Episode 3 - DNA& Drugs

Hannah: [00:00:00] This is DNA& and the podcast bringing you the latest science and innovation in DNA and our health.

Angelos: Hello and welcome to today's episode on DNA and drugs. In this episode, we will discuss how differences in our DNA can alter the effect that medicines have on our body. Stay tuned to find out how investigating our DNA can offer valuable insight and allow us to prescribe more precise, effective treatments and minimize unwanted side effects.

Welcome. We are your hosts. I'm Angelos.

Hannah: And I'm Hannah.

Angelos: And today we're discussing how differences in our DNA, or as mentioned in previous episodes, DNA variants can affect how drugs are processed by our body. And we're very excited that our guest today [00:01:00] is Dr. Emma Magavern, who works both clinically and in research of pharmacogenomics. So you'll hear more from her later in the episode.

Hannah: Today, we're looking at the natural variation in how people respond to medications, including how unwanted side effects can affect some people, but not others. We're also going to look at the biology behind these adverse reactions, and we're going to discuss the exciting application of research and how we can use DNA to predict and prevent such side effects.

Angelos: Not only that, we will also look at why some drugs just don't work for some people, but going back to the term adverse drug reactions, this term is used to describe unwanted side effects from taking medications and hospitalizations because of these side effects account for up to 16. 5 percent of all hospitalizations[1]. Now, there are different reasons for this, including drugs which react with other medications or even certain foods in your diet, different medical conditions and things like age and sex, but some of these [00:02:00] reactions are due to natural variation in our DNA.

Hannah: So, the effects of adverse drug reactions can pose significant burden to the NHS. And particularly with an aging population, right, because this population is taking more medications for more conditions. So financially, this is estimated to cost the NHS 530 million pounds annually in hospital admissions[2,3]. Although a recent study last year by researchers at the University

of Liverpool, they extrapolated and estimated that it's more like 2.2 billion pounds annually[1], which is huge. Yeah. So, it's a problem that needs a solution. The current prescription system has been designed in this one size fits all manner, but we now have the tools to understand how natural variation amongst people can sometimes lead to these drugs causing unwanted side effects or making them less effective. So, in order to understand this, we first need to look at how prescribed drugs are processed by our bodies. You can take medicinal drugs in different ways, the most common being oral, like a pill, or by injection. Of course, it might seem like our job is done once we've swallowed a pill or taken the injection, but it doesn't stop there. This is when our bodies get busy processing.

Angelos: Yes, that's absolutely right. [00:03:00] Since there is a lot of different substances that can enter our body, we have many different metabolic pathways suited for each one of them. A pathway is simply a series of chemical reactions that are happening in our body.

A good metaphor would be cooking. As you take the carrots, you need to peel them and chop them before eating them. In the case of drugs, we're talking about metabolic pathways, which will maybe break down the substance and use the products to build something else entirely.

Hannah: Yes, we like our drugs peeled, not with the skin on.

Angelos: Yeah.

Hannah: So these reactions, of course, need energy. But nature has found a nice way of reducing the energy required with what we call enzymes. Going back to the kitchen analogy, which I like very much, you can think of, I don't know, a peeler, like the enzyme, as it catalyzes the process of peeling, so it's quite important.

The key part here, and why this is all relevant for the DNA& podcast, is that enzymes are basically proteins. But, they're made from instructions in, you guessed it, our DNA.

Angelos: Yeah, and I really like the example of the [00:04:00] peeler because the name there is pretty boring. You're peeling, so you need a peeler. And it's the same with enzymes actually, so proteins that hydrolyze, they're called hydrolases. So it's a very boring name giving as well there.

Hannah: True. I just want to point out though that scientists are not always boring. There is a protein called Sonic the Hedgehog. And there's one called Pikachurin, so if you're a, Pikachurin, if you're a fan of Pokemon, it's because it catalyzes reaction in a lightning fast manner, like Pikachu.

Angelos: Yeah, um, it's actually one of the proteins I found significant in my models yesterday.

Hannah: Interesting.

