles. Genetic polymorphisms associated with neurotransmission pathways substantially impact the intensity of pain experienced and the responsiveness to various interventions. By focusing on these genetic profiles, healthcare providers can devise pain management plans that are not just about better pain relief but also optimise overall treatment outcomes while minimising potential risks and side effects ([Kaye et al., 2019](#)).

Pharmacogenomics, a groundbreaking field that explores an individual's genetic composition and their reactions to drugs, has been surfaced as a glue that binds genetics and pharmacology ([Oates et al., 2018](#)). By identifying genetic polymorphisms, researchers and healthcare experts can learn about the different metabolic processes and responses to certain drugs among different individuals. The transformative capacity resonates throughout multiple health arenas, prominently featuring pain relief and the therapeutic treatment of depression ([Chadwick et al., 2009](#)).

Pain management represents a multifaceted and intricate dimension of healthcare, given the subjective nature of pain perception, with individual responses ([Mackey, 2016](#)). While classical methods of relieving pain typically involve the administration of analgesic medications, such as opioids, the performance and potential adverse effects of these drugs can vary from one patient to another ([Nyorong et al., 2021](#)). Then enters pharmacogenomics, the science that allows researchers and healthcare providers to pinpoint specific genetic variations that influence an individual's response to pain medications. With this information, they can now develop personalised pain management plans that aim to achieve the best pain relief possible while also avoiding unwanted reactions ([Herman et al., 2022](#); [Pathan et al., 2012](#)).

Antidepressants play a significant role in pain management by targeting neurotransmitters in the brain involved in both mood regulation and pain perception. While originally developed for depression treatment, certain classes of antidepressants, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), have been found to be effective in managing various types of chronic pain conditions. These medications work by modulating neurotransmitters like serotonin and norepinephrine levels in the brain and spinal cord, thereby alleviating pain signals and improving pain tolerance. Additionally, some antidepressants exhibit direct analgesic effects independent of their antidepressant properties ([Bonilla-Jaime et al., 2022](#); [Obata, 2017](#)).

Antidepressants are commonly used in treating conditions such as neuropathic pain, fibromyalgia, chronic low back pain, and migraine headaches. They are often preferred over opioids for chronic pain management due to their lower risk of addiction and overdose ([Dowell et al., 2022](#)). Overall, antidepressants serve as valuable components of a comprehensive pain management strategy, particularly for chronic pain conditions associated with alterations in mood and neurotransmitter function ([Nekovářová et al., 2014](#)). On the other hand, genetic variations play a role in an individual's response to antidepressants, affecting aspects such as drug metabolism, receptor interactions, and potential side effects. By analysing an individual's genetic profile, healthcare providers can customise an antidepressant treatment plan for individuals, thereby increasing the chances of success and lowering the risk of adverse effects. However, extensive research and

validation are needed to establish dependable guidelines for incorporating genetic information into pain alleviation practices ([Zięba et al., 2023](#)).

Genetic variations matter significantly when it comes to an individual's response to antidepressants, affecting aspects such as drug metabolism, receptor interactions, and potential side effects. Through the analysis of an individual's genetic profile, healthcare providers can customise an antidepressant treatment plan that is just fit for them, upping the chances of success and lowering the risk of harmful side effects. Still, extensive research and validation are needed to establish dependable guidelines for using genetic information in pain alleviation practices. On the bright side, the growing field of pharmacogenomics brings much hope for the future of pain management. This allows for highly accurate and personalised approaches that consider the diverse needs of patients dealing with pain.

This review explores the intersection of genetics, neurotransmission, pharmacogenomics, and pain management. This entails a comprehensive examination of how genetic variations influence neurotransmission, subsequently affecting the efficacy of pharmacological interventions for pain management. The goal is to bridge gaps in understanding between these various fields to optimise pain management strategies based on individuals' genetic profiles. This likely involves identifying genetic variations that impact how individuals respond to pain medications, potentially leading to personalised approaches for pain management that are more effective and tailored to each patient's unique genetic makeup.

## 2.0 METHODOLOGY AND LITERATURE SEARCH

The review was conducted through a literature search on pain management and genetic variation studies across PubMed, Web of Sciences, and Google Scholar databases. The search terms or keywords utilised were genetics, bioinformatic, neurotransmission, pharmacogenomics, and pain management, with no language or publication date restriction. Our review and discussion included non-indexed local journals, clinical case reports, and reports from the Ministry of Health Malaysia.

## 3.0 GENETIC INFLUENCES ON PAIN MANAGEMENT

Pain management is a multifaceted and intricate aspect of healthcare, as everyone subjectively experiences and responds to pain differently. Even though analgesic medications, including opioids, are traditionally used to alleviate pain, their effectiveness and the possibility of

risky side effects can differ significantly among individuals ([Anekar et al., 2023](#); [Scarborough et al., 2018](#)). By harnessing the power of pharmacogenomics, researchers and clinicians can identify specific genetic variations that influence an individual's response to pain medications. This information enables the development of personalised pain management plans to optimise pain relief while minimising the risk of side effects ([Bright et al., 2021](#)).

In recent years, the connection between pain and depression has caught the attention of scientific researchers. Chronic pain is not just a standalone issue; it often triggers, and can even worsen, depressive symptoms, making the treatment process trickier ([Sheng et al., 2017](#)). Interestingly, genetic variations could influence both pain sensitivity and the risk of depression, indicating that the two seemingly different health conditions might be interconnected at a genetic level ([Barnes et al., 2017](#)). Through the use of pharmacogenomics-driven approaches, medical practitioners aim to not only soothe physical pain but also, perhaps indirectly, lighten the burden of depression in those wrestling with both issues.

There exist different types of pain, and genetic variations can have a significant impact on pain management across various categories, including acute pain, chronic pain, nociceptive pain, and neuropathic pain. Each type possesses a distinct definition closely associated with its influence on individuals' perception, severity, and duration of pain experienced ([Marcianò et al., 2023](#)). Acute pain is typically sudden and short-lived, often resulting from injury, surgery, or medical procedures, and its management involves medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids for severe pain. Non-pharmacological interventions like ice packs, elevation, and physical therapy may also be used ([Dowell et al., 2022](#)).

Chronic pain, persisting for an extended period, usually beyond the expected time for tissue healing, commonly associated with conditions like neuropathic pain, fibromyalgia, and arthritis, requires a multidisciplinary approach, including medications like antidepressants, anticonvulsants, opioids, and non-opioid analgesics. Physical therapy, cognitive-behavioural therapy, acupuncture, and other complementary therapies are also utilised ([Marcianò et al., 2023](#)). Nociceptive pain, resulting from tissue damage or inflammation, is typically well-localised and can be acute or chronic. Treatment focuses on addressing the underlying cause

of the pain, such as injury or inflammation, with NSAIDs, acetaminophen, opioids, or other medications targeted at reducing inflammation or blocking pain signals ([Prescott & Ratté 2017](#)). Neuropathic pain arises from nervous system damage or dysfunction, often being chronic and challenging to treat. Medications such as antidepressants, anticonvulsants, and certain opioids may be used to manage neuropathic pain. Additionally, interventions like nerve blocks, spinal cord stimulation, and physical therapy may provide relief ([El-Tallawy et al., 2021](#)).

Pharmacogenomics, a field at the intersection of pharmacology and genetics, has revolutionised how researchers and healthcare practitioners understand how an individual's genetic composition impacts their drug response ([Oates et al., 2018](#)). By identifying genetic polymorphisms, this discipline equips them with crucial information about how individuals might process or react to particular drugs. This approach is incredibly transformative in numerous medical domains, such as pain management and depression treatment ([Chadwick et al., 2021](#)).

