UNIT 9 - PHARMACOGENOMICS

Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev

Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

Unit 9 Contents

Attribution

9.1 UNIT OVERVIEW

Learning Objectives

- Describe how genetic differences influence drug responses.
- Explain the clinical significance of pharmacogenomic testing.
- Explore resources to aid in translating genetic test results into actionable decisions.
- Connect genomic data to real-world applications in drug therapy.
- Describe the limitations of pharmacogenomic testing.

Outline

Topics covered in this chapter include:

- Pharmacogenomics overview
- Genomic variation in drug response
- Personalized drug therapy
- Limitations of pharmacogenomic testing

Competencies Nurses will Develop in this Chapter

ANA (2023):

Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential

environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

Identification:

- Identifies credible, accurate, appropriate, and current genomic information, resources, services, and technologies specific to given clients.

Provision of education, care, and support:

- Performs interventions appropriate to clients' genomic health care needs.

NHS (2023):

Identify individuals who might benefit from genomic services and information as part of assessing needs and planning care:

- recognizing the critical indicators of a potential genetic condition or clinical situation where genomics-informed healthcare would be appropriate.

Demonstrate knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

Apply knowledge, understanding and context of genomic testing and information to underpin care and support for individuals and families before, during and following decision-making:

- including types, uses and limitations of genomic tests to prevent, predict or treat a health condition, and an awareness of the processes for testing and return of results

Obtain and communicate reliable, current information about genomics for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so; and
- applying critical appraisal skills to assess the quality of information accessed.

Key terminology

Haplotype

A combination of multiple nucleotide changes within a particular gene. Please note that this term can have other meanings.

Pharmacogenomics

The study of how variation across the genome influences drug response. This term is often used interchangeably with pharmacogenetics or abbreviated to "PGx."

Star allele

A method of labeling haplotypes in genes (e.g. *2, *3 etc.). Star allele definitions can be found at PharmVar.

Attribution & References

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- Pharmacogenomics Glossary by PharmGKB, CC BY-SA 4.0

References

American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

National Health Service (NHS). (2023). *The 2023 genomic competency framework for UK nurses*. https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2023/12/2023-Genomic-Competency-Framework-for-UK-Nurses.pdf

9.2 PHARMACOGENOMICS OVERVIEW

Understanding Pharmacogenomics

The sequence of one's genome can determine how they respond to certain medications? Understanding **pharmacogenomics**, or tailoring a person's medications based on their genome, is only possible by sequencing the genomes of many people and comparing their responses to medicines.

Recall from pharmacology classes that in order for the human body to use some medicines properly (pharmacodynamics), the drug must be distributed to the tissues where it will exert its action and metabolized into an active form. If we want to ensure this happens, it makes sense to target the pathways of our bodies that involve changing the medicine's form or getting medication to the right places. For example, you probably know someone who takes an antidepressant. Many of these medicines get to the right places by interacting with a protein called ABCB1 (http://www.genecards.org/cgi-bin/carddisp.pl?gene=ABCB1), which works like a traffic cop outside your cells. In this analogy, the "traffic" is the movement of drugs into, within, and out of cells, and their distribution to target tissues. This represents the pharmacokinetics (ADME). ABCB1 is a transporter protein that regulates the flow of certain drugs across cell membranes.

Given ABCB1's important role in controlling traffic, you might imagine that if someone has a genomic variant that changes the shape or function of their ABCB1 protein, they might have a different response than usual to any number of medicines. We now know that is the case for some antidepressants, as well as other medications (https://www.pharmgkb.org/gene/PA267/clinicalAnnotation) like statins for cholesterol and certain chemotherapy medicines. As a result, at least 18 pharmacogenomic tests for variants in *ABCB1* are listed in the NIH's Genetic Test Registry (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5243%5Bgeneid%5D), suggesting that you be tested for these variants to help determine the correct dose for certain medications.

Concept in Action

Concept in Action (text version)
Watch Pharmacogenomics: The Right Drug, for the Right Patient, at the Right Dose (2 mins) on YouTube (https://youtu.be/WSf6vyP11aQ) for an overview of how pharmacogenomics helps to tailor drug treatments.