Angelos: Pikachurin. Yeah, that's how I found out. I was like, what is this? Does it come from Pikachu? Yeah, it does.

Hannah: Yeah, scientists are nerds, what can I say?

Angelos: So, as you said, all these instructions are written in our DNA, therefore, differences in our DNA can sometimes lead to differences in how our body processes substances, including prescribed drugs.

It's also astonishing that in our bodies, there are at least 8,000 known enzymes catalyzing these chemical reactions[4]. And [00:05:00] there's a rough estimate of 1 billion chemical reactions happening in a single human cell every second. And these reactions may convert specific substances to more effective or ineffective compounds.

So, if you think about it, our bodies are basically chemical power plants with all the blueprints and the instructions written in our DNA.

Hannah: I like that! Very cool. Alright, so on the note of examples, so we've been talking about drugs which have different effects depending on your DNA. So an example would be codeine. And codeine is a widely used opioid painkiller. For context, so in 2017, 13% of the adult population was prescribed an opioid painkiller[5]. And codeine is the most popular. However, the codeine molecule is not actually the one that relieves the pain. So in our body, specifically our liver, needs to convert codeine to morphine, which is the active substance which relieves pain.

Angelos: Yeah, that's right. And in fact, only 5-10 percent of the codeine we take is converted to morphine. More than 80 percent of the drug is not [00:06:00] used basically[6]. On that note, we should talk a bit more about the liver, which is where most drugs are processed. However, just like in disease,

it's possible that some pieces of the machinery which process the drugs may not operate properly.

Hannah: Yes, I'm glad you brought up the liver because I actually, I study this in my daily job so it's my favourite organ to talk about.

Angelos: It's a very interesting organ and it does sound like a very interesting job. So the enzyme responsible for the conversion of codeine to morphine is called cytochrome P450 and it's the sixth member of the D sub family of the second family of cytochrome's P450 enzymes.

Hannah: What?

Angelos: I know, I know.

Hannah: I'm not going to ask you to say that again. Okay. So it's CYP 2D6, but we should call it CYP2D6 actually.

Angelos: CYP2D6 sounds fine.

Hannah: That's a bit more catchy.

Angelos: Very short.

Hannah: Yeah. So CYP2D6 is a very important player in the metabolism of drugs since it doesn't just convert codeine to morphine, but it also metabolizes [00:07:00] beta blockers, opioid analgesics like codeine and antidepressants such as paroxetine. [7]

Angelos: So, most people are normal metabolizers of codeine. This means that the average dose of codeine that is prescribed to them is enough to relieve their pain, but not high enough to cause any toxic side effects.

But some people are what we call poor metabolizers, and that's around 8 to 10 percent of the population.

Hannah: That's really high!

Angelos: Yeah, it's basically one out of ten people and others are what we call ultra fast metabolizers and that's more rare. It's only around one in a hundred

people. However, it can be more common in some groups of people from different ancestries.

Hannah: Oh, can I talk about the genetics?

Angelos: Yes, I can't stop you.

Hannah: I'm a geneticist, by the way, have I said?

Angelos: DNA detective.

Hannah: Yes, okay, listen to the previous episodes for that reference. So you said some people are what we call poor metabolizers, and this is because they have DNA variants in the gene, so the DNA which codes for CYP2D6, and it disrupts the CYP2D6, so you don't get a [00:08:00] functional copy.

The other interesting part is the ultra fast metabolizers. So, in their case, there's actually something called a DNA duplication. So the gene for CYP2D6 has been copied. So you'd usually inherit one copy from mum, one copy from dad, but somewhere there's been a duplication. So these people have a third copy. So they actually have 50 percent more of the enzyme than other people.

Angelos: Oh, I see. So continuing from the chemical power plant metaphor, it means they have 50 percent more manpower. Okay, but this is not necessarily good. See, poor metabolizers will convert less than 5 to 10 percent of codeine into morphine, which will effectively not be enough to offer any analgesic effect. However, ultra fast metabolizers will convert more than 5 to 10 percent of codeine to morphine. This means that even normally prescribed doses can lead to symptoms of morphine overdose. And this is particularly risky for children prescribed codeine after an operation, and that is why it's [00:09:00] no longer recommended.

