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REPORT

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Complications of Psychotropic and Pain Medications in an Ultrarapid Metabolizer Patient at the Upper 1% of Cytochrome P450 (CYP450) Function Quantified by Combinatorial CYP450 Genotyping

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ABSTRACT

A 44-year-old Caucasian woman presented with a history of empirical treatment with 20 pain and psychotropic medications, as well as dual comorbidity of intractable pain and depression. A multiple gain-of-function profile in the CYP450 family of cytochrome P450 (CYP450) drug metabolism isoenzymes was discovered. The patient was a homozygote of suprafunctional alleles for both *CYP2D6* (*35/*35) and *CYP2C19* (*17/*17) genes and functional alleles for *CYP2C9* (*1/*1), which account for aggregate drug metabolism function at the upper 1% of the population. The patient improved clinically with discontinuation of psychotropics and pain medications that were substrates of CYP2D6 and/or CYP2C19, suggesting that much of her symptomatology was drug induced. Combinatorial genotyping of CYP450 genes is diagnostically useful in individuals with histories of multiple side effects or drug resistance, which could be avoided by genetically informed therapeutics in behavioral health.

Introduction

Functionality for the cytochrome P450 (CYP450) enzymes CYP2D6, CYP2C19, and CYP2C9, all predominantly expressed in the liver, can be predicted by determining their genetic mutations and polymorphisms. Heterogeneous drug metabolism phenotypes are predictable for individuals from inherited CYP450 gene alleles, ranging in function from poor to ultrarapid metabolizers.

Extremes of function have the most potential clinical impact. We had presented the case of a patient profoundly deficient in drug metabolism due to being a carrier of multiple null and deficient alleles in *CYP2D6, CYP2C19*, and *CYP2C9*.[1] Combinatorial genotyping served to identify this rare multigene variant combination and explain a 6-year history of adverse drug reactions to multiple psychiatric drugs. A patient who was a poor metabolizer for both *CYP2D6* and *CYP2C19* had been presented as a rare case (prevalence of 0.06%) prone to adverse drug reactions with many antidepressants.[2] These cases demonstrated that combinatorial genotyping is a powerful tool to identify and prevent somatic adverse drug reactions to psychotropics.

Here, we present a case at the extreme opposite end, a patient ultrarapid for *CYP2D6 *35/*35* and *CYP2C19 *17/*17* with a clinical history of treatment with psychotropic and pain medications. We are aware of three case studies reporting effects of the *CYP2D6* ultrarapid status, all related to codeine and carriers of *CYP2D6* gene duplications. The opioid effects of codeine are associated with high plasma morphine concentrations produced after codeine intake and its conversion via CYP2D6.

One case report described a psychiatric patient with subtherapeutic blood levels of duloxetine, fluvoxamine, aripiprazole, venlafaxine, quetiapine, and paroxetine. Genotyping characterized the patient as *CYP2D6 *2XN/*2* and *CYP2C19 *1/*1*.[3] The patient was then treated with sulpiride, which is not hepatically metabolized. The second case reported a cancer patient given codeine for cough suppression, which led to respiratory arrest.[4] Codeine is bioactivated by CYP2D6 into morphine, which then undergoes further glucuronidation. Genotyping characterized the patient as a *CYP2D6* ultrarapid metabolizer. The patient was treated with naloxone and fully recovered. In the third codeine case,

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the newborn of a mother who was a *CYP2D6* ultra-rapid metabolizer (with a functional gene duplication) died 13 days after birth. It was determined that breastfeeding from the mother taking codeine was the source of lethal doses of morphine for the baby.[5] It has been suggested that codeine should be avoided in breastfeeding mothers who are ultrarapid metabolizers of *CYP2D6*.

Previously, we had developed a scoring system based on a novel method of analysis of *CYP2D6, CYP2C19*, and *CYP2C9* using combinatorial genotypes.[6] We demonstrate an immediate utility of the indices by presenting the distributions and rankings of index scores in a psychiatric population of 1199 patients. Charting the index rankings enables the visualization of an individual in the context of a wider population, which in itself is a clinically informative benchmark. We demonstrated that the combinatorial indices provide informative and actionable quantitative (index values) and qualitative (ranking charts) representations of CYP450 drug metabolism capacity as measured by gene polymorphisms and their effect on liver enzyme functionality.