Watch Introduction to Pharmacogenomics (10 mins) on YouTube (https://youtu.be/

lM7j1v5PInc) from the Pharmacogenomics Knowledgebase (PharmGKB), an NIH-funded resource.

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9.3 GENOMIC VARIATION IN DRUG RESPONSE

Genetic variation affects whether a patient reacts badly to a medicine or how well a patient responds to a medicine by changing a drug's pharmacokinetics (https://www.pharmgkb.org/page/glossary#pharmacokinetics) and pharmacodynamics (https://www.pharmgkb.org/page/glossary#pharmacodynamics). Genetic variation in genes encoding proteins involved in a drug's pharmacokinetics can alter how a drug is metabolized. If a drug is metabolized too quickly, it might be less effective. Alternatively, if the drug is metabolized too slowly, it may build up in the body and cause dangerous side effects.

Genes involved in a drug's pharmacodynamics can encode proteins that the drug may need to bind to to affect the body. Genetic variation can change the structure of a protein, affecting how well the drug binds to the protein. This can change how well the drug works.

Below, find out more about how variation in different types of genes can affect pharmacokinetics and pharmacodynamics:

Drug transporters

Transporters move molecules in and out of cells. Variation in genes encoding drug transporters can affect their function, changing how well drugs can enter or exit cells and increasing or decreasing drug concentrations in different body parts. If the concentration of the drug at the site of action is too low, the drug may not work as well. If the drug concentration becomes too high, it could cause toxic side effects.

Examples on PharmGKB: *SLCO1B1, (https://www.pharmgkb.org/gene/PA134865839) ABCB1 (https://www.pharmgkb.org/gene/PA267), ABCG2 (https://www.pharmgkb.org/gene/PA390)*

Drug metabolizing enzymes

Variations in drug-metabolizing enzymes can affect how quickly a drug is broken down in the body. This can have different effects depending on the specific drug. If an active drug is metabolized too quickly, it will be inactivated too quickly and may not work well. If it is metabolized too slowly, toxic concentrations of the

drug might build up. Alternatively, some drugs have to be metabolized to become active. For medications like these, being metabolized too quickly increases the concentrations of active molecules in the body and increases the risk of toxic side effects while being metabolized too slowly can reduce how effective the drug is.

Examples on PharmGKB: *CYP2C9 (https://www.pharmgkb.org/gene/PA126), CYP2D6 (https://www.pharmgkb.org/gene/PA128), CYP2C19 (https://www.pharmgkb.org/gene/PA124), CYP3A5 (https://www.pharmgkb.org/gene/PA131), TPMT (https://www.pharmgkb.org/gene/PA356), UGT1A1 (https://www.pharmgkb.org/gene/PA420)*

Human leukocyte antigen (HLA) genes

HLA proteins form part of your immune system. Some HLA alleles are associated with an increased risk for an allergic response to certain medications, which can result in severe skin reactions such as Stevens-Johnson syndrome (SJS) (https://www.pharmgkb.org/disease/PA445738) or toxic epidermal necrolysis (TEN) (https://www.pharmgkb.org/disease/PA444059).

Examples on PharmGKB: *HLA-A (https://www.pharmgkb.org/gene/PA35055), HLA-B (https://www.pharmgkb.org/gene/PA35056)*

Drug targets

Variations in genes coding for proteins which are drug targets can affect how well a drug works by altering the amount of the target protein in the body or by preventing the drug from being able to bind to the protein. For example, the anti-coagulant drug warfarin prevents the vitamin K recycling needed for blood clotting. Warfarin does this by blocking the protein that controls the recycling (VKORC1). Genetic variation that increases or decreases the amount of VKORC1 can affect the dose of warfarin needed to prevent blood clotting.

Examples on PharmGKB: *VKORC1 (https://www.pharmgkb.org/gene/PA133787052), CFTR (https://www.pharmgkb.org/gene/PA109)*

Most work in pharmacogenomics focuses on variation in DNA that is passed down through your family

(germline variation (https://www.pharmgkb.org/page/glossary#germline-variation)). However, somatic variation is also important within pharmacogenomics. Somatic variations are genetic changes that arise spontaneously within cells but are only passed on to other cells and are not passed on to children. Somatic variation is involved in the development of cancer, and some anticancer drugs target specific somatic variations to try to treat the cancer.