Genetic variations can influence an individual's response to pain medications, affecting their efficacy and side effects. Pharmacogenomics, the study of how genetic differences affect drug responses, has identified specific genetic markers associated with variations in drug metabolism, receptor sensitivity, and drug transporters ([Kaye et al., 2019](#)). For example, genetic variations in genes encoding drug-metabolizing enzymes like cytochrome P450 enzymes can affect how quickly a person metabolises certain pain medications, leading to differences in drug efficacy or toxicity. Similarly, genetic variations in opioid receptors or neurotransmitter pathways can influence an individual's susceptibility to opioid addiction, tolerance, and side effects. Understanding these genetic variations can assist healthcare providers in tailoring pain management strategies to individual patients, optimising medication selection, dosage, and monitoring for better pain control and reduced risk of adverse effects ([Bugada et al., 2020](#)). Additionally, ongoing research in pharmacogenomics may lead to the development of personalised pain management approaches based on a patient's genetic profile, improving treatment outcomes and patient safety.

Pharmacogenomics is a rapidly advancing field that is actively being included in clinical practice. While personalised pain management and depression treatment show great promise, further research is

needed to cement clear guidelines and recommendations for integrating pharmacogenomics in these domains. Solid scientific investigations must be applied to ensure that these pharmacogenomics methods are reliable, efficient, and safe to implement in the management of pain and depression.

#### 4.0 PAIN MANAGEMENT AND NEUROTRANSMITTERS

Neurotransmitters are chemical messengers in the nervous system that play a critical role in pain management ([Teleanu et al., 2022](#)). They are the communication lifeline between nerve cells (neurons) and play a part in various processes related to pain perception, modulation, and regulation.

**Table 1** is a rundown of some key neurotransmitters that are at the forefront of pain management. These neurotransmitters interact with different receptors and neural pathways to govern pain perception, transmission, and modulation ([Yam et al., 2018](#)). Pharmacological interventions targeting these neurotransmitter systems can be used in pain management strategies to alleviate pain or modulate pain responses. Nevertheless, it is important to note that pain is a complex phenomenon, and neurotransmitters are just one aspect of the broader mechanisms involved in pain processing in the body ([Answine, 2018](#)).

#### 5.0 ASSOCIATIONS BETWEEN GENE POLYMORPHISMS AND PAIN

A mounting body of evidence suggests that gene polymorphisms, which are variations in DNA sequences, can leave a footprint on an individual's susceptibility to pain and their response to pain management ([Young et al., 2012](#)). Specific gene polymorphisms have been associated with pain perception, sensitivity, and onset of chronic pain conditions (**Table 2**). The situation is rather complex when it comes to associations between gene polymorphisms and pain. These associations are subject to various factors, from a specific type of pain an individual experiences to the various environmental factors, not to mention the complex interactions between genes ([Kim et al., 2009](#)). Moreover, the effects of gene polymorphisms on pain can vary among individuals. So, not everyone carrying a specific gene variant will undergo pain in the same way ([James, 2013](#)).

Antidepressants are commonly prescribed medications for the treatment of depression and certain anxiety disorders. However, they are also used in pain

management, particularly for conditions such as neuropathic pain and fibromyalgia. Genetic variations can significantly impact the response to antidepressants, both in terms of efficacy and side effects. To understand these genetic variations, clinicians can utilise pharmacogenetic testing to personalise antidepressant therapy. This involves selecting medications and dosages more likely to be effective and well-tolerated for individual patients based on their genetic makeup. By identifying genetic factors that could influence antidepressant response, clinicians can make informed treatment decisions, ultimately enhancing outcomes in depression and related disorders.

#### 6.0 ENZYMATIC CATALYSTS FOR NEUROTRANSMITTER BREAKDOWN ASSOCIATED WITH PAIN

The process of neurotransmitter breakdown, particularly related to pain, involves the activity of several enzymes. These enzymes play a crucial role in maintaining the appropriate levels of neurotransmitters in the synaptic cleft, which in turn affects pain signalling and perception ([Yam et al., 2018](#)).

**Table 3** summarizes key enzymes that participate in the degradation of neurotransmitters associated with pain, such as monoamine oxidase (MAO), catechol-O-methyltransferase (COMT), acetylcholinesterase (AChE), dipeptidyl peptidase-IV (DPP-IV), and gamma-aminobutyric acid transaminase (GABA-T). These enzymes operate with a complex system that controls neurotransmitter levels' balance and affects pain signals' routes ([Yam et al., 2018](#); [Yang et al., 2019](#)). Any imbalance or fluctuations in their activities can significantly impact pain sensations, their regulation, and the onset of chronic pain conditions. Studying these enzymes and their involvement in neurotransmitter disassembly can paint a picture of innovative pain relief interventions and, eventually, the birth of novel therapies ([Wyns et al., 2023](#)).

#### 7.0 BIOINFORMATICS AND PAIN MANAGEMENT

Bioinformatics has become handy in pain management research and clinical practice today ([Baskozos et al., 2019](#)). It involves the application of computational methods, data analysis, and statistical techniques to understand biological systems and processes. In the following passages, the authors explore multiple avenues through which the discipline of bioinformatics can contribute to pain management.

**Table 1: Key neurotransmitters that are at the forefront of pain management**

Neurotransmitter	Descriptions	Related genes	Reference(s)
Endorphins	Endorphins are natural pain-relieving chemicals produced by the body. They bind to opioid receptors in the brain and spinal cord to reduce pain perception and promote a sense of well-being. Often referred to as the "feel-good" neurotransmitters, these chemicals are released in response to positive stimuli, exercise, and stress.	<ul style="list-style-type: none"> <li>• Preproopiomelanocortin (<i>POMC</i>) gene</li> <li>• Opioid-receptor mu 1 (<i>OPRM1</i>) gene</li> </ul>	Pathan et al. ( <a href="#">2012</a> ); Sprouse-Blum et al. ( <a href="#">2010</a> )
Serotonin	Serotonin is not just important for mood control but also helps in controlling pain. It regulates pain by tempering the manner pain is relayed in the spinal cord. Medications that raise serotonin levels, for instance, selective serotonin reuptake inhibitors (SSRIs), are sometimes used for chronic pain conditions.	<ul style="list-style-type: none"> <li>• Solute carrier family 6 member 4 (<i>SLC6A4</i>) gene</li> <li>• Serotonin-transporter-linked promoter region (5-<i>HTTLPR</i>) gene</li> </ul>	Parades et al. ( <a href="#">2019</a> )
Gamma-aminobutyric acid ( <i>GABA</i> )	GABA is an inhibitory neurotransmitter involved in moderating pain signals. It quells neuronal activity, reducing the transmission of pain messages. Drugs that potentiate GABAergic activity, such as benzodiazepines, can impart pain-relieving effects.	<ul style="list-style-type: none"> <li>• Glutamic acid decarboxylase (<i>GAD</i>) gene</li> <li>• GABA receptor gene</li> <li>• GABA transporter gene</li> </ul>	Allen et al. ( <a href="#">2023</a> )
Glutamate	Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS). Although it does not directly suppress pain, it is responsible for transmitting pain signals. High levels of glutamate can act as a trigger for an increased sense of pain and cause chronic pain conditions.	<ul style="list-style-type: none"> <li>• Glutamate receptor genes</li> <li>• Glutamate transporter genes</li> <li>• Glutamate-ammonia ligase (<i>GLUL</i>) gene</li> </ul>	Yang et al. ( <a href="#">2019</a> )
Substance P	Substance P is a neuropeptide linked to pain transmission. It enhances pain perception and promotes inflammation in the body. Its release is often triggered by a tissue injury or an inflammation, and its levels can spike in chronic pain conditions.	<ul style="list-style-type: none"> <li>• Tachykinin precursor 1 (<i>TAC1</i>) gene</li> <li>• Tachykinin receptor 1 (<i>TACR1</i>) gene</li> </ul>	Navratilova et al. ( <a href="#">2019</a> )
Norepinephrine	Norepinephrine is a neurotransmitter that works in two ways: it can relieve pain (analgesic effect) and promote pain (prenociceptive effect) depending on the receptor subtype it activates. Additionally, it is involved in balancing pain signals and managing the emotional aspects of pain.	<ul style="list-style-type: none"> <li>• Dopamine beta-hydroxylase (<i>DBH</i>) gene</li> <li>• Norepinephrine transporter gene (<i>SLC6A2</i>)</li> </ul>	Zieglgänsberger, ( <a href="#">2019</a> )