Case report

In June 2012, a 41-year-old Caucasian woman presented with a history of left calf atrophy after an injury incurred while playing baseball approximately 3 years prior and was seen at the Hartford Hospital Pain Treatment Center (West Hartford, CT). She complained of increased pain with outdoor activities, such as biking and hiking, and she described that standing on her toes created a sharp, shooting pain. She rated her pain on the visual analog scale as a 7/10, which moderately interfered with her daily activities.[7] She was gainfully self-employed as a caregiver. Since the injury in 2009, she had noted that the atrophy had become increasingly severe.

The patient was treated with various interventional procedures to reduce her pain, which intermittently radiated into her hip, her sacrum, and her piriformis muscle. Injections of bupivacaine (Marcaine), and later, lidocaine (Xylocaine) with methylprednisolone (Depo Medrol), initially offered her some temporary relief. The patient then began to complain of breakthrough pain and was given hydrocodone with acetaminophen (Norco) and oxycodone with acetaminophen (Percocet) at different times in her treatment in an attempt to help control the pain. However, the patient reported low efficacy of treatment and continued to experience pain. Physical therapy was prescribed but was not successful. The patient reported instability in her pelvic region that prevented her compliance with the therapy. Chiropractic care was also recommended and obtained by the patient but offered only temporary relief. Within 6 months of her initial visit in June 2012, she had become increasingly preoccupied with her pain, focusing on the inadequacy of the medications. No longer employed as of March 2013, the patient was pending a sacroiliac fusion surgery to address her pelvic instability that her insurance company was denying. Due to a history of depression, the patient was being treated by a psychiatrist but had decreased coping mechanisms, in turn leading to impacted relationships. The patient's family history was negative for behavioral or psychiatric disorders.

While trialing various narcotic and opioid medications and opioid rotations to treat her pain, the patient was treated on tapentadol (Nucynta ER) at 150 mg every 12 hr in June 2013. Within 3 weeks of starting the medication as-needed, the patient reported worsening mood, depression, and suicidal thoughts. The patient was then weaned off tapentadol and reported initially that she was "able to feel like herself again."

However, throughout the next 15 months, the patient noticed a relapse of her depression and the onset of a new symptom of persistent insomnia in addition to her recurring pain. She was admitted to a regional outpatient program for suicidal ideation in the fall of 2014. The patient's baclofen, gabapentin (Neurontin), clonazepam (Klonopin), and bupropion (Wellbutrin) were discontinued, and the patient was started on duloxetine (Cymbalta) and trazodone (Desyrel) 100 mg every bedtime, which was then decreased to 50 mg every bedtime with concurrent use of eszopiclone (Lunesta).

Hydromorphone (Dilaudid) was continued for her pain, as it was more effective than the previously prescribed hydrocodone and oxycodone (either independently or combined with acetaminophen). The outpatient program also gave her combination capsules of butalbital, caffeine, and acetaminophen (Fioricet) for headache relief but would not prescribe these long term. Upon return to the office of a physician associated with the outpatient program in December 2014, trazodone and eszopiclone were discontinued and the patient was prescribed alprazolam (Xanax).

Approximately 2 months later in February 2015, the patient attempted suicide with an overdose of a family member's zolpidem (Ambien) pills. She was admitted to a psychiatric unit in a regional hospital and later discharged to the outpatient program. She stated that the suicide attempt stemmed from her unrelenting pain, the resulting depression, and the subsequent erosion of her family support. She felt that many people were abandoning her. Furthermore, she believed clinicians were treating her as if she did not have an organic cause for her condition and said that her family considered her symptoms to be "all in her head." In addition to the physical disabilities, her inability to maintain gainful employment added greatly to her financial stressors. It had become evident that the patient was not tolerant of most opioids. Despite very high levels of pain, proportionately, there was not an adequate regimen to sustain her while an alternative long-term solution was found. In addition, the patient had been dealing with insurance barriers to care that had hurt her financially, having to pay "out of pocket" for procedures to gain even temporary pain relief.

Concerns arose in March 2015 about the patient having access to short-acting hydromorphone because of the patient's prior suicide attempt with zolpidem pills. Consequently, the patient's therapy was changed to a fentanyl patch (Duragesic). The patient was at a crossroads with uncontrollable pain, continued suicidal thoughts, failing relationships with a looming divorce, and inadequate functionality to be an active member of society. In June 2015, the possibility of alterations in drug-metabolizing capacity was considered clinically relevant for pharmacogenetic assessment.