Concept in Action

Review this module, Making SNPs Make Sense, (https://learn.genetics.utah.edu/content/precision/snips/) to learn how single nucleotide polymorphisms (SNPs), which we learned about in an earlier unit, related to pharmacogenomics.

Read

Saunders, H., Harris, D., & Chirilă, R. M. (2020). Pharmacogenomics: introduction and use in clinical practice. *Romanian Journal of Internal Medicine*, *58*(2), 69-74. https://doi.org/10.2478/rjim-2020-0001

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Attribution & References

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- What is Pharmacogenomics by PharmGKB, CC BY-SA 4.0

References

Whirl-Carrillo, M., Huddart, R., Gong, L., Sangkuhl, K., Thorn, C. F., Whaley, R., & Klein, T. E. (2021). An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clinical Pharmacology and Therapeutics.* https://doi.org/10.1002/cpt.2350

9.4 PERSONALIZED DRUG THERAPY

Clinical Implications of Pharmacogenomics

What is CPIC®?

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) (http://www.ncbi.nlm.nih.gov/pubmed/?term=21270786)is an international consortium of individual volunteers and a small dedicated staff interested in facilitating pharmacogenetic test use for patient care.

One barrier to implementing pharmacogenetic testing in the clinic is translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

CPIC® aims to address this barrier to the clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (visit their website to view all CPIC® publications (https://cpicpgx.org/publications/)). CPIC® guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology (https://www.ncbi.nlm.nih.gov/pubmed/27441996), are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics (http://www.nature.com/clpt/index.html)) with simultaneous posting to cpicpgx.org, where they are regularly updated.

CPIC® started as a shared project between PharmGKB (https://www.pharmgkb.org/) and the Pharmacogenomics Research Network (PGRN) (http://www.pgrn.org/)in 2009. CPIC® guidelines are indexed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) as clinical guidelines, endorsed (https://cpicpgx.org/endorsements/) by ASHP (https://www.ashp.org/Pharmacy-Practice/Policy-Positions-and-Guidelines/Browse-by-Document-Type/Endorsed-Documents) and ASCPT (https://www.ascpt.org/Resources/Knowledge-Center/Tools-and-resources), and referenced in ClinGen (https://www.clinicalgenome.org/) and PharmGKB (http://www.pharmgkb.org/).

Guidelines

Figure 9.1 Pills. Photo by Myriam Zilles, Unsplash license

CPIC (https://cpicpgx.org/)® (http://www.ncbi.nlm.nih.gov/pubmed/?term=21270786) guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A fundamental assumption underlying the CPIC® guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. Several professional societies have endorsed CPIC®'s guidelines, processes and projects.

Each CPIC® guideline adheres to a standard format and includes a standard system for grading levels of evidence linking genotypes to phenotypes (https://cpicpgx.org/levels-of-evidence/), how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation (https://cpicpgx.org/strength-of-recommendations/).

Exploring CPIC® Guidelines

Visit the CPIC® Guidelines website (https://cpicpgx.org/guidelines/). Under the *Drugs* column, select a drug you provide frequently in clinical practice and explore the associated genes and guidelines. For example, the *CYP2D6* gene is common in several medication pathways, including those for opioids, SSRIs, TCAs, beta-blockers, and more. Variants in this gene can significantly impact how individuals metabolize many medications.

The PharmGKB YouTube channel (https://www.youtube.com/@PharmgkbOrg) has brief videos summarizing CPIC® guidelines for various drugs and genes.

Examples of Pharmacogenomics in Clinical Practice

Avoiding adverse drug effects

Healthcare professionals and researchers constantly seek to optimize medical treatments and avoid adverse reactions to treatments, which are estimated to affect between 7 percent and 14 percent of hospitalized patients. This makes adverse reactions a significant cause of added days (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm#ADRs:%20Prevalence%20and%20Incidence) spent in a hospital and the fourth leading cause of death in the United States.