Hannah: Right, so there there are guidelines on how codeine should be prescribed. The Clinical Pharmacogenetics Implementation Consortium states that for ultra fast metabolizers, clinicians should avoid certain medications, including codeine, because it can lead to this toxicity[6].

Angelos: Yeah, if we know how someone will respond to a drug based on their DNA, it is easier to prescribe the most effective drug and skip the ones that might cause toxicity. And as research into pharmacogenomics keeps unfolding, we find new genetic variants which influence drug efficacy. At the same time, we can start implementing a screening as a standard clinical practice, but this

should only be for genetic variants which we're certain have an influence on the drug. So before we dive any deeper, let's take a quick break and then when we're back, we'll chat about the strengths and limitations of implementing pharmacogenomics in clinical practice. So stay tuned.

Hannah: So let's talk about [00:10:00] implementing pharmacogenomics knowledge in clinical practice. So an example of this is the NHS new screening effort to identify newborns who are at risk of adverse responses to specific antibiotics.

Angelos: Ah yes, I've heard about this. For instance, gentamicin is very commonly prescribed to newborns with bacterial infections.

However, approximately 1 in 500 people in the UK are born with a small change in their DNA that can cause them to become susceptible to gentamicin toxicity[8,9].

Hannah: Yes, so to be specific, for these individuals, gentamicin can cause an abnormal development of the sensory hair cells in the inner ear. So, this unfortunately means that even after one standard dose of gentamicin, These individuals can potentially lose their hearing permanently.

Angelos: And this story involves mitochondria and involves evolution as well. So many, many, many, many years ago, we had cells with a nucleus and they merged with [00:11:00] bacteria and they made something like a pact. So it was, so you can stay here, but you have to give me energy. So that's how our cells, the eukaryotic cells evolved mitochondria the powerhouse of the cell. Now, antibiotics come in and antibiotics are very specific to fighting bacterial infections because they target the machinery of bacteria, but mitochondria used to be bacteria so small changes in the machinery of mitochondria will cause the gentamicin to identify mitochondria as bacteria[10] but these are not bacteria. These are part of our own cells. Yeah So this is how toxicity is manifesting.

Hannah: So i've got one more fact on the er on the topic of mitochondria so I'm hoping some of our listeners will be familiar with something called Star Wars. So the force is actually caused by midichlorians, which were inspired [00:12:00] by mitochondria. So there you go.

Angelos: So, we talked about gentamicin causing hearing loss in some individuals, but let's not panic. Gentamicin is an incredibly effective last line antibiotic which is mostly given to babies in intensive care units and saves many lives. This adverse reaction is incredibly rare.

Hannah: But, there are other antibiotics which can be used as an alternative. Therefore, it has been discussed that the NHS should start testing for the DNA variants by screening babies before they administer gentamicin, or another immunoglycoside antibiotic. But the cutting-edge advances here is a recent technology which can produce a really fast result, which is critical for patients in intensive care who need rapid treatment.

So the technology is called gene drive and can give back results about the DNA variant in 20 to 30 minutes and it has been provisionally approved by NICE[11] the national institute for healthcare and excellence And they determine which drugs and technologies are to be prescribed or used by the NHS.

Angelos: Okay, so let's [00:13:00] rewind Gentamicin induced hearing loss is a very important side effect, right? And that's an example of a DNA-drug interaction. But most of the time, we talk about drug-drug interactions. For example, opioids and antihistamines should not be taken together as they pose a respiratory hazard[12]. Oh, and also it's not just drugs, right? Certain foods, too, like grapefruit juice, which I love, shouldn't be taken with simvastatin[13]. That's a type of statin which are drugs that lower cholesterol. It more than doubles the levels of simvastatin in the blood if taken at the same time.