In June 2015, the patient was referred to the Genomas Laboratory of Personalized Health (Hartford, CT, USA). She was referred for treatment resistance and lack of efficacy of her current regimen. Her diagnoses at referral were Lumbago (ICD9 [International Classification of Diseases Ninth Revision] code 724.2, ICD10 M54.5), Major depressive disorder, single episode, unspecified (ICD9 code 311, ICD10 F32.1), Bursitis of left hip (ICD9 code 726.5, ICD10 M70.72), and Iliotibial band syndrome (ICD9 code 728.89, ICD10 M76.30). The patient was being treated with duloxetine, trazodone, and fentanyl.

Results of the testing demonstrated several gain-of-function CYP450 alterations. The pharmacogenetic clinical decision support (CDS) report demonstrated the inadequacy of many medications she had received

in the past. At the time of the results and report, fortunately, the patient had already been rotated to a fentanyl patch, an appropriate opioid according to the CDS report. However, duloxetine and trazodone, both contraindicated according to the pharmacogenetic therapeutic guidance, were still in the patient's regimen. The combinatorial genotyping results and the CDS report were forwarded by the Pain Treatment Center to the patient's psychiatrist. Unfortunately, this psychiatrist told the patient that he was not familiar with the test, yet, he "honestly did not believe in it." The Pain Treatment Center and her primary care physician then tapered down and discontinued duloxetine and trazodone and referred the patient to a psychiatrist versed in pharmacogenetic therapeutic guidance.

The patient reported feeling validated by the pharmacogenetic results and CDS report because, concerning her predicament, "it wasn't all in (her) head." She states that the results had definitely improved her quality of life and helped her to understand the physiological reasons behind the sequence of events she had experienced. She also had evidence, which has helped her to repair and build a more supportive relationship with her physicians. Her family and friends also had a clearer understanding of her treatment difficulties, allowing for a more effective support network. She is now gainfully employed again. Her pain medications (fentanyl patch 50 μg every 72 hours and hydromorphone 2 mg three times daily as-needed), along with injections of bupivacaine, are allowing her to cope with the pain that she still experiences and pursue a normal, active life, while being treated by a new psychiatrist.

Methods

Patient referral

The patient was referred to the Laboratory of Personalized Health (LPH) at Genomas, Inc. (Hartford, CT, USA), in June 2015 by the Hartford Hospital Pain Treatment Center (West Hartford, CT, USA). The patient was a community-dwelling Connecticut resident. CYP450 diagnostic genotyping was part of the clinical care of the patient because of efficacy and safety problems related to her medications. The patient signed an informed consent form agreeing to DNA testing. Prior to publication of this case, the patient provided verbal consent to the Pain Treatment Center for

the anonymized analysis and description of her case for educational purposes.

DNA extraction and analysis were performed at the Laboratory of Personalized Health, a high-complexity, clinical DNA testing center licensed by the Connecticut Department of Public Health (CL-0775) and certified by the Centers for Medicare and Medicaid Services (ID no. 07D1036625) under CLIA (Clinical Laboratory Improvement Amendments) since 2005. A buccal swab sample was collected with foam-tipped polystyrene plastic rods. DNA was extracted from the collected epithelial tissue using the Qiagen EZ-1 DNA Tissue Kit processed in the Qiagen EZ1 biorobotic instrument (Qiagen, Germantown, MD, USA).

Quantitative combinatorial genotyping

The xTAG CYP2D6 Kit version 3 mutation detection assays (Luminex, Austin, TX) were utilized for genotyping 20 sites of variability in CYP2D6 gene.[8] The INFINITI® CYP2C19 Assay[9] and the INFINITI 2C9-VKORC1 Multiplex Assay for Warfarin[10] (AutoGenomics, Vista, CA) were employed for genotyping the CYP2C19 and CYP2C9 genes, respectively. Samples are analyzed on the Luminex xMAP® 100 or 200 and AutoGenomics INFINITI Analyzer instruments.

A custom laboratory information system (LIS) was used to call the result. In the LIS, a combination of automated calling (AC) and expert calling (EC) is implemented.[11] The output from the Luminex analyzer encompasses 20 signals for CYP2D6: 18 sites of single-nucleotide polymorphism (SNP) or microdeletion, one for gene duplication, and another for gene deletion. The DNA variants are organized into 17 haplotypes.[11] The output from the INFINITI® analyzers encompasses *2 (681 G→A), *3 (636 G→A), and *17 (−806 C→T) for CYP2C19 and *2 (430 C→T) and *3 (1075 A→C) for CYP2C9.