Stevens-Johnson syndrome

One example of such an adverse reaction is Stevens-Johnson syndrome (SJS), a severe allergic reaction also called "scalded skin syndrome." It can be caused by infections and very common medications like ibuprofen, anti-seizure medicines, or antibiotics. Patients may go from taking two pain pills to ending up in the hospital burn unit fighting for their lives (http://www.nbcnews.com/id/42501090/ns/health-health_care/t/worst-side-effect-youve-never-heard/) if SJS progresses to a worse condition called toxic epidermal necrolysis (TEN). TEN is diagnosed when patients shed at least one-third of their skin off their bodies. Needless to say, anything we can do to prevent this allergic reaction is vitally important.

In Taiwan, married scientists Wen-Hung Chung (a physician) and Shuen-Iu Hung (an immunologist) noticed that SJS/TEN was much more common in patients taking carbamazepine, used to treat epilepsy and seizures, or allopurinol, used to treat gout. They showed that this was due to genomic variants in the *HLA-B* gene (https://ghr.nlm.nih.gov/condition/stevens-johnson-syndrome-toxic-epidermal-necrolysis#genes). Not surprisingly, this gene helps control the immune response. As a result of their work, the country of Thailand has implemented genomic testing (https://www.theatlantic.com/science/archive/2015/10/south-east-asia-genetic-disorder-stevens-johnson-syndrome/408736/) before these medications are prescribed. The results of this "pharmacogenomic test" are used to decide whether it is safe to give a specific patient certain medicines, like carbamazepine or allopurinol. Thailand's government even covers the cost of this testing, and the frequency of SJS/TEN has been drastically reduced. We have since learned that different ancestries are associated with different *HLA-B* genomic variants, so countries may need different approaches (https://www.genome.gov/27560487/research-directions-in-geneticallymediated-stevensjohnson-syndrometoxic-epidermal-necrolysis//research-directions-in-geneticallymediated-stevensjohnson-syndrometoxic-epidermal-necrolysis/) to monitor which medications are most likely to be linked to SJS/TEN.

Concept in Action

Watch Pharmacogenomic Testing – Karen's story (3 mins) on YouTube (https://youtu.be/TVZVehYWLYw) for a personal story of Karen's experience with SJS.

Mercaptopurine

Although the field is still young, doctors already use pharmacogenomics to treat their patients. Acute lymphoblastic leukemia (ALL) is a type of cancer that mainly affects children and is often treated with the medicine mercaptopurine (https://www.pharmgkb.org/chemical/PA450379).

Children with certain genetic changes in the gene *TPMT* can have a severe reaction to this drug. Doctors will often test for these changes, and if they are present, will give the child a lower dose of mercaptopurine or use a different medicine.

Mercaptopurine belongs to a class of medicines called thiopurines. It is broken down in the body by several proteins, some of which convert mercaptopurine to active molecules that help kill cancer cells. Mercaptopurine is also broken down by a protein called TPMT, encoded for by the *TPMT* gene.

When TMPT breaks down mercaptopurine, it is inactivated. This inactivation prevents dangerous concentrations of active molecules from building up. Changes in the *TPMT* gene, such as the haplotypes *2, *3A or *3C, can reduce or stop the inactivation of mercaptopurine by the TPMT protein. This causes too many active molecules to build up in the body and can lead to a severe decrease in immune system activity, known as myelosuppression. Myelosuppression can be fatal.

Testing for *TPMT* variants is widely available: the Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) provides over 20 laboratories currently offering this test. In Europe, testing before administration of thiopurines is becoming routine clinical practice – a survey in the United Kingdom found that 67% of clinicians ordered a *TPMT* test before prescribing azathioprine, another drug that is broken down by TPMT.

In the United Kingdom, testing for TPMT status is mandatory for children and young adults before treatment on the ALL2011 trial protocol, and the British Association of Dermatologists guidelines for the safe and effective prescribing of azathioprine states that TPMT activity should be checked in all patients before receiving azathioprine. The Clinical Pharmacogenetics Implementation Consortium (CPIC®) has also provided dosing guidance (https://www.pharmgkb.org/guidelineAnnotation/PA166104945) based on the *TPMT* genotype for thiopurines.

Tamoxifen

We have also learned that a person's genome sequence is not everything regarding

medication responses. The human body is a highly complex machine, and the instructions written in our DNA are just part of the process.