**Table 2: Gene polymorphisms associated with pain**

Genes	Descriptions	Reference(s)
opioid-receptor mu 1 ( <i>OPRM1</i> ) gene	Changes in the <i>OPRM1</i> gene, which codes for the mu-opioid receptor, have been reported to be associated with differences in opioid analgesic response. For instance, the A118G variant, a specific polymorphism of this gene, can result in less effective opioid analgesics and increased sensitivity to pain.	Taqi et al. (2019)
Catechol-O-methyltransferase ( <i>COMT</i> ) gene	The <i>COMT</i> gene encodes an enzyme that deals with the metabolism of catecholamines, i.e., dopamine. Certain polymorphisms in this gene, such as the Val158Met variant, have been associated with the levels of pain sensitivity. This could mean a higher chance of developing chronic pain conditions such as fibromyalgia and temporomandibular disorders.	Tunbridge et al. (2010)
Sodium voltage-gated channel alpha subunit 9 ( <i>SCN9A</i> ) gene	Variations in the <i>SCN9A</i> gene, which codes the Nav1.7 sodium channel, are connected to changes in pain perception. Rare mutations in the <i>SCN9A</i> gene can cause hypoalgesia (inability to feel pain) or hyperalgesia (greater sensitivity to pain).	Majeed et al. (2018)
Guanosine-5'-triphosphate cyclohydrolase 1 ( <i>GCH1</i> ) gene	The <i>GCH1</i> gene is involved in the synthesis of tetrahydrobiopterin ( <i>BH4</i> ), an important cofactor in the production of neurotransmitters like serotonin and dopamine. Certain polymorphisms in this gene have been tied to different mechanisms of pain processing and an increased vulnerability to chronic pain conditions, such as neuropathic pain.	Latremoliere et al. (2011; 2015)
Interleukin-6 ( <i>IL-6</i> ) gene	The <i>IL-6</i> gene encodes IL-6, a pro-inflammatory cytokine. Genetic variations in the <i>IL6</i> gene have been identified as a factor in increased pain sensitivity and the development of chronic pain disorders, such as osteoarthritis pain.	Tanaka et al. (2014)
<i>CYP2D6</i> gene	The <i>CYP2D6</i> gene report indicates a highly polymorphic gene, with more than 130 core alleles identified and named. Extensive studies of <i>CYP2D6</i> alleles have been conducted across diverse geographic, ancestral, and ethnic groups, revealing significant differences in allele frequencies. The most reported alleles are categorised into functional groups, such as those with normal function.	Crews et al. (2021)
Serotonin transporter ( <i>SLC6A4</i> ) gene	The serotonin transporter protein, encoded by the <i>SLC6A4</i> gene, is the target of SSRIs. Genetic variations, such as the serotonin transporter gene-linked polymorphic region ( <i>5-HTTLPR</i> ), can influence serotonin reuptake efficiency and response to SSRIs. Some variations in this gene have been associated with differences in antidepressant efficacy and susceptibility to side effects.	Margoob et al. (2008; 2011)
Brain-derived neurotrophic factor ( <i>BDNF</i> ) gene	<i>BDNF</i> is a protein involved in neuronal growth and survival and plays a role in the mechanism of action of antidepressants. Genetic variations in the <i>BDNF</i> gene have been implicated in the pathophysiology of depression and the response to antidepressant treatment. Certain <i>BDNF</i> gene polymorphisms have been associated with treatment response and the severity of depressive symptoms.	Correia et al. (2023); Porter et al. (2022)
Dopamine receptor ( <i>DRD</i> ) genes	Dopamine receptors are involved in mood regulation and are targeted by some antidepressants. Genetic variations in dopamine receptor genes, such as <i>DRD2</i> and <i>DRD4</i> , have been studied for their potential influence on antidepressant response and the development of side effects.	Porcelli et al. (2011); Zhao et al. (2022)
Transporter proteins	Genetic variations in genes encoding transporter proteins, such as the serotonin transporter ( <i>SERT</i> ) and norepinephrine transporter ( <i>NET</i> ), can affect the reuptake of neurotransmitters targeted by antidepressants, impacting treatment response.	Radosavljević et al. (2023)

**Table 3: Key enzymes that participate in the degradation of neurotransmitters associated with pain**

Enzymes	Descriptions	Reference(s)
Monoamine oxidase (MAO)	MAO is an enzyme that breaks down monoamine neurotransmitters, i.e., serotonin, dopamine, and norepinephrine. By degrading these neurotransmitters, MAO actively participates in the regulation of their levels and influences pain modulation. Variations in MAO activity have been associated with altered pain responses and susceptibility to chronic pain conditions.	Bortolato et al. ( <a href="#">2008</a> )
Catechol-O-methyltransferase (COMT)	COMT is an enzyme involved in metabolising catecholamines, e.g., dopamine and norepinephrine. Essentially, it catalyses the transfer of a methyl group to these neurotransmitters, causing them to break down. Certain COMT actions, similar to the Val158Met polymorphism, can affect an individual's sensitivity to pain and occasionally lead to chronic pain conditions.	Ahlers et al. ( <a href="#">2013</a> ); Nagatsu ( <a href="#">2007</a> )
Acetylcholinesterase (AChE)	AChE is an enzyme that breaks down acetylcholine, an essential neurotransmitter in the peripheral and central nervous systems. Although acetylcholine has no direct connection with pain perception, its breakdown by AChE can adjust the way pain is transmitted, specifically in certain painful conditions, such as neuropathic pain.	Trang et al. ( <a href="#">2023</a> ); Walczak-Nowicka et al. ( <a href="#">2021</a> )
Dipeptidyl peptidase-IV (DPP-IV)	DPP-IV is an enzyme involved in the breakdown of neuropeptides, one example being substance P. Substance P is a neurotransmitter associated with pain signal delivery and inflammation in the body. DPP-IV can cleave substance P, thus influencing pain signalling and regulating inflammatory responses.	Barchetta et al. ( <a href="#">2022</a> ); Gupta et al. ( <a href="#">2019</a> )
Gamma-aminobutyric acid transaminase (GABA-T)	GABA-T is an enzyme involved in the breakdown of GABA, the primary inhibitory neurotransmitter in the CNS. GABA-T catalyses the conversion of GABA into succinic semialdehyde. Alterations in GABA-T activity can impact GABA levels, which can in turn affect pain modulation and sensitivity.	De Leon et al. ( <a href="#">2023</a> )
Cytochrome P450 (CYP)	Cytochrome P450 (CYP) enzymes are responsible for metabolizing many antidepressants. Genetic variations in genes encoding these enzymes can affect the rate at which antidepressants are metabolised in the body. For example, variations in the <i>CYP2D6</i> gene can lead to differences in the metabolism of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), affecting both drug efficacy and the risk of side effects.	Forster et al. ( <a href="#">2021</a> ); Radosavljević et al. ( <a href="#">2023</a> )

In the study of genetics, the importance of bioinformatics in analyzing pain-related genetic data cannot be overstated. Researchers sift through the massive datasets from genome-wide association studies (GWAS) and whole-genome sequencing. On top of that, they make full use of bioinformatics tools and algorithms to identify genetic variations that correlate with pain sensitivity, responses to analgesics, and the development of chronic pain disorders. Bioinformatics has dual functionalities: an expert interpreter of genetic revelations and a guide to finding potential therapeutic targets ([Adam et al., 2021](#); [Xiang et al., 2020](#)).