Hannah: Wow, but yeah, the conversation really needs to include DNA as well, because it's just as important as those drug-drug and drug-food interactions. So actually, we should highlight one really interesting study. So this one was published in The Lancet earlier this year, and they estimated that a single pharmacogenetic test, which looked at variation in just 12 genes, was able to reduce adverse drug reactions in the population by 30%, which is massive[14].

Angelos: And this is just 12 genes, you don't have to read the whole DNA, it's [00:14:00] pretty simple. And 30 percent is a, it's a huge decrease.

Hannah: So I guess a futuristic view of healthcare, such as with the newborn genome screen, which we discussed in the previous episode, would be that everyone would know their own genetic type, or a GP would know it, so they could look at your genetic information and use that to inform which medications they then prescribe you.

Angelos: Also, flying ambulances.

Hannah: Pardon? What the?

Angelos: Because you talk about a futuristic view of healthcare.

Hannah: That's so random.

So we're very excited to welcome Dr. Emma Magavern onto the podcast. So Emma is a clinical research fellow at Queen Mary University of London. In the center of clinical pharmacology and precision medicine. So Emma, you were co secretary of a pretty important report on pharmacogenomics and personalized prescribing, which was published last year by the Royal College of Physicians and the British Pharmacological Society. So we're very grateful to have you on the podcast [00:15:00] today to share some insight.

Emma: Thank you so much for the invitation Hannah.

Angelos: So Emma, can you tell us a bit about your background and maybe about pharmacogenomics from your perspective?

Emma: So I'm a clinician and because of that I'm really interested in what we all know from daily experience that different people can respond in really different ways to the same medication and some people might not get the benefit, unfortunately, that they hope for when they take a medicine, and some people also can unfortunately suffer from side effects. So our mission as prescribers is really to try to get the best ratio there between risk and benefit, the highest chance of getting a benefit from a medicine with the lowest risk of having a harmful or unpleasant reaction.

And the thing that makes genetics really important here Is that we know that there are common genetic markers that can help us to see who might be more likely to benefit or not from a medication and who might have a very high risk of a bad reaction.

Hannah: That's really interesting. Could you give us some examples?[00:16:00]

Emma: So one example in clinical practice that is quite useful because everyone does it now, is a medication for HIV, for human immunodeficiency virus, and it's called abacavir. So medications have really changed the meaning of living with HIV and help a lot of people. But some people used to rarely have a really severe, bad reaction to this medication, abacavir, and it could be life threatening. So it was really a serious concern. But because the genetic marker was found that could predict risk of this severe reaction now if someone needs to be started on the medication, they can have this gene checked, and then if they have a genetic risk for this severe reaction, they're prescribed a different medication, so we've got all that benefit, but made it safer[15]. And another

example is testing of, a gene that can make an enzyme responsible for breaking down some cancer medications. So we now check for several genetic variants in the UK. And if people [00:17:00] have that genetic risk, for a bad reaction to that medication in the gene, then we don't give it to them. Therefore, again, it's safer now[16].

Angelos: That's very interesting. And I was completely unaware of the HIV case. And we've shared a few examples where DNA can influence how medications work. And a few of these have been quite extreme, like the example of codeine and ultra-fast metabolizers or gentamicin induced hearing loss. So what's the process to recommend these medications, especially when we know these side effects are possible?

Emma: Yeah, it's a really, really important point, Angelos. Medications undergo a rigorous process for approval to ensure that benefits outweigh the harms to make sure that people are being treated in a safe way. So there's dedicated agencies everywhere. In the UK, that's called the medicines and healthcare products regulatory agency. It referred to as the MHRA. And this is a body [00:18:00] that continually monitors events to ensure that the benefit of medications outweigh the risk to a population, but these approaches are often one size fits all. So they don't have the benefit of having genetic information to look at how benefit versus risk might be different for individuals with a specific DNA variation. Now this is changing. NICE, the organization responsible for recommending changes to clinical practice in the UK has put out a draft guidance suggesting that we will shortly be testing a gene to help choose medication after a stroke and also a new medication for an inherited heart disease will be available shortly, but it will require testing for that same gene.

Hannah: So, I guess the idea would be that prescribers, say a GP, would be informed by the results of a genetic test. So is there anywhere else that you would like to see this applied?

