Southern Illinois University Edwardsville School of Pharmacy

Discordances Among CYP2D6 Genetic Test Results and Actual Patient Metabolic Phenotype

Anthony Negri, PharmD. Candidate 2021, Southern Illinois University Edwardsville
Ronald Worthington, PhD., Southern Illinois University Edwardsville

BACKGROUND

- Cytochrome P450 2D6 (CYP2D6) is responsible for ~25% of our clinically used drugs
- Substrates: selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), analgesics, tamoxifen
- Highly polymorphic with thousands of simple nucleotide variants (SNV) comprising 382 haplotypic alleles
- Structural variants copy number variation conversions and CYP2D6-CYP2D7 hybrid genes
- Metabolic phenotype: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultrarapid metabolizer (UM)
- Extreme amounts of variability in CYP2D6 resulting in a wide dynamic range of metabolic activity, a discordance between metabolic phenotype predicted from a patient's genetic test results and their actual metabolic phenotype
- Phenoconversion can be drug induced and comorbidity effects, hybrid alleles, copy number variations, or missing heritability

Objective

• Provide a review on factors that can disturb the accuracy of predicting CYP2D6 metabolic phenotype using genetic testing results along with other patient-specific information and thus enhance the clinical utility of pharmacogenomic guidance

Substrates	
Codeine	**Psychotropics**
Hydrocodone	Amitriptyline
Oxycodone	Amphetamine
Tramadol	Aripiprazole
Antiestrogens	Citalopram
Tamoxifen	Donepezil
Cardiovascular	Duloxetine
Carvedilol	Escitalopram
Clonidine	Fluoxetine
Flecainide	Nortriptyline
Metoprolol	Paroxetine
Nebivolol	Venlafaxine

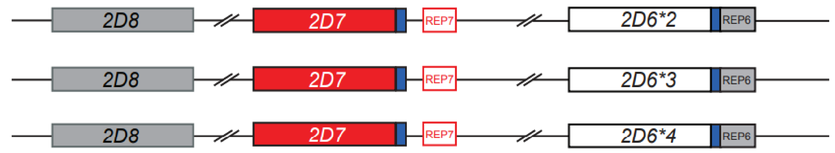
Inhibitors		
Weak	**Moderate**	**Strong**
Amiodarone	Abiraterone	Bupropion
Celecoxib	Cinacalcet	Fluoxetine
Cimetidine	Duloxetine	Paroxetine
Escitalopram	Lorcaserin	Quinidine
Fluvoxamine	Mirabegron	Terbinafine
Labetalol		
Ritonavir		
Sertraline		

Phenoconversion

- Phenomenon that causes a patient's phenotype to be converted to another due extrinsic factors
- Breast cancer patients receiving tamoxifen therapy can be at risk of possible treatment failure due to being co-prescribed an SNRI
- Many different analgesic agents are substrates for CYP2D6, including hydrocodone, codeine, and tramadol
- Depression and pain may be common among patients
- When therapies are co-administrated patients are at risk of failing drug therapy and having poorer outcomes
- Chronic inflammatory disease states such as HIV, Hepatitis C, and liver transplantation have been shown to phenotypically change a patient who is genotyped to be an EM to a PM.

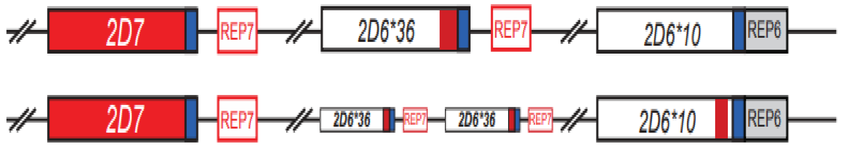
Copy Number variations (CNV)

- Structural variation where the gene is deleted or multiplied
- Leads to both increased and decreased function
- common haplotypes are CYP2D6*1xN; 2xN; and 4xN
- Sensitivity of genetic assays for CNVs can vary between tests and most can only accurately show 2
- Problematic example is *1/*4 with CNV of 4
  - UM (*1x3/4), EM (*1x2/*4x2), and IM(*1/*4x3)



Hybrid Alleles

- Gene locus for CYP2D6 is extremely polymorphic and is composed of CYP2D6 and the two nonfunctioning pseudogenes, CYP2D7 and CYP2D8
- Hybrid alleles can form when CYP2D6 fuses with the pseudogenes, such as CYP2D6-2D7 and CYP2D7-2D6
- Can be found as a singleton or tandem repeat with reduced or no function
- Exon 9 region contained in CYP2D6 is from CYP2D7
- Genetic assays may not test for this exon 9 region and may improperly identify the phenotype
- CYP2D6*10 is commonly miscalled for CYP2D6*36
- Multiple studies have shown that a significant number of patients have been miscalled and incorrectly phenotyped



Discussion

- Drug induced phenoconversion appears to be one of the biggest reasons for these discordances and the clinical impact can be quite profound regarding pain management, psychiatric conditions, and in even cancer therapies.
- As genetic assay tests and PGx guidelines become more standardized this will lead to better accuracy in predicting CYP2D6 metabolic phenotype and then help expand the clinical impact that pharmacogenomics has on patient outcomes.

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- Significant impact in both clinical care and genotype-focused clinical research studies.
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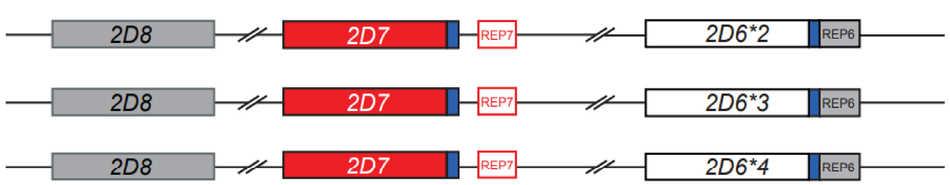

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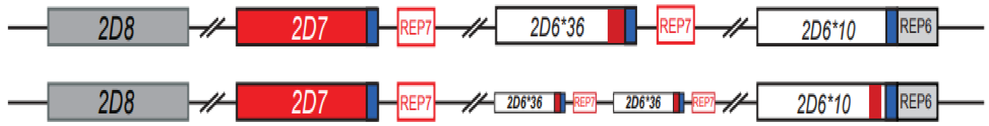

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Missing Heritability

- Statically method used in determining the phenotypic differences due to genetic variations
- Categorical scale showed 54% phenotype predictability
- Continuous scale improved to 79% phenotype predictability