

<p>Slide 1</p>	<h2 style="text-align: center;">Pharmacogenetics and Drug Interactions</h2> <h3 style="text-align: center;">Variability in Pharmacokinetics and Pharmacodynamics</h3> <p style="text-align: center;">Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland</p>	
<p>Slide 2</p>	<h2 style="text-align: center;">Objectives</h2> <ul style="list-style-type: none"> ● Understand how between individual variation may contribute to : <ul style="list-style-type: none"> » drug effectiveness » adverse reactions » drug interactions ● Understand how identification of genes that contribute to disease pathophysiology can be used to: <ul style="list-style-type: none"> » identify new targets for drug therapy and the » potential to "customise" pharmacotherapy <p><small>©NHG Holford, 2011, all rights reserved.</small></p>	
<p>Slide 3</p>	<h2 style="text-align: center;">Pharmacogenomics and Pharmacogenetics</h2> <p>ICH-E15 Guideline : "Terminology and Definition in Pharmacogenomics", Step-4, 2007</p> <ul style="list-style-type: none"> ● Pharmacogenomics (PGx) is defined as the investigation of variations of DNA and RNA characteristics as related to drug response (genome science) ● Pharmacogenetics (PGt) is a subset of PGx and is defined as the influence of variations in DNA sequence on drug response (clinical relevance) <ul style="list-style-type: none"> » PGx and PGt are applicable to activities such as drug discovery, drug development, and clinical practice. » Drug response includes drug disposition (pharmacokinetics) and drug effect (pharmacodynamics). <p><small>©NHG Holford, 2011, all rights reserved.</small></p>	<p>ICH. DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES E15 http://www.ich.org/LOB/media/MEDIA3383.pdf. 2007; Step 4.</p>

<p>Slide 4</p>	<h2 style="text-align: center; color: red;">Variability</h2> <ul style="list-style-type: none"> ● “Predictable” <ul style="list-style-type: none"> » 50% of total » Genetic <ul style="list-style-type: none"> eg fast acetylator » Environmental <ul style="list-style-type: none"> eg renal function ● “Unpredictable” <ul style="list-style-type: none"> » 50% of total <p><small>©NHG Halford, 2011, all rights reserved.</small></p>	
<p>Slide 5</p>	<h2 style="text-align: center; color: red;">Predictable Variability</h2> <ul style="list-style-type: none"> ● Pharmacokinetics (Clearance) <ul style="list-style-type: none"> » Cytochrome P450 <ul style="list-style-type: none"> - CYP1A1 - CYP2C9,19 - CYP2D6 - CYP2E1 - CYP3A4, CYP3A5 » Non-Cytochrome Metabolism <ul style="list-style-type: none"> - Acetylation - Glucuronidation - Purine breakdown - Alcohol/Acetaldehyde Dehydrogenase » Transporter <ul style="list-style-type: none"> - P-Glyco-Protein - Organic Anion ● Pharmacodynamics (EC50) <ul style="list-style-type: none"> » Vitamin K Epoxide Reductase VKORC1 <p><small>©NHG Halford, 2011, all rights reserved.</small></p>	
<p>Slide 6</p>	<h2 style="text-align: center; color: red;">CYP3A5</h2> <ul style="list-style-type: none"> ● Marker Drug: Tacrolimus ● Clinically Relevant Drugs <ul style="list-style-type: none"> » Tacrolimus <ul style="list-style-type: none"> » Used as an immunosuppressant e.g. kidney transplant ● Clearance by CYP3A5 <ul style="list-style-type: none"> » *1/1 genotype “expressors” have 2 fold increased CL » *3/*3 “non-expressors” ● Genotype guided dosing leads to better achievement of tacrolimus target concentration <ul style="list-style-type: none"> » No difference in clinical outcome (study too small?) (Thervet 2010) ● Ethnicity: <ul style="list-style-type: none"> » 80% Caucasians but only 25% of African descent are *3/*3 <p><small>©NHG Halford, 2011, all rights reserved.</small></p>	<p>Thervet E, Lorient MA, Barbier S, Buchler M, Ficheux M, Choukroun G, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-6.</p>

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Acetylation

- Marker Drug ***procainamide***
- Clinically Relevant Drugs
 - » anti-arrhythmic (procainamide)
 - » anti-tuberculous (isoniazid)
- Ethnicity (% with low clearance)
 - » Caucasian 50%
 - » African 30%
 - » Asian 10%

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Glucuronidation

- Marker Drug ***bilirubin?***
 - » Hereditary hyperbilirubinaemia
 - Gilbert syndrome (3-10% of population)
- Clinically Relevant Drugs
 - » Anti-cancer drug (Irinotecan)
- Active metabolite (SN-38) is eliminated by glucuronidation (UGT1A1)
 - » Severe neutropenia and diarrhoea in 25% of patients
 - » Variant UGT1A1 in 10% of Caucasians predicts those who will get toxicity
- Ethnicity?

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Purine Metabolism

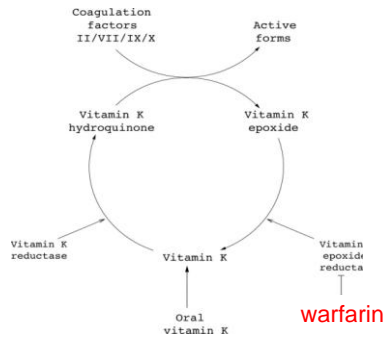
- Marker Drug: **6-mercaptopurine**
- Clinically Relevant Drugs
 - » 6-mercaptopurine
 - Childhood acute lymphocytic leukaemia
 - » Azathioprine (prodrug for 6-MP)
 - Crohn's disease, rheumatoid arthritis
- Severe toxicity (diarrhoea and neutropenia)
 - » Thio-Purine-Methyl-Transferase (TPMT) genotype
 - Homozygote deficiency 1 in 300
 - Heterozygote partial deficiency 1 in 10
 - 10 fold dose reduction required in homozygotes
- Ethnicity?