Genotypes were analyzed in the EC-integrated LIS to report haplotypes and phenotypes. The LIS integrates data from all three genes and computes the Drug Metabolism Reserve Physiotype.[12] We have developed four novel drug metabolism indices as part of the physiotype calculated from the combinatorial genotyping data and scored them for each patient, creating distributions and rankings of innate drug metabolism capacity to which individuals can be compared.[6] We utilized the Drug Metabolism Reserve Index (metabolic reserve). This index is designed to represent a series of discrete, quantitative CYP450 metabolic phenotypes, from null to ultrarapid. A higher index indicates a greater innate drug metabolism capacity of the individual. The LIS also provides clinical decision support via its MEDtuning™ module, which is proprietary to Genomas and which has been presented previously.[13,14]

Clinical decision support

Clinical decision support (CDS) comprises algorithmic customization of a drug regimen for the patient guided by the Drug Metabolism Reserve Physiotype.[12] This guidance is achieved by evaluating relative contributions to Drug Metabolism Reserve Physiotype index values and rankings on a gene-by-gene basis, considering CYP2D6, CYP2C19, and CYP2C9 and is delivered with semaphore-themed color highlights for display of each drug with red, yellow, or green. Gene-specific index values associated with substantially decreased or increased metabolic reserve lead to recommendations to avoid those drugs that are a substrate of the isoenzymes coded by the altered gene(s). A warning, denoted by a red highlight ("red drug") on the display, is provided if the altered isoenzyme constitutes the primary or sole metabolic pathway for that drug. If a gene's index contribution value is determined to indicate ultrarapid metabolism, the physician is notified that a normal dose may prove ineffective for a drug metabolized by the respective enzyme, and that there would be an increased risk for side effects if the patient is prescribed a prodrug activated by the respective enzyme. Moderately decreased or increased metabolic reserve will prompt a warning, denoted by a yellow highlight ("yellow drug") on the display, advising to monitor with caution those drugs that are a substrate of the altered isoenzymes. If a given gene's relative contribution to the index values and ranking indicates that the respective isoenzyme is functional, drugs metabolized primarily by that isoenzyme will be recommended to the physician with a green highlight ("green drugs"). Drugs bypassing the enzymes coded by the three CYP450 genes analyzed are also highlighted as "green." In summary, the proportional contribution of each gene to the Drug Metabolism Reserve Physiotype indices is used to guide physicians to choose appropriate medications for their patients, which are metabolized primarily by isoenzymes for which the patient has the most metabolic reserve and least metabolic alteration.

Table 1. Summary of CYP450 alleles, molecular defects, and resulting phenotypes determined by combinatorial genotyping for the patient.

CYP450 gene	DNA allele	Molecular change	Functional change	Metabolic phenotype	Index value
CYP2D6	*35	−1584 C→G	Promoter ↑	Rapid	1.5
		31 G→A	11 Val→Met		
CYP2C19	*17	−806 C→T	Promoter ↑	Rapid	1.5
CYP2C9	*1	Normal	Reference	Functional	1.0

Note. The "Molecular change" column indicates the base pair substitution, and the specific location in the gene. The "Functional change" column indicates the amino acid substitution or promoter disruption caused by the DNA change. The "Metabolic phenotype" is provided for each allele, together with its Drug Metabolism Reserve Index value.

Toxicology

Three urine toxicology test series (Millenium, San Diego, CA, and Avutox, Rocky Mount, NC, USA) were available to this case review, two performed before genotyping and one after. These were performed to monitor prescribed drugs and metabolites as well as drugs of abuse and were performed by liquid chromatography and mass spectrometry (LC-MS).

Results

Combinatorial genotyping

The genotypes observed in the patient are shown together with their predicted phenotypic changes and metabolizer properties in Table 1. The patient was homozygous for the *CYP2D6* promoter polymorphism *35 (*rs769258*), which predicts ultrarapid CYP2D6 enzyme activity. She was also homozygous for the CYP2C19 promoter polymorphism *17 (rs12248560)*, which similarly predicts ultrarapid CYP2C19 enzyme activity. She was functional for CYP2C9 with two normal *1 alleles. The predicted phenotype for both CYP2D6 and CYP2C19 is ultrarapid (Figure 1). The patient is thus supranormal and normal for the three CYP450 genes tested.