There are some cases, as with the breast cancer treatment tamoxifen, where a small study showed that there might be a relationship between someone's response to the medicine and a variant in the *CYP2D6* gene. However, this finding did not appear true in a larger study involving many more people. That's why, at this time, the U.S. Food and Drug Administration (FDA) labelling for tamoxifen does not recommend *CYP2D6* pharmacogenomic testing. However, the issue is still being reviewed (https://www.ncbi.nlm.nih.gov/books/NBK247013/) as more research is conducted.

Another gene in the same *CYP* family, called *CYP2C19*, has variations which affect how your body can use clopidogrel (https://www.pharmgkb.org/chemical/PA449053) (more commonly known as Plavix), an anticoagulant to prevent blood clots, and thus reduce the risk of stroke heart attack. If an individual has a variant causing malfunction of the *CYP2C19* protein, they cannot process clopidogrel (http://mayoresearch.mayo.edu/center-for-individualized-medicine/cyp2c19-clopidogrel.asp) and either require a different dose or a different medication. As it turns out, these variants in *CYP2C19* are also more common in those with Asian ancestry. Testing for variants in this gene is also not routinely recommended. However, individuals may wish to speak with their healthcare provider about the test if clopidogrel is prescribed, particularly if they have East Asian family members.

Pharmacokinetic and Pharmacodynamic Pathways

The PharmGKB website has excellent resources for examining the pharmacokinetic and pharmacodynamic pathways of various drugs and their pharmacogenomic associations. Below is an example of two commonly prescribed medications, Amitriptyline and Nortriptyline. Search the PharmGKB Pathways (https://www.pharmgkb.org/pathways) for other drugs of interest. For example, returning to our aminoglycoside ototoxicity example from an earlier unit, review the pathway and pharmacogenomic implications. (https://www.pharmgkb.org/pathway/PA166254101)