Pharmacogenomics is a specialised branch of study that concentrates on how genetic variations affect individual

responses to pain medications. Combining genetic data with drug response profiles, bioinformatics tools are excellent at identifying genetic markers that predict drug efficacy, dosage requirements, and the risk of adverse reactions. This information sets the course for personalised pain management strategies and optimises medication choices for each patient ([Oates et al., 2018](#); [Ventola, 2013](#)).

Transcriptomics and gene expression analysis are two applications in bioinformatics. Bioinformatics enables the analysis of gene expression profiles to unfold the molecular mechanisms beneath the pain phenomenon. Advanced techniques such as microarrays and RNA sequencing generate large-scale gene expression data.

These datasets can be analysed using bioinformatics tools to identify differentially expressed genes, biological pathways involved in pain processing, and potential domains for novel therapeutic targets ([Ji et al., 2018](#); [Zhao et al., 2018](#)). Bioinformatics helps combine various data types, including genetic, genomic, transcriptomic, proteomic, and clinical data, to get a full picture of pain. Integrative analysis helps identify molecular pathways, protein-protein interactions, and biomarkers associated with pain conditions, illuminating disease mechanisms and potential therapeutic interventions ([Manzoni et al., 2018](#); [Raja et al., 2017](#); [Xiang et al., 2020](#)). In other words, bioinformatics makes sharing and assimilating pain-related datasets easier through open-access databases and platforms.

This way, researchers and clinicians can work side by side, pooling extensive data for meta-analyses, replication studies, and discovering new pain-associated genes, pathways, and drug targets concerning pain ([Adewuyi et al., 2022](#); [Mittal et al., 2023](#)). With new technology, predictive modeling and machine learning experts utilise machine learning algorithms and predictive modelling to create models capable of predicting pain outcomes, treatment responses, and possible adverse events. Such models are precious in clinical settings, especially for assisting healthcare professionals in making educated decisions, performing accurate risk assessments, and devising personalised pain management approaches that cater to the needs of different individuals ([Habehh et al., 2021](#); [Sanchez-Martinez et al., 2022](#)).

By and large, bioinformatics plays a major part in analysing, interpreting, and integrating complex pain-related data. It calls for understanding pain mechanisms, identifying therapeutic targets, and developing personalised pain management strategies. Acting as a bridge between genomics, molecular biology, and clinical pain management, bioinformatics facilitates translational research and significantly uplifts patient care.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline outlines the importance of genetic testing for *CYP2D6*, *OPRM1*, and *COMT* genes in selecting appropriate therapy. Specifically, it recommends optimizing therapy with codeine and tramadol based on *CYP2D6* genotype test results. While there is limited data for other opioids, such as hydrocodone, oxycodone, and methadone, the guideline emphasises the significant impact of genetic variability on drug-related phenotypes, particularly in

terms of pain relief and adverse events. Evidence strongly links genetic variability to variability in drug response, such as the association between *CYP2D6* metaboliser phenotype and morphine formation from codeine. Poor metabolisers typically exhibit lower serum morphine levels and reduced analgesia with codeine, while ultrarapid metabolisers may experience heightened analgesia but are at risk of severe side effects due to increased conversion of codeine to morphine. Similar associations are observed with tramadol, where poor metabolisers demonstrate reduced efficacy and lower active metabolite plasma concentrations ([Crews et al., 2021](#)). The guideline underscores the potential benefit of *CYP2D6* genotype testing in identifying patients at higher risk of ineffective analgesia or adverse events, facilitating the administration of alternative analgesics. However, it emphasises the importance of reliable genotyping in qualified laboratories to mitigate the risk of errors with long-term adverse health implications for patients.

## 8.0 PHARMACOGENOMICS-GUIDED ANALYSIS

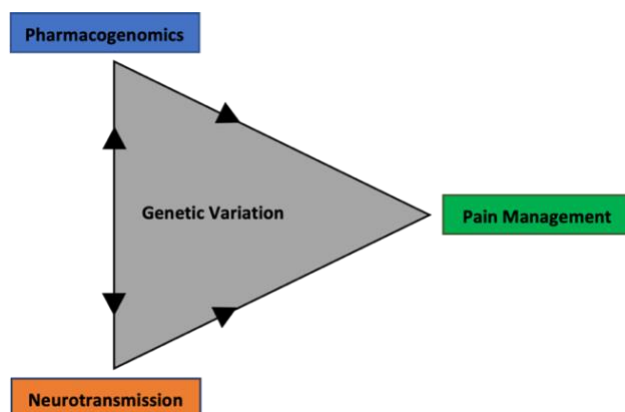
Pharmacogenomics and pharmacogenetics have forged as crucial players, unwinding the complex genetic canvas that influences how individuals respond to pharmaceutical interventions. These disciplines investigate the dynamic relationship between an individual's genetic makeup and drug interactions, aiming to customise therapeutic approaches to the distinctive genetic signatures that set one person apart ([Su et al., 2015](#)).

Pharmacogenetics focuses articulately on the genetic variations that succour individual responses to drugs. This multi-dimensional exploration studies the genetic details that dictate drug metabolism enzymes, drug receptors, and other molecular targets, shedding clarity on the genetic components that can decisively contribute to the possibility of successful therapies and the occurrence of untoward effects in the milieu of pharmacogenomics and pharmacogenetics, where the vernacular of genes meets the pharmacological vista. As we make our way through the complexities of genetic variations and their impact on drug responses, we discover the potential for a foreseeable future where medical treatments are precisely adapted to the unique genetic makeup of an individual, marking a new period of targeted and personalised therapeutic interventions, particularly with regards to pain management. **Figure 1** illustrates the connection between pharmacogenomics and neurotransmission, which lies in their common genetic variations associated with pain management.

The findings from genetic mapping, executed using a suite of bioinformatics tools, were analyzed for core pharmacogenetic markers, including *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A5*, *DPYD*, *SLCO1B1*, *UGT1A1*, and *VKORC1*. This mapping effort was undertaken to identify pharmacogenetic profiles relevant to drug usage ([Hussein et al., 2023](#); [McInnes et al., 2021](#)). These genes are included in the list of esteemed pharmacogenetic directories such as the Pharmacogenomics Knowledge Base (PharmGKB), Clinical Pharmacogenetics Implementation Consortium (CPIC), and Dutch Pharmacogenetics Working Group (DPWG) and are also annotated in PharmGene Variation Consortium (PharmVar). The resultant data showed that variance. Different algorithm designs and genetic variance influenced these variations, and each bioinformatics was calibrated to assess them ([Gaedigk et al., 2020](#)).