Metabolic ranking

Figure 1 also tabulates the Drug Metabolism Reserve Index for the patient by adding the gene-specific scores. Presence of two rapid alleles at each *CYP2D6* and *CYP2C19* represents a calculus of 3.0 for each gene. The presence of two normal alleles for *CYP2C9* represents 2.0. Adding these, a value of 8.0 was determined for the patient's Drug Metabolism Reserve Index.

The metabolic ranking curves can be used to determine where an individual fits in the index distribution. Such placement provides the clinician with a clearer understanding of the patient's metabolic status in relation to the median individual and provides a level of
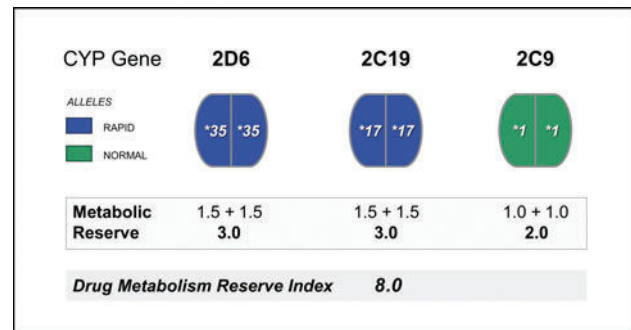

Figure 1. Combinatorial genotyping results for the patient and predicted metabolizer phenotypes for each allele. The genotypes for the two alleles inherited for *CYP2D6, CYP2C19*, and *CYP2C9* are denoted alongside semiovals for each gene. Conventions for naming the alleles according to the Human Cytochrome P450 (CYP) Allele Nomenclature Committee using the star nomenclature are followed.[38] Background colors blue and green indicate, respectively, rapid and normal alleles. The metabolic reserve is added for each allele to provide the metabolic reserve of the genes. The values for the metabolic reserve of genes *CYP2D6, CYP2C19*, and *CYP2C9* are, 3.0, 3.0, and 2.0, respectively. The metabolic reserve of the three genes is added to provide the aggregate value of 8.0 for the Drug Metabolism Reserve Index for the patient.

clinical guidance that significantly augments single-gene scores. Based on a metabolic index score of 8.0, this patient was above the range we previously published, which represents standing in the upper 1% of the population (Figure 2).

Clinical decision support

The substrate dependence of each of the medications prescribed can be examined with regard to the corresponding metabolic reserve of the patient using clinical decision support (CDS). The metabolic dependence is shown in Figure 3 for the 20 medications prescribed over the patient's history of treatment. Based on a mismatch between the substrate affinities for CYP2D6, CYP2C19, and CYP2C9 of these drugs and the functional capacity determined from the combinatorial genotype of the patient, the CDS classifies six medications as contraindicated, denoted by red highlighting: duloxetine, hydrocodone, lidocaine, oxycodone,
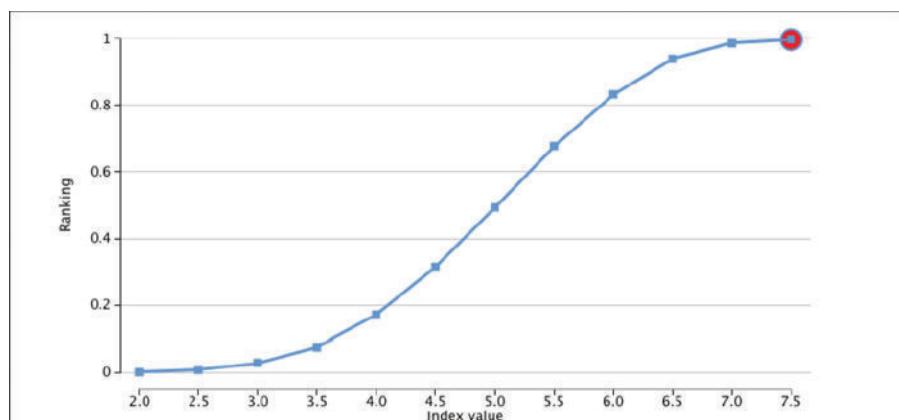
Figure 2. Population ranking of patient based on the Drug Metabolism Reserve Index. The metabolic ranking curve calculates the patient's position (0 to 100%) for the Drug Metabolism Reserve Index. The curve uses the distribution of 1199 psychiatric referrals previously reported as a reference range to determine where an individual fits in the index's distribution.[6] The placement provides a clear quantitative benchmarking of the patient's innate functional status for drug metabolism in relation to the "average" (50%) individual. In conjunction with the index score, the display provides an understanding of a patient's absolute metabolic ability in addition to metabolic ability in relation to the reference population. The index value of 8.0 for this patient exceeds the upper value of the range previously published for this distribution[6] and places the patient in the upper 1% of the population.