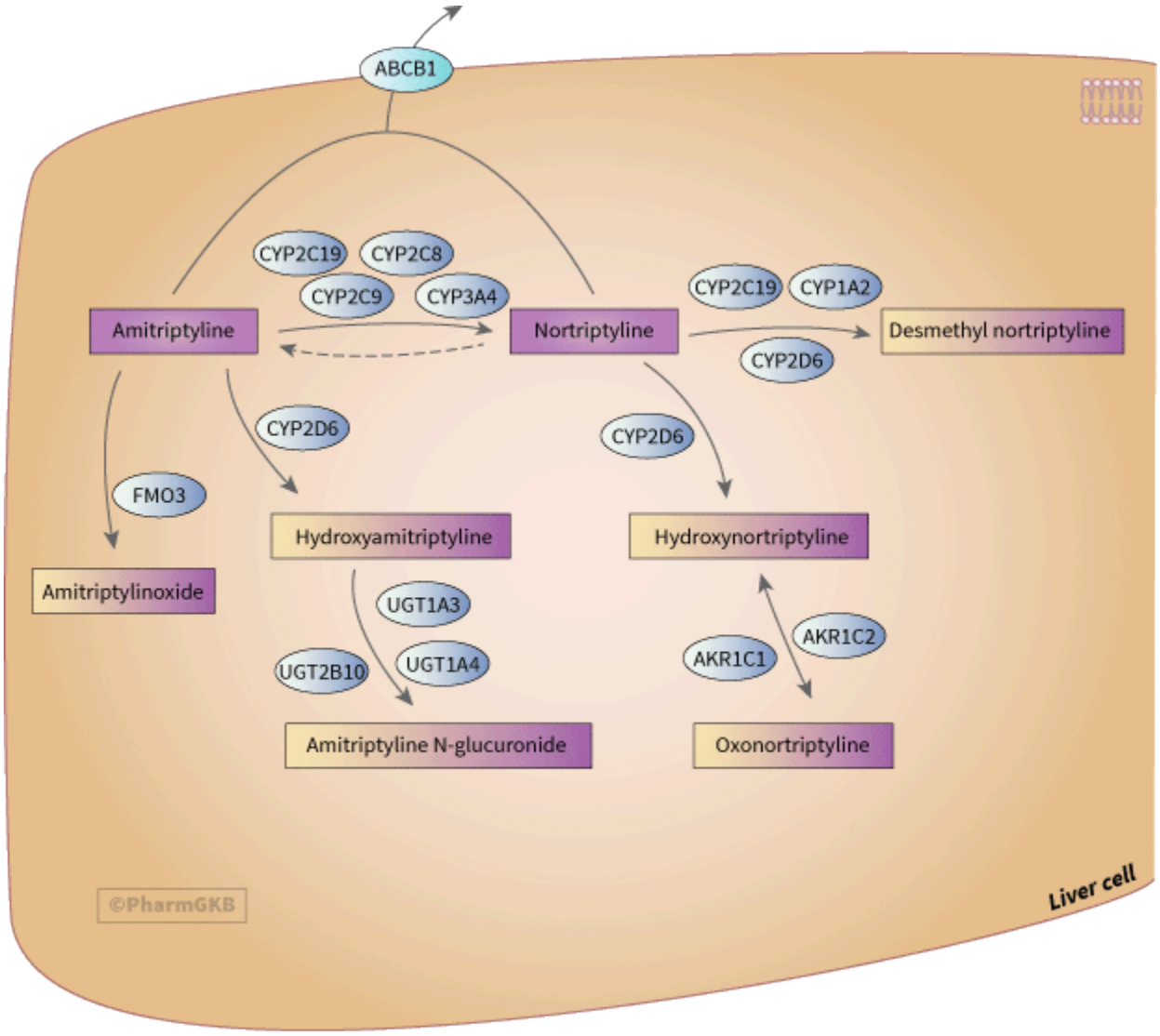

Figure 9.2 Representation of the candidate genes involved in the metabolism of amitriptyline and nortriptyline in the liver. View the diagram legend. **Source:** PharmGKB, CC BY-SA 4.0

Background

Amitriptyline and nortriptyline are tricyclic antidepressants initially designed for use in the treatment of depression. Amitriptyline is also used to treat various types of pain, such as fibromyalgia and neuropathic pain [Article:15554244 (https://www.pharmgkb.org/pmid/15554244)]. Nortriptyline is a metabolite of amitriptyline and a drug in its own right [Articles:15554244 (https://www.pharmgkb.org/pmid/15554244), 18359012 (https://www.pharmgkb.org/pmid/18359012)]. Both drugs are non-selective monoamine reuptake inhibitors, preventing the reuptake of norepinephrine and serotonin at nerve terminals via interaction with their respective transporters, *SLC6A2 (https://www.pharmgkb.org/gene/PA310)* and *SLC6A4 (https://www.pharmgkb.org/gene/PA312)*, and potentiating the action of these neurotransmitters. Additional effects and side effects occur due to cross-reactivity with opioid, cholinergic

and adrenergic receptors [Articles:8736630 (https://www.pharmgkb.org/pmid/8736630), 10319193 (https://www.pharmgkb.org/pmid/10319193)].

Metabolism

Amitriptyline and nortriptyline are readily absorbed in the GI tract and subject to extensive hepatic metabolism, with less than 5% of the drug eliminated unchanged (reviewed in [Article:10319193 (https://www.pharmgkb.org/pmid/10319193)]). The main metabolizing enzymes with clinical significance for amitriptyline are *CYP2C19 (https://www.pharmgkb.org/gene/PA124)* and *CYP2D6 (https://www.pharmgkb.org/gene/PA128)* [Articles:23486447 (https://www.pharmgkb.org/pmid/23486447), 27997040 (https://www.pharmgkb.org/pmid/27997040)]. *CYP2C19 (https://www.pharmgkb.org/gene/PA124)* is the primary enzyme responsible for demethylation at physiological concentrations, while *CYP2D6 (https://www.pharmgkb.org/gene/PA128)* carries out hydroxylation to less active metabolites [Articles:15554244 (https://www.pharmgkb.org/pmid/15554244), 18359012 (https://www.pharmgkb.org/pmid/18359012)]. Hydroxynortriptyline is the most abundant metabolite of both amitriptyline and nortriptyline in humans [Article:10319193 (https://www.pharmgkb.org/pmid/10319193)]. There are two enantiomers of hydroxynortriptyline and the E enantiomer is produced at a rate of around 5 times that of the Z enantiomer [Article:10319193 (https://www.pharmgkb.org/pmid/10319193)]. Methylation of nortriptyline to amitriptyline has been reported in vivo in some case studies. A study that examined metabolite and prescription data from an extensive network of medical centers for whom amitriptyline measurements were available found that approximately 15% of patients receiving nortriptyline had significant levels of amitriptyline (above 28ng/ml) despite not having received the parent drug [Article:16553509 (https://www.pharmgkb.org/pmid/16553509)]. The mechanism for methylation was not elucidated.