Emma: So I think, Hannah, you spoke earlier about that [00:19:00] publication in the Lancet of a clinical trial that showed that you can get a lot of information about how genes interface with multiple drugs from just doing a limited panel with 12 genes. And you can have that information in advance of prescribing. And this is what I would love to see happen in the UK. So if the UK adopted a pre-emptive panel approach like that, where they looked at very well validated, very well understood variants, in a few genes that impact on prescribing for a lot of different medications. And you can have that information before you prescribe. So instead of a trial-and-error approach, we could take a more targeted approach from the get go. Now this would be the ideal, but I think that

for this to work, maybe a few genes that impact on prescribing for several different and commonly used medications need to come first. So talking about medications like codeine, like antidepressants, like antiplatelets that are prescribed broadly to a lot of [00:20:00] people who have a lot of different medical problems, not just in a specialist clinic. So here I think we need to talk about the story of the CYP2C19 gene.

Angelos: Oh yes, my favourite gene, which is the 19th member of the c sub family of the second family of cytochrome P450 enzymes. Sorry. Yeah, it's your favourite. Just love saying that. Yeah, yeah, yeah.

Hannah: So CYP2D6 is not?

Angelos: Um, maybe it's my second favourite, but then there's Pikachurin as well.

Hannah: Yeah. I don't think we're allowed to have favourites. CYP2C19, so this is similar to the example that we talked about earlier in the episode of CYP2D6 right?

Emma: Yes, exactly. So this protein is encoded by the gene of the same name and is responsible for activating clopidogrel, which is a medicine used after stroke and heart attack to prevent further stroke or heart attacks. So clopidogrel is a prodrug and that means that it's not active in the form that you swallow it in. It needs to be activated in your body by that enzyme, which is encoded by that gene. If you have these common variants [00:21:00] in your DNA you won't be able to activate clopidogrel well. And this then means that clopidogrel will work less well for you. And ideally, if we knew that from the get-go, because we had your genetic information, we could give you a different medicine instead.

So that's the ideal scenario. There's really important health equality implications here, because although those genetic variants that mean you can't activate clopidogrel as well as other people are really common across all groups, they're more common in some groups than in others. So for example, Asian and Pacific island groups are known to have very high prevalence, so really commonly have these genetic markers. And that means that we need to look at how commonly people in those groups might need the medicine and then also how likely they are to not respond to it[17].

So, for example, in the UK, people of South Asian ancestry are really important to talk about with clopidogrel and heart attacks, because it's a group where sadly we know [00:22:00] people are more likely to have a heart attack and then also

they are very likely to carry these genetic variants[18]. That means they might not get the full benefit of clopidogrel because they can't activate it. Now, unfortunately, they are also a group of people that weren't represented well in clinical trials for these therapeutic agents or also in the trials looking at how we can use genetics to prescribe so we need to be really mindful of inclusive representation and implications on health equality.

Hannah: So where would you see this technology being employed, so would your GP, for example, change prescriptions based on a test?

Emma: That's a really tough and a really good question and I think you're exactly right. GPs are the really key people here. They're a best place to ensure that prescribing for chronic medications for conditions, which people will have for a lifetime rather than acutely takes genetic information on board. And GPs are also incredibly important because that's where ongoing care is, so there's [00:23:00] that aspect of trust and ongoing communication between people and their GPs.

However, some medications are also given in acute hospital settings like for example medicines after heart attack or antibiotics that are given through the vein for sepsis, so for a severe infection that has you in hospital. So what we really need to get it right and get the most benefit from genetic information is a system whereby GPs, hospitals, community pharmacies, and clinics all have access to that genetic information that could inform prescribing.

And really it would be best if patients could have that information available to them and take it between care settings. This is not a small task in terms of coding and sharing of information and also education of prescribers, but work is underway. So there's a wonderful program of work led by doctors and scientists from Manchester trying to answer some of these complex questions, as well as national education initiatives to support prescribers and these are being launched in real time as we [00:24:00] speak. And so very exciting moment for pharmacogenetics.