Theoretically, the potential of drug-drug and gene interactions of each patient was evaluated based on the final projected metaboliser phenotypes or star alleles. Their phenotypic profiles were merged with registered demographic data, a list of medications, and clinical symptoms ([Idda et al., 2022](#); [Taylor et al., 2020](#)). Taking advantage of the extant resources as a model for phenoconversion can unfold possible differences between a person's genotype-based prediction drug metabolism and their actual ability to do so. Together, pharmacogenomics and bioinformatics unlock a potent pain management strategy that is personalised and grounded in solid evidence. By leaning on genetic information for treatment decisions, healthcare providers can choose the right medications, making them safer and more effective while reducing the risk of drug reactions ([Brandl et al., 2021](#); [Oates et al., 2018](#)). This can improve the lives of patients with chronic pain. Pharmacogenomics and healthcare are essential fields that, when joined forces, promise to improve patient outcomes.

In fact, the synergy between pharmacogenomics and pain management is evident. Pharmacogenomic research can help identify genetic variations that may raise the chances of unfavourable drug reactions or reduce drug effectiveness, especially among specific population subsets ([Micaglio et al., 2021](#); [Shaw et al., 2011](#)). Next up, epidemiological studies step into the picture, further investigating the commonality of these genetic variations across different populations while identifying potential risk factors that may underlie drug reaction susceptibilities ([Chang et al., 2018](#); [Wilke et al., 2007](#)).



**Figure 1:** The correlation between pharmacogenomics and neurotransmission, which share the same genetic variations related to pain management.

## 9.0 CONCLUSION AND FUTURE PERSPECTIVES

In Malaysia, pharmacogenomics has the potential to revolutionise pain management through personalised medicine approaches tailored to individual genetic profiles. However, implementing pharmacogenomics in clinical practice faces several challenges. Several potential applications and challenges are moving forward regarding pain management in Malaysia. Pharmacogenomics research in Malaysia is gradually gaining momentum, with ongoing studies investigating genetic variations associated with drug responses, including pain medications.

Some academic institutions and research centres are actively involved in pharmacogenomics research, contributing to understanding how genetic variations influence drug efficacy and toxicity. Pharmacogenetic testing services are available in certain healthcare facilities, albeit on a limited scale, primarily for specific drugs or patient populations. The identification of genetic variations associated with opioid metabolism and response aids in optimizing opioid therapy for pain management while minimising the risk of adverse effects and addiction. Personalised selection of antidepressants and anticonvulsants based on genetic factors, improving treatment outcomes for neuropathic pain and fibromyalgia. Tailored non-opioid analgesic therapy based on individual genetic profiles, optimising pain relief while reducing the likelihood of side effects.

Despite these advancements, limited awareness, and education among healthcare professionals about pharmacogenomics and its applications in pain management persist. Lack of standardised guidelines for integrating pharmacogenomic testing into clinical practice, leading to variability in testing protocols and

interpretation of results. Cost constraints associated with pharmacogenetic testing and the need for infrastructure development to support its widespread adoption in healthcare settings. Ethical, legal, and societal considerations regarding patient privacy, consent, and genetic discrimination necessitate clear policies and regulations to address these issues. Limited diversity in genetic databases and research cohorts potentially leads to disparities in pharmacogenomic-guided therapy for different population groups. Addressing these challenges will require collaborative efforts involving healthcare providers, researchers, policymakers, and industry stakeholders. Increased investment in education and training programs, national

guidelines and standards development, and initiatives to enhance public awareness and engagement will be crucial for successfully integrating pharmacogenomics into pain management practice in Malaysia, ultimately leading to more personalised and effective treatment approaches for patients.

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## References

- Adam, Y., Samtal, C., Brandenburg, J. T., Falola, O., & Adebisi, E. (2021). Performing post-genome-wide association study analysis: overview, challenges and recommendations. *F1000Research*, *10*, 1002. <https://doi.org/10.12688/f1000research.53962.1>
- Adeyemi, E. O., O'Brien, E. K., Nyholt, D. R., Porter, T., & Laws, S. M. (2022). A large-scale genome-wide cross-trait analysis reveals shared genetic architecture between Alzheimer's disease and gastrointestinal tract disorders. *Communications Biology*, *5*(1), 691. <https://doi.org/10.1038/s42003-022-03607-2>
- Ahlers, S. J., Elens, L. L., van Gulik, L., van Schaik, R. H., van Dongen, E. P., Bruins, P., Tibboel, D., & Knibbe, C. A. (2013). The Val158Met polymorphism of the COMT gene is associated with increased pain sensitivity in morphine-treated patients undergoing a painful procedure after cardiac surgery. *British Journal of Clinical Pharmacology*, *75*(6), 1506–1515. <https://doi.org/10.1111/bcp.12052>
- Allen, M. J., Sabir, S., & Sharma, S. (2023). GABA Receptor. In *Trends in Pharmacological Sciences* (Vol. 2, Issue C). StatPearls Publishing. [https://doi.org/10.1016/0165-6147\(81\)90264-9](https://doi.org/10.1016/0165-6147(81)90264-9)
- Anekar, A. A., Hendrix, J. M., & Cascella, M. (2023). WHO Analgesic Ladder. In *Journal of the Royal College of Physicians of Edinburgh* (Vol. 38, Issue 3). StatPearls Publishing. [https://doi.org/10.1007/978-3-642-28753-4\\_102537](https://doi.org/10.1007/978-3-642-28753-4_102537)
- Answine, J.F. (2018). A Basic Review of Pain Pathways and Analgesia. McMahon Publishing. Available from: <https://www.anesthesiologynews.com/Review-Articles/Article/10-18/A-Basic-Review-of-Pain-Pathways-and-Analgesia/52868>
- Barchetta, I., Cimini, F. A., Dule, S., & Cavallo, M. G. (2022). Dipeptidyl Peptidase 4 (DPP4) as A Novel Adipokine: Role in Metabolism and Fat Homeostasis. *Biomedicines*, *10*(9), 2306. <https://doi.org/10.3390/biomedicines10092306>
- Barnes, J., Mondelli, V., & Pariante, C. M. (2017). Genetic Contributions of Inflammation to Depression. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*, *42*(1), 81–98. <https://doi.org/10.1038/npp.2016.169>
- Baskozos, G., Dawes, J. M., Austin, J. S., Antunes-Martins, A., McDermott, L., Clark, A. J., Trendafilova, T., Lees, J. G., McMahon, S. B., Mogil, J. S., Orengo, C., & Bennett, D. L. (2019). Comprehensive analysis of long noncoding RNA expression in dorsal root ganglion reveals cell-type specificity and dysregulation after nerve injury. *Pain*, *160*(2), 463–485. <https://doi.org/10.1097/j.pain.0000000000001416>
- Bonilla-Jaime, H., Sánchez-Salcedo, J. A., Estévez-Cabrera, M. M., Molina-Jiménez, T., Cortes-Altamirano, J. L., & Alfaro-Rodríguez, A. (2022). Depression and pain: use of antidepressants. *Current Neuropharmacology*, *20*(2), 384–402. <https://doi.org/10.2174/1570159x19666210609161447>
- Bortolato, M., Chen, K., & Shih, J. C. (2008). Monoamine oxidase inactivation: from pathophysiology to therapeutics. *Advanced Drug Delivery Reviews*, *60*(13-14), 1527–1533. <https://doi.org/10.1016/j.addr.2008.06.002>