Figure 3. Clinical decision support display provided for the therapeutic guidance for the patient. The guidance is provided for 20 drugs prescribed over the course of this clinical case. The generic name is followed by italicized US trademark. Prodrugs are denoted by § (active metabolite is enclosed in brackets). The guidance on drug selection is provided with colors analogous to the lights of a traffic semaphore. Drugs highlighted with red are not indicated. Drugs highlighted with yellow can be prescribed and monitored with dosage changes. Drugs highlighted with green and denoted by ◊ can be prescribed according to the drug label at the recommended dose, as their metabolism is not dependent on CYP2D6, CYP2C19, or CYP2C9. Corresponding grayscale shadings for green, red, and yellow colors are, dark, intermediate, and light, respectively. The guidance on dosing is qualitative and is provided with respect to the recommendations in the drug label. Dosing above the range in the drug label is represented by double solid ovals (above normal). Dosing in the normal dosage range is conveyed by a single solid oval. Dosing below the range is represented by a single empty oval (below normal).

trazodone, and zolpidem. For these medications, a dosage above the range in the Food and Drug Administration (FDA) label would be required for the drugs, indicated by double ovals, and dosage below the range would be advised for the opioid prodrugs, indicated by an empty oval. Classified as cautionary, and highlighted in yellow, are another four medications (acetaminophen, bupropion, caffeine, tapentadol). The other 10 medications are not substrates of CYP2D6, CYP2C19, or CYP2C9 (alprazolam, baclofen, bupivacaine, butalbital, clonazepam, eszopiclone, fentanyl, gabapentin, hydromorphone, and methylprednisolone). These nonsubstrates are not affected by alterations in any of these genes and are represented with a green highlight.

Toxicology

A report dated January 2013 was positive for benzodiazepines (clonazepam, diazepam), norhydrocodone, and zolpidem. The toxicology report was negative for both hydrocodone and hydromorphone, despite the patient's prescribed use of hydrocodone. The patient's hydrocodone levels fell below the 95% inclusion range for creatinine-corrected concentrations (2 to 4 ng drug/mg creatinine). A report dated March 2015 was positive for duloxetine, trazodone, hydromorphone, fentanyl, and norfentanyl. A report dated September 2015 (after the pharmacogenetic guidance was implemented) was positive for fentanyl and norfentanyl. None of the reports were positive for drugs of abuse.

Discussion

Case highlights

We present a case in which the discovery of multiple cytochrome P450 enzyme gain-of-function variants in a patient resulted in a dramatic change in treatment approach. The patient presents a case of double-promoter regulatory polymorphisms, rendering the individual an ultrarapid metabolizer without gene duplications. Thus, this case represents a remarkable example of polymorphism in gene expression. We had previously reported a patient with the opposite profile, multiple alleles with poor or deficient function.[1] Each case represents an extreme of metabolic function. The present patient is on the upper 1% of function, and the prior, on the lower 1%.

This case illustrates the comorbidity of pain with psychiatric disorders. Dual treatment with psychotropics and analgesics is a consequence of this comorbidity. In this patient, the multimodal pharmacotherapeutic strategy is exemplified by the drug regimen composed of 20 medications throughout the history of the case. The roster includes anticonvulsants (butalbital, gabapentin), antidepressants (bupropion, duloxetine, trazodone), antispasmodics (baclofen), anxiolytics (alprazolam, clonazepam) opioids and opiates (fentanyl, hydrocodone, hydromorphone, oxycodone, tapentadol), anesthetics (bupivacaine, lidocaine), antiinflammatory agents (acetaminophen, methylprednisolone), hypnotics (eszopiclone, zolpidem), and stimulants (caffeine). Upon referral for pharmacogenetic testing, the patient was on three medications: duloxetine, trazodone, and fentanyl. Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) mostly prescribed for major depressive disorder, generalized anxiety disorder, fibromyalgia, and neuropathic pain. Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) antidepressant that has anxiolytic and hypnotic effects. Fentanyl is a potent synthetic opioid pain medication (μ-opioid receptor agonist) with a rapid onset of action but with a short duration.