Angelos: Yeah, so my other question would be, what barriers would you see in rolling out such a pharmacogenetic testing and what major steps would need to be taken first?

Emma: I think that these are, again, really important things to discuss. We're really lucky to live in an age where we have digital media and quite advanced technology because a lot of this with clinical decision support is that instead of handing people a difficult to interpret genetic test, we hand them something

with clinical decision support. So it doesn't just say, your genetic code has this variant that's an A instead of a T. It tells the prescribers what they need to know to action that and what it means. So that's really important.

But I think the biggest bottom line is that there needs to be public conversations like these. People need to know how DNA can impact on response to medications [00:25:00] and how this use of genetic testing is different from prior uses of genetic testing, which is really around disease prediction which is very different, because these variants, they don't tell you if you're sick today or if you're going to be sick tomorrow, they don't predict disease or confirm it, they just tell you how you're going to respond to medications.

So the public needs to be on board and be included in the development of this new clinical service from the inception to make it fit for purpose. And what we've heard from people so far in consultation is that it needs to be easy, convenient. The necessary data needs to be available to patients and clinicians across settings. And we need really robust information governance. Clinicians who don't generally encounter genetic data need to know what to do with it and these things can't happen without consulting the public. And that can't happen if they've never heard of it. So basically, I think you're doing the hardest job and the most important job of all by talking about it.

Hannah: Thank you. That's very kind [00:26:00] of you to say. So, um, Well, this has been a fantastic conversation, but I think that's a really great place to end the discussion for today.

So Emma, thank you so much for joining us. I think we've covered some really interesting examples. We've really got a good idea of where the field's at at the moment, and I'm very motivated and excited to continue following it and seeing what changes will be happening in the clinic and the next five to 10 years.

And for our listeners who are also interested in finding out more about this topic and following the updates, we'll definitely be sharing more updates on our Twitter, although we have to call it X now, don't we? So our, our, our X, I'm not a fan.

Angelos: No,

Hannah: no. Our X slash Twitter handle is at @DNAandPod with and spelt A N D. So we'll be sharing materials on there and keep an eye out because we might have a website coming soon. But Emma, do you have anywhere else to recommend where our listeners could have a look to find out more?

Emma: I think that the personalized prescribing report, which you highlighted from the Royal College of Physicians and British Pharmacologic Society is a really nice broad [00:27:00] overview for anyone who's interested, I would also recommend that people have a look at the GeNotes resource (https://www.genomicseducation.hee.nhs.uk/genotes/), which will be launched to support healthcare practitioners and prescribers around pharmacogenomics this week. And that's being launched by NHS England.

Angelos: Yep. Thank you very much, Emma for joining and for giving us your insight on pharmacogenomics. It's good that we have two geneticists here and one clinician. I think the dynamic here is really... powerful and the discussion was really helpful as well.

Emma: Thank you so much and thanks so much for the opportunity to speak with you both and have this conversation today.

Hannah: So that was our episode on DNA& drugs. As always, thank you to the UK Genetics Society for supporting this podcast. You can contact us and find out more via our Twitter/X handle @DNAandPod with and spelt A N D and a capital P for pod. We'll also be having some book competitions to celebrate the release of our episodes, so do keep an eye out.

Angelos: Did you notice [00:28:00] how we released DNA& bugs and DNA& drugs back-to-back?

Hannah: Ooh, it's not intentional at all.

Angelos: So, some of you that have been listening very carefully, you might think, what if DNA from bugs affects the way drugs are metabolized by our human body?

Hannah: Ooh.

Angelos: Yeah, we can make such an episode, right?

Hannah: That's a very good question.

Angelos: Let us know on Twitter/X if you'd be interested in listening to such an episode.

Hannah: What about in the future? The bugs are flying the ambulances.

Angelos: We've domesticated the bugs to fly the ambulances.

Hannah: They are the ambulances. You know, like epic big beetles flying around .

Angelos: That's it. Yeah. That's it.

Hannah: Yep. Nailed it.

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