- Brandl, E., Halford, Z., Clark, M. D., & Herndon, C. (2021). Pharmacogenomics in Pain Management: A Review of Relevant Gene-Drug Associations and Clinical Considerations. *The Annals of Pharmacotherapy*, 55(12), 1486–1501. <https://doi.org/10.1177/10600280211003875>
- Bright, D. R., Petry, N., Roath, E., & Gibb, T. (2021). Engaging pharmacogenomics in pain management and opioid selection. *Pharmacogenomics*, 22(14), 927–937. <https://doi.org/10.2217/pgs-2021-0044>
- Bugada, D., Lorini, F. L., Fumagalli, R., & Allegri, M. (2020). Genetics and Opioids: towards more appropriate prescription in cancer pain. *Cancers*, 12(7), 1951. <https://doi.org/10.3390/cancers12071951>
- Chadwick, A., Frazier, A., Khan, T. W., & Young, E. (2021). Understanding the Psychological, Physiological, and Genetic Factors Affecting Precision Pain Medicine: A Narrative Review. *Journal of Pain Research*, 14, 3145–3161. <https://doi.org/10.2147/JPR.S320863>
- Chadwick, P., Hughes, S., Russell, D., Russell, I., & Dagnan, D. (2009). Mindfulness groups for distressing voices and paranoia: A replication and Randomized feasibility trial. *Behavioural and Cognitive Psychotherapy*, 37(4), 403–412. <https://doi.org/10.1017/s1352465809990166>
- Chang, M., He, L., & Cai, L. (2018). An Overview of Genome-Wide Association Studies. In *Methods in Molecular Biology* (Vol. 1754, pp. 97–108). Humana Press, New York. [https://doi.org/10.1007/978-1-4939-7717-8\\_6](https://doi.org/10.1007/978-1-4939-7717-8_6)
- Correia, A. S., Cardoso, A., & Vale, N. (2023). BDNF unveiled: Exploring its role in major depression disorder serotonergic imbalance and associated stress conditions. *Pharmaceutics*, 15(8), 2081. <https://doi.org/10.3390/pharmaceutics15082081>
- Crews, K. R., Monte, A. A., Huddart, R., Caudle, K. E., Kharasch, E. D., Gaedigk, A., Dunnenberger, H. M., Leeder, J. S., Callaghan, J. T., Samer, C. F., Klein, T. E., Haidar, C. E., Van Driest, S. L., Rúaño, G., Sangkuhl, K., Cavallari, L. H., Müller, D. J., Prows, C. A., Nagy, M., & Skaar, T. C. (2021). Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. *Clinical Pharmacology & Therapeutics*, 110(4), 888–896. <https://doi.org/10.1002/cpt.2149>
- De Leon, A. S., & Tadi, P. (2023). Biochemistry, Gamma Aminobutyric Acid. In *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK551683/>
- Dowell, D., Ragan, K., Jones, C. M., Baldwin, G. T., & Chou, R. (2022). CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022. *Morbidity and Mortality Weekly Report*, 71(3), 1–95. <https://doi.org/10.15585/mmwr.rr7103a1>
- El-Tallawy, S. N., Nalamasu, R., Salem, G. I., LeQuang, J. A., Pergolizzi, J. V., & Christo, P. J. (2021). Management of Musculoskeletal Pain: An Update with Emphasis on Chronic Musculoskeletal Pain. *Pain and Therapy*, 10(1), 181–209. <https://doi.org/10.1007/s40122-021-00235-2>
- Forster, J. L., Duis, J., & Butler, M. G. (2021). Pharmacogenetic Testing of Cytochrome P450 Drug Metabolizing Enzymes in a Case Series of Patients with Prader-Willi Syndrome. *Genes*, 12(2), 152. <https://doi.org/10.3390/genes12020152>
- Gaedigk, A., Whirl-Carrillo, M., Pratt, V. M., Miller, N. A., & Klein, T. E. (2020). PharmVar and the Landscape of Pharmacogenetic Resources. *Clinical Pharmacology and Therapeutics*, 107(1), 43–46. <https://doi.org/10.1002/cpt.1654>
- Gilbert, D. G., Zuo, Y., Rabinovich, N. E., Riise, H., Needham, R., & Huggenvik, J. I. (2009). Neurotransmission-related genetic polymorphisms, negative affectivity traits, and gender predict tobacco abstinence symptoms across 44 days with and without nicotine patch. *Journal of Abnormal Psychology*, 118(2), 322–334. <https://doi.org/10.1037/a0015382>
- Gupta, S., & Sen, U. (2019). More than just an enzyme: Dipeptidyl peptidase-4 (DPP-4) and its association with diabetic kidney remodelling. *Pharmacological Research*, 147, 104391. <https://doi.org/10.1016/j.phrs.2019.104391>
- Habehh, H., & Gohel, S. (2021). Machine Learning in Healthcare. *Current Genomics*, 22(4), 291–300. <https://doi.org/10.2174/1389202922666210705124359>
- Herman, T. F., Cascella, M., & Muzio, M. R. (2023). Mu Receptors. In *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK551554/>
- Hussein D. (2023). In Silico Investigation of the Human GTP Cyclohydrolase 1 Enzyme Reveals the Potential of Drug Repurposing Approaches towards the Discovery of Effective BH4 Therapeutics. *International Journal of Molecular Sciences*, 24(2), 1210. <https://doi.org/10.3390/ijms24021210>