Drug substrates and clinical decision support

Of the medications the patient had taken, those in which CYP2D6 is a major substrate include duloxetine, hydrocodone, lidocaine, oxycodone, trazodone, and zolpidem. The patient is a homozygote of rapid alleles for this gene, which contraindicates these medications, especially long-acting, extended-release forms. In addition, trazodone is a minor substrate for CYP2C19. The suprafunctional status would warrant a higher dose and close monitoring for adverse drug reactions. Hydrocodone and oxycodone are prodrugs and thus would be immediately metabolized to hydromorphone and oxymorphone in this patient, resulting in a rapidly increased concentration of these metabolites.[15,16] Such reactivity would result in a bolus of hydromorphone and oxymorphone unlikely to reach therapeutic steady state. Hence, the therapeutic guidance for these prodrugs is for dosing below the range in the label. In contrast, hydromorphone administered directly will be more manageable in this patient. This regimen proved successful for the patient. Drugs not primarily metabolized by the three CYP450

isoenzymes (CYP2D6, CYP2C19, and CYP2C9) analyzed genetically in the patient included fentanyl, which also proved to be effective.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has issued valuable guidances for various drugs in psychiatry and pain management: amitriptyline, citalopram, codeine, escitalopram, fluvoxamine, nortriptyline, paroxetine, and sertraline.[17–19] However, none of these drugs with guidelines were given to the patient. In fact, none of the drugs prescribed in this case, an example of multimodal therapy spanning from opioids to antidepressants, has a CPIC guideline. This void in guidances demonstrates the need and value for an algorithmic, heuristic logic such as the one provided in this case based on quantitative logic.

Molecular characterization

The *CYP2D6* allele *35 was discovered as a gain-of-function polymorphism in the promoter region and was found to confer higher enzymatic activity and prevent a poor-metabolizer status in some patients with paired deficient alleles.[20–22] It was confirmed in *CYP2D6* duplication-negative subjects who manifested the ultrarapid metabolizer phenotype.[23] The *35 allele is composed of a haplotype consisting of a promoter polymorphism at position −1584 (C→G) and a coding polymorphism at position 31 (G→A) that results in a substitution in amino acid 11 of the enzyme (valine to methionine).

The *CYP2C19* polymorphism *17 was discovered with two SNPs in the 5′-flanking region associated with increased CYP2C19 in vivo activity in two different ethnic populations (Swedes and Ethiopians).[24,25] It was shown that that *17 specifically binds nuclear proteins to its 5′-flanking region and mediates increased gene transcription in vitro. It was concluded that *17 is likely to cause therapeutic failures in drug treatment with some antidepressants and most proton pump inhibitors. The specific effect of the *17 polymorphism has been studied by assessing drug levels of escitalopram and sertraline in the blood.[26,27] In the case of escitalopram, which is a CYP2C19 major substrate, a homozygous *17 genotype is associated with lower serum concentration, which might imply an increased risk of therapeutic failure. In the case of sertraline, which has a shared substrate affinity among CYP2C19, CYP2D6, and CYP2C9, it was not associated with

lower serum concentration of escitalopram. Clinical implications of the *CYP2C19* *17 rapid metabolism have been documented for proton pump inhibitors, concluding that ultrarapid metabolizers do not respond to the standard dose and benefit from genotyping, particularly for hyperacidic conditions.[28]

Geographic distribution and ethnic differences

Several ethnic differences in CYP450 metabolism have been identified for the CYP450 enzymes.[29] Correlations between phenotype and genotypes segregating according to ethnicity and geography have been established for CYP2C19 and CYP2D6 for both loss-of-function and gain-of-function alleles. It has been speculated that evolutionary selection conditioned for dietary sustenance could be at the root of this phenomenon.

There is a well-documented geographic clade for higher incidence of *CYP2D6* duplication in the Mediterranean and Middle East. In a study of the Ethiopian population, it was found 29% of the individuals investigated carried alleles with duplicated or multiduplicated *CYP2D6* genes, indicative of ultrarapid metabolism.[30] Similarly, in a sampling of Saudi Arabian individuals, 21% were carriers of duplicated *CYP2D6* genes.[31] The prevalence of *CYP2D6* gene duplication among Italians is high compared with northern European populations, leading to 8.3% frequency of *CYP2D6* ultrarapid phenotype in the Mediterranean area.[32] The *CYP2D6* allele *35, was discovered in many duplication-negative ultrarapid metabolizers. It has been posited to explain the ultrarapid phenotype in northern European Caucasian individuals, where *CYP2D6* expansions are less frequent than in Mediterranean or Middle Eastern populations.