Pharmacogenomics

Many studies have examined variations in drug-metabolizing enzymes for their impact on amitriptyline and nortriptyline pharmacokinetics, with most focusing on *CYP2D6 (https://www.pharmgkb.org/gene/PA128)* and *CYP2C19 (https://www.pharmgkb.org/gene/PA124)*. CPIC guidelines are available for both *CYP2D6* and *CYP2C19* and amitriptyline [Article:23486447 (https://www.pharmgkb.org/pmid/23486447)]. Links to individual papers can be found under the PGx Research tab for amitriptyline and nortriptyline and clinical annotation summaries by haplotype under the Clinical PGx tab.

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  CPIC guidelines and content are subject to updates and modifications, and users should refer to cpicpgx.org to confirm they are accessing the most current content
- Amitriptyline and Nortriptyline Pathway, Pharmacokinetics by Carolyn F. Thorn, PharmGKB, CC BY-SA 4.0

9.5 LIMITATIONS OF PHARMACOGENOMIC TESTING

Star Allele System

Many key genes in pharmacogenomics use a 'star allele' (https://www.pharmgkb.org/page/glossary#star-allele) system, where a single star allele (e.g. *3) defines a certain combination of one or more genetic variants found together in that allele. You can find many of these definitions on the PharmVar website (https://www.pharmvar.org/). Genes can have many star alleles; the enzyme *CYP2C9 (https://www.pharmgkb.org/gene/PA126)*, for example, has over 60 known star alleles.'

Figure 9.3 A person shakes pills from a bottle into their hand. **Source:** Photo by Towfiqu barbhuiya, Unsplash license

Pharmacogenomic tests tend to only test for some of the most common star alleles, meaning that rare alleles will not be detected. Additionally, different tests may test for different alleles. For example, one test may test for the presence of the *2, *3, *5, *8 or *11 alleles of *CYP2C9,* while another may only test for *2 or *3.

If a person has a star allele not detected by the pharmacogenomic test, they default to the *1 allele, which is the 'reference' or 'normal' version of the gene. However, this does not mean that the person definitely has the *1 allele, and there is a significant possibility that they may carry a star allele, which could affect drug response, but the pharmacogenomic test does not detect that.

Some pharmacogenomic tests may test for the presence of a certain star allele by only looking for one particular change found in that star allele rather than all the changes which define the star allele. As some changes can be found in several different star alleles of the same gene, this can confuse which allele is actually present.

Finally, as pharmacogenomics research continues, new star alleles are found, while other star alleles may have their function assignment changed (e.g. an 'uncertain function' star allele may be changed to 'decreased function' based on new evidence). PharmVar is regularly updated with new star alleles and their functions as information becomes available.

To learn more about **star alleles**, **watch the video Haplotypes and Star Alleles (8 mins) on YouTube (https://youtu.be/PcmCohIhWUM)**

Attribution & References

9.6 UNIT SUMMARY AND REVIEW

Key Takeaways

Pharmacogenomics involves tailoring medications based on a person's genome, which influences drug response and susceptibility to adverse effects. This field relies on sequencing the genomes of many individuals to identify genetic variations that affect drug metabolism (pharmacokinetics) and drug-target interactions (pharmacodynamics). Examples include genomic variants that are linked to severe reactions like Stevens-Johnson syndrome. Guidelines from organizations like CPIC facilitate integrating genetic test results into clinical practice to optimize therapy. Challenges include translating test results into actionable recommendations and addressing variations in testing methods and allele detection.

Additional Optional Readings

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Attribution and References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com