- Idda, M. L., Zoledziewska, M., Urru, S. A. M., McInnes, G., Bilotta, A., Nuvoli, V., Lodde, V., Orrù, S., Schlessinger, D., Cucca, F., & Floris, M. (2022). Genetic Variation among Pharmacogenes in the Sardinian Population. *International Journal of Molecular Sciences*, 23(17), 10058. <https://doi.org/10.3390/ijms231710058>
- James S. (2013). Human pain and genetics: some basics. *British Journal of Pain*, 7(4), 171–178. <https://doi.org/10.1177/2049463713506408>
- Ji, F., & Sadreyev, R. I. (2018). RNA-seq: Basic Bioinformatics Analysis. *Current Protocols in Molecular Biology*, 124(1), e68. <https://doi.org/10.1002/cpmb.68>
- Kaye, A. D., Garcia, A. J., Hall, O. M., Jeha, G. M., Cramer, K. D., Granier, A. L., Kallurkar, A., Cornett, E. M., & Urman, R. D. (2019). Update on the pharmacogenomics of pain management. *Pharmacogenomics and Personalized Medicine*, 12, 125–143. <https://doi.org/10.2147/PGPM.S179152>
- Kaye, A. D., Garcia, A., Hall, O. M., Jeha, G. M., Cramer, K. D., Granier, A. L., Kallurkar, A., Cornett, E. M., & Urman, R. D. (2019). Update on the pharmacogenomics of pain management. *Pharmacogenomics and Personalized Medicine*, 12, 125–143. <https://doi.org/10.2147/pgpm.s179152>
- Kerpagam, S.R.N., Usha, S.R., Kumaravadivel, T.D. & Muniandy, R.K. (2023). Medication Compliance of Patients Attending a Pain Clinic at a Tertiary Hospital in Malaysia. *Borneo Journal of Medical Sciences*, 17(2), 18–24. <https://doi.org/10.51200/bjms.v17i2.3884>
- Kim, H., Clark, D., & Dionne, R. A. (2009). Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. *The Journal of Pain*, 10(7), 663–693. <https://doi.org/10.1016/j.jpain.2009.04.001>
- Knezevic, N. N., Tverdohle, T., Knezevic, I., & Candido, K. D. (2018). The Role of Genetic Polymorphisms in Chronic Pain Patients. *International Journal of Molecular Sciences*, 19(6), 1707. <https://doi.org/10.3390/ijms19061707>
- Latremoliere, A., & Costigan, M. (2011). GCH1, BH4 and pain. *Current Pharmaceutical Biotechnology*, 12(10), 1728–1741. <https://doi.org/10.2174/138920111798357393>
- Latremoliere, A., Latini, A., Andrews, N., Cronin, S. J., Fujita, M., Gorska, K., Hovius, R., Romero, C., Chuaiphichai, S., Painter, M., Miracca, G., Babaniyi, O., Remor, A. P., Duong, K., Riva, P., Barrett, L. B., Ferreirós, N., Naylor, A., Penninger, J. M., Tegeder, I., Zhong J., Blagg J., Channon K. M., Johnsson K., Costigan M., Woolf, C. J. (2015). Reduction of Neuropathic and Inflammatory Pain through Inhibition of the Tetrahydrobiopterin Pathway. *Neuron*, 86(6), 1393–1406. <https://doi.org/10.1016/j.neuron.2015.05.033>
- Ma, G., Fan, H., Shen, C., & Wang, W. (2016). Genetic and Neuroimaging Features of Personality Disorders: State of the Art. *Neuroscience Bulletin*, 32(3), 286–306. <https://doi.org/10.1007/s12264-016-0027-8>
- Mackey S. (2016). Future Directions for Pain Management: Lessons from the Institute of Medicine Pain Report and the National Pain Strategy. *Hand Clinics*, 32(1), 91–98. <https://doi.org/10.1016/j.hcl.2015.08.012>
- Majeed, M. H., Ubaidulhaq, M., Rugnath, A., & Eriator, I. (2018). Extreme Ends of Pain Sensitivity in SCN9A Mutation Variants: Case Report and Literature Review. *Innovations in Clinical Neuroscience*, 15(11-12), 33–35.
- Manzoni, C., Kia, D. A., Vandrovicova, J., Hardy, J., Wood, N. W., Lewis, P. A., & Ferrari, R. (2018). Genome, transcriptome and proteome: the rise of omics data and their integration in biomedical sciences. *Briefings in Bioinformatics*, 19(2), 286–302. <https://doi.org/10.1093/bib/bbw114>
- Marcianò, G., Vocca, C., Evangelista, M., Palleria, C., Gallelli, L., Galati, C., Monea, F., Sportiello, L., De Sarro, G., Capuano, A., & Gallelli, L. (2023). The Pharmacological Treatment of Chronic Pain: From guidelines to daily clinical practice. *Pharmaceutics*, 15(4), 1165. <https://doi.org/10.3390/pharmaceutics15041165>
- Margoob, M. A., & Mushtaq, D. (2011). Serotonin transporter gene polymorphism and psychiatric disorders: Is there a link? *Indian Journal of Psychiatry*, 53(4), 289. <https://doi.org/10.4103/0019-5545.91901>
- Margoob, M. A., Mushtaq, D., Murtza, I., Mushtaq, H., & Ali, A. (2008). Serotonin transporter gene polymorphism and treatment response to serotonin reuptake inhibitor (escitalopram) in depression: An open pilot study. *Indian Journal of Psychiatry*, 50(1), 47. <https://doi.org/10.4103/0019-5545.39759>
- McInnes, G., Lavertu, A., Sangkuhl, K., Klein, T. E., Whirl-Carrillo, M., & Altman, R. B. (2021). Pharmacogenetics at Scale: An Analysis of the UK Biobank. *Clinical Pharmacology and Therapeutics*, 109(6), 1528–1537. <https://doi.org/10.1002/cpt.2122>
- Micaglio, E., Locati, E. T., Monasky, M. M., Romani, F., Heilbron, F., & Pappone, C. (2021). Role of Pharmacogenetics in Adverse Drug Reactions: An Update towards Personalized Medicine. *Frontiers in Pharmacology*, 12, 651720. <https://doi.org/10.3389/fphar.2021.651720>

- Mittal, D., Mease, R., Kuner, T., Flor, H., Kuner, R., & Andoh, J. (2022). Data management strategy for a collaborative research center. *GigaScience*, 12, giad049. <https://doi.org/10.1093/gigascience/giad049>
- Nagatsu T. (2007). The catecholamine system in health and disease - Relation to tyrosine 3-monooxygenase and other catecholamine-synthesizing enzymes. *Proceedings of the Japan Academy (Series B): Physical and Biological Sciences*, 82(10), 388–415. <https://doi.org/10.2183/pjab.82.388>
- Nahin, R. L., Feinberg, T., Kapos, F. P., & Terman, G. W. (2023). Estimated Rates of Incident and Persistent Chronic Pain Among US Adults, 2019–2020. *JAMA Network Open*, 6(5), e2313563. <https://doi.org/10.1001/jamanetworkopen.2023.13563>
- Navratilova, E., & Porreca, F. (2019). Substance P and inflammatory pain: getting it wrong and right simultaneously. *Neuron*, 101(3), 353–355. <https://doi.org/10.1016/j.neuron.2019.01.034>
- Nekovářová, T., Yamamotová, A., Valeš, K., Stuchlík, A., Fricová, J., & Rokyta, R. (2014). Common mechanisms of pain and depression: are antidepressants also analgesics? *Frontiers in Behavioral Neuroscience*, 8, 99. <https://doi.org/10.3389/fnbeh.2014.00099>
- Nyorong, M., Nadapdap, T. P., & Yanthy, L. (2021). Analysis of Factors Associated with Compliance with Taking Medicines for Pulmonary Tuberculosis Patients at Lut Tawar Health Center, Central Aceh Regency. *Journal of Asian Multicultural Research for Medical and Health Science Study*, 2(4), 82–94. <https://doi.org/10.47616/JAMRMHSS.V2I4.222>
- Oates, J. T., & Lopez, D. (2018). Pharmacogenetics: An Important Part of Drug Development with A Focus on Its Application. *International Journal of Biomedical Investigation*, 1(2), 111. <https://doi.org/10.31531/2581-4745.1000111>
- Obata, H. (2017). Analgesic Mechanisms of Antidepressants for Neuropathic Pain. *International Journal of Molecular Sciences*, 18(11), 2483. <https://doi.org/10.3390/ijms18112483>
- Paredes, S., Cantillo, S., Candido, K. D., & Knezevic, N. N. (2019). An Association of Serotonin with Pain Disorders and Its Modulation by Estrogens. *International Journal of Molecular Sciences*, 20(22), 5729. <https://doi.org/10.3390/ijms20225729>
- Pathan, H., & Williams, J. (2012). Basic opioid pharmacology: an update. *British Journal of Pain*, 6(1), 11–16. <https://doi.org/10.1177/2049463712438493>
- Porter, G. A., & O'Connor, J. C. (2022). Brain-derived neurotrophic factor and inflammation in depression: Pathogenic partners in crime? *World Journal of Psychiatry*, 12(1), 77–97. <https://doi.org/10.5498/wjp.v12.i1.77>
- Prescott, S. A., & Ratté, S. (2017). Somatosensation and pain. In Elsevier eBooks (pp. 517–539). <https://doi.org/10.1016/b978-0-12-802381-5.00037-3>
- Porcelli, S., Drago, A., Fabbri, C., Gibiino, S., Calati, R., & Serretti, A. (2011). Pharmacogenetics of antidepressant response. *Journal of Psychiatry & Neuroscience*, 36(2), 87–113. <https://doi.org/10.1503/jpn.100059>
- Radosavljević, M., Štrac, D. Š., Jančić, J., & Samardžić, J. (2023). The role of pharmacogenetics in personalizing the antidepressant and anxiolytic therapy. *Genes*, 14(5), 1095. <https://doi.org/10.3390/genes14051095>
- Raja, K., Patrick, M., Gao, Y., Madu, D., Yang, Y., & Tsoi, L. C. (2017). A Review of Recent Advancement in Integrating Omics Data with Literature Mining towards Biomedical Discoveries. *International Journal of Genomics*, 2017, 6213474. <https://doi.org/10.1155/2017/6213474>
- Sanchez-Martinez, S., Camara, O., Piella, G., Cikes, M., González-Ballester, M. Á., Miron, M., Vellido, A., Gómez, E., Fraser, A. G., & Bijmens, B. (2022). Machine Learning for Clinical Decision-Making: Challenges and Opportunities in Cardiovascular Imaging. *Frontiers in Cardiovascular Medicine*, 8, 765693. <https://doi.org/10.3389/fcvm.2021.765693>
- Scarborough, B. M., & Smith, C. B. (2018). Optimal pain management for patients with cancer in the modern era. *CA: A Cancer Journal for Clinicians*, 68(3), 182–196. <https://doi.org/10.3322/caac.21453>
- Shaw, K., Amstutz, U., & Carleton, B. C. (2011). Using pharmacogenetics to understand adverse drug reactions in children. *Paediatrics & Child Health*, 16(9), 537–538. <https://doi.org/10.1093/pch/16.9.537>
- Sheng, J., Liu, S., Wang, Y., Cui, R., & Zhang, X. (2017). The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. *Neural Plasticity*, 2017, 9724371. <https://doi.org/10.1155/2017/9724371>
- Sprouse-Blum, A. S., Smith, G., Sugai, D., & Parsa, F. D. (2010). Understanding endorphins and their importance in pain management. *Hawaii Medical Journal*, 69(3), 70–71.