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<p>Slide 10</p>	<h2 style="text-align: center; color: red;">Alcohol/Acetaldehyde Dehydrogenase</h2> <ul style="list-style-type: none"> ● Marker Drug <i>ethanol</i> ● Clinically Relevant Drugs <ul style="list-style-type: none"> » Recreational drug (ethanol) ● Alcohol Dehydrogenase <ul style="list-style-type: none"> » Increased activity ADH2*2 -> increased acetaldehyde ● Aldehyde Dehydrogenase <ul style="list-style-type: none"> » Decreased activity ALDH2*2 -> increased acetaldehyde Or » Increased activity ALDH2*2 -> decreased acetaldehyde ● Ethnicity <ul style="list-style-type: none"> » 50-80% of Asians have excessive flushing with ethanol because of increased acetaldehyde formation » Others can tolerate larger quantities of ethanol <p style="font-size: small; margin-top: 10px;">©NHG Holland, 2011, all rights reserved.</p>	<p>Wall TL, Peterson CM, Peterson KP, Johnson ML, Thomasson HR, Cole M, et al. Alcohol metabolism in Asian-American men with genetic polymorphisms of aldehyde dehydrogenase. <i>Ann Intern Med.</i> 1997;127(5):376-9.</p>
<p>Slide 11</p>	<h2 style="text-align: center; color: red;">P-Glyco-Protein Transporter</h2> <ul style="list-style-type: none"> ● Multi-drug resistance to treatment <ul style="list-style-type: none"> » Cancer » Rheumatoid Arthritis » Inflammatory Bowel Disease » Epilepsy ● Common Mechanism <ul style="list-style-type: none"> » Increased activity of PGP transporter » Drug absorption decreased » Transport out of brain & tumour increased » PGP activity associated with ABCB1 polymorphism? ABC=ATP Binding Cassette ● Ethnicity? <p style="font-size: small; margin-top: 10px;">©NHG Holland, 2011, all rights reserved.</p>	
<p>Slide 12</p>	<h2 style="text-align: center; color: red;">Organic Anion Transporter</h2> <ul style="list-style-type: none"> ● Statins are among the most widely used and effective medicines in New Zealand ● Myopathy (rhabdomyolysis, myositis) occur 1 in 10,000 ● <i>SLCO1B1</i> gene encodes the organic anion-transporting polypeptide OATP1B1, which has been shown to regulate the hepatic uptake of statins ● Transporter deficiency leads to lower statin clearance and higher statin concentrations ● 16 x higher risk of myopathy with <i>SLCO1B1</i> mutation 'CC' <p style="font-size: small; margin-top: 10px;">©NHG Holland, 2011, all rights reserved.</p>	<p>The SCG. <i>SLCO1B1</i> Variants and Statin-Induced Myopathy -- A Genomewide Study. <i>N Engl J Med.</i> 2008;NEJMoa0801936.</p>

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Warfarin and VKOR



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Hall AM, Wilkins MR. Warfarin: a case history in pharmacogenetics. *Heart*. 2005;91(5):563-4.

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Warfarin Sensitivity and Resistance

- Genetic differences in VKORC1
 - » Vitamin K epoxide Reductase
 - » "Normal Daily Dose"
 - 5 mg/day
 - » Sensitivity (Group A)
 - Decreased VKORC1 activity
 - 80% of Asians
 - 3 mg/day
 - » Resistance (Group B)
 - Increased VKORC1 activity
 - 60% Caucasians
 - Perhaps also mutant enzyme does not bind warfarin well
 - 6 mg/day (but some need much higher doses)

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There are two kinds of VKOR haplotypes:

Group A: These patients have a VKOR mutation with reduced activity. This makes them more sensitive to the action of warfarin. For this reason they need a lower dose.

Group B: These patients are those who have been previously called familial warfarin resistance. They appear to have higher VKOR activity (as shown by higher messenger RNA levels in liver samples) and thus need a higher dose. It is also possible that some VKOR mutants do not bind warfarin efficiently and thus higher concs (and thus doses) are needed to give the required degree of inhibition.

See <http://en.wikipedia.org/wiki/Warfarin> and

http://www.sciencedirect.com/science?_ob=MIimg&_imagekey=B6T1C-4MJBTGM-1-1&_cdi=4887&_user=140507&_orig=search&_coverDate=12%2F31%2F2007&_sk=998799998&view=c&wchp=dGLbVlz-zSkWz&md5=e8c21a1b9c8c28737abed5cab77a9a46&ie=/sdarticle.pdf

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Pharmacogenetics Personal View



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Resources

Pharmacogenetics

[http://www.merck.com/pubs/mmanual/section22/
chapter301/301a.htm](http://www.merck.com/pubs/mmanual/section22/chapter301/301a.htm)

<http://www.fda.gov/Cder/genomics/presentations.htm>

Cytochrome P450 and Drugs

<http://medicine.iupui.edu/flockhart/>

Drug Interactions

[http://www.merck.com/pubs/mmanual/section22/
chapter301/301b.htm](http://www.merck.com/pubs/mmanual/section22/chapter301/301b.htm)