- Su, D., Singer, E. A., & Srinivasan, R. (2015). Molecular pathways in renal cell carcinoma: recent advances in genetics and molecular biology. *Current Opinion in Oncology*, 27(3), 217–223. <https://doi.org/10.1097/CCO.000000000000186>
- Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. *Cold Spring Harbor Perspectives in Biology*, 6(10), a016295. <https://doi.org/10.1101/cshperspect.a016295>
- Tanguay-Sabourin, C., Fillingim, M., Guglietti, G. V., Zare, A., Parisien, M., Norman, J., Sweatman, H., Da-Ano, R., Heikkala, E., PREVENT-AD Research Group, Perez, J., Karppinen, J., Villeneuve, S., Thompson, S. J., Martel, M. O., Roy, M., Diatchenko, L., & Vachon-Preseau, E. (2023). A prognostic risk score for development and spread of chronic pain. *Nature Medicine*, 29, 1821–1831. <https://doi.org/10.1038/s41591-023-02430-4>
- Taqi, M. M., Faisal, M., & Zaman, H. (2019). OPRM1 A118G Polymorphisms and Its Role in Opioid Addiction: Implication on Severity and Treatment Approaches. *Pharmacogenomics and Personalized Medicine*, 12, 361–368. <https://doi.org/10.2147/PGPM.S198654>
- Taylor, C., Crosby, I., Yip, V., Maguire, P., Pirmohamed, M., & Turner, R. M. (2020). A Review of the Important Role of CYP2D6 in Pharmacogenomics. *Genes*, 11(11), 1295. <https://doi.org/10.3390/genes11111295>
- Teleanu, R. I., Niculescu, A. G., Roza, E., Vladăncenco, O., Grumezescu, A. M., & Teleanu, D. M. (2022). Neurotransmitters-Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. *International Journal of Molecular Sciences*, 23(11), 5954. <https://doi.org/10.3390/ijms23115954>
- Trang, A., & Khandhar, P. B. (2023). Physiology, Acetylcholinesterase. In *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK539735/>
- Tunbridge E. M. (2010). The catechol-O-methyltransferase gene: its regulation and polymorphisms. *International Review of Neurobiology*, 95, 7–27. <https://doi.org/10.1016/B978-0-12-381326-8.00002-8>
- Ventola C. L. (2013). Role of pharmacogenomic biomarkers in predicting and improving drug response: part 1: the clinical significance of pharmacogenetic variants. *Pharmacy and Therapeutics*, 38(9), 545–560.
- Walczak-Nowicka, Ł. J., & Herbet, M. (2021). Acetylcholinesterase Inhibitors in the Treatment of Neurodegenerative Diseases and the Role of Acetylcholinesterase in their Pathogenesis. *International Journal of Molecular Sciences*, 22(17), 9290. <https://doi.org/10.3390/ijms22179290>
- Wilke, R. A., Lin, D. W., Roden, D. M., Watkins, P. B., Flockhart, D., Zineh, I., Giacomini, K. M., & Krauss, R. M. (2007). Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. *Nature reviews. Drug Discovery*, 6(11), 904–916. <https://doi.org/10.1038/nrd2423>
- Wyns, A., Hendrix, J., Lahousse, A., De Bruyne, E., Nijs, J., Godderis, L., & Polli, A. (2023). The Biology of Stress Intolerance in Patients with Chronic Pain-State of the Art and Future Directions. *Journal of Clinical Medicine*, 12(6), 2245. <https://doi.org/10.3390/jcm12062245>
- Xiang, C., Cong, S., Liang, B., & Cong, S. (2020). Bioinformatic gene analysis for potential therapeutic targets of Huntington's disease in pre-symptomatic and symptomatic stage. *Journal of Translational Medicine*, 18(1), 388. <https://doi.org/10.1186/s12967-020-02549-9>
- Yam, M. F., Loh, Y. C., Tan, C. S., Khadijah Adam, S., Abdul Manan, N., & Basir, R. (2018). General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. *International Journal of Molecular Sciences*, 19(8), 2164. <https://doi.org/10.3390/ijms19082164>
- Yang, S., & Chang, M. C. (2019). Chronic Pain: Structural and Functional Changes in Brain Structures and Associated Negative Affective States. *International Journal of Molecular Sciences*, 20(13), 3130. <https://doi.org/10.3390/ijms20133130>
- Young, E. E., Lariviere, W. R., & Belfer, I. (2012). Genetic basis of pain variability: recent advances. *Journal of Medical Genetics*, 49(1), 1–9. <https://doi.org/10.1136/jmedgenet-2011-100386>
- Zhao, F., Cheng, Z., Piao, J., Cui, R., & Li, B. (2022). Dopamine receptors: Is it possible to become a therapeutic target for depression? *Frontiers in Pharmacology*, 13, 947785. <https://doi.org/10.3389/fphar.2022.947785>
- Zhao, S. J., Zhou, W., Chen, J., Luo, Y. J., & Yin, G. Y. (2018). Bioinformatics analysis of the molecular mechanisms underlying traumatic spinal cord injury. *Molecular Medicine Reports*, 17(6), 8484–8492. <https://doi.org/10.3892/mmr.2018.8918>
- Zieglgänsberger W. (2019). Substance P and pain chronicity. *Cell and Tissue Research*, 375(1), 227–241. <https://doi.org/10.1007/s00441-018-2922-y>
- Zięba, A., Matosiuk, D., & Kaczor, A. A. (2023). The role of genetics in the development and pharmacotherapy of depression and its impact on drug discovery. *International Journal of Molecular Sciences*, 24(3), 2946. <https://doi.org/10.3390/ijms24032946>