The geographical distribution of *CYP2C19* *17 evidences major ethnic differences. Several studies consistently estimate its allele frequency at 20% (range: 18%–27%) in both European and African populations, and only 2% (range: 1%–4%) in Asian populations.[33]

Quantitative combinatorial CYP450 genotyping

Before now, analysis of drug metabolism capacity based on single genes has laid the foundation for much of pharmacogenetics. Parallel combinatorial genotyping

of several drug-metabolizing genes may reveal sensitivities observed only in multiply individuals who inherit an ensemble of rapid alleles neither parent had alone. The prevalence of the *35 allele is 4.34%, based on a survey of 2406 referred patients to our clinical service.[11] The CYP2C19 *17 allele frequency is 20%, according to previous reports.[22] The carrier frequency for the normal allele of CYP2C9 is approximately 67%.[34,35] When the CYP2D6 rapid metabolizers are compounded with their simultaneous status as carriers of rapid for CYP2C19 and normal for CYP2C9 genes, the predicted frequency for a patient with the combinatorial genotype reported here is the product of the squared frequencies, or 0.004%. We believe that this case is a dramatic demonstration of sensitivity phenotypes observed in patients with multiply rapid drug metabolizer status who are at enhanced risk of drug reactions and potentially some environmental exposures as well.

Attempts at standardizing nomenclature of phenotypes have historically and even recently been based on qualitative, single-gene descriptors.[36] We and others have advocated for the use of quantitative descriptors instead.[6,37] When contemplating multigene classifiers with multiple variants, some with opposing consequences in the same patient, only quantitative indices would provide the functional status of the patient. Quantitative terminologies for metabolizer phenotyping include "activity score,"[38] "gene dose,"[39] and "metabolic reserve."[6] In general, these scales assign 0 to poor alleles and 1.0 to functional ones. Deficient alleles are scored intermediately at 0.5, and rapid ones at 2.0. We are the first to score alleles at the boundary of functional and rapid status as 1.5. We believe this scoring is particularly valuable for *17 in CYP2C19 and *35 in CYP2D6. We adjudicate the ultrarapid assignment to a metabolic reserve of 3.0, which is seen in rapid homozygotes only.

The metabolic reserve has been validated in the behavioral health settings pertinent to this case. In our previous study of 1199 community psychiatric patients, the distribution of the metabolic reserve was normal, with a median value of 5.0 and boundaries for the 1st and 5th quintiles were 4.0 and 6.0.[6] Metabolic reserve was correlated with dyslipidemia measures (low-density lipoprotein cholesterol [LDLc], high-density lipoprotein cholesterol [HDLc], LDLc:HDLc ratio) in psychiatric patients treated with diverse psychotropics. Patients with a greater drug metabolism reserve evidenced lower LDLc, lower LDLc:HDLc ratio, and

higher HDLc values.[40] In a pediatric pain case series, it was found that the metabolic reserve distribution was bimodal.[14] Patients selected on strictly clinical grounds (lack of efficacy and side effects) were predominantly below and above the average found in our reference publication. This finding provides support for referred patients with a history of analgesic ineffectiveness or adverse events being considered for pharmacogenetic guidance of their analgesic therapy. Finally, the combinatorial genotyping approach has been illustrated in published case reports for two psychiatric patients with very low metabolic reserve values.[1,13]

Limitations

CYP3A4 and CYP3A5 are not genotyped routinely in our clinical practice. We have regarded functional variability in these genes as primarily dependent on inhibition or induction by other drugs, rather than genetic polymorphism.[41] Drug interactions at the extremes of CYP450 function remain largely unexplored, but there is experimental evidence that CYP2D6 function in ultrarapid metabolizer individuals may be difficult to inhibit.[3] Pharmacodynamic genes relevant to pain perception (e.g., OPRM1, opiate receptor μ type 1, and OPRD1, opiate receptor δ type 1) and depression (e.g., COMT, catechol-O-methyltransferase) were not examined in this study.[42] The pharmacodynamic dimension (e.g., receptors, transporters) is temporally distal to the acute events (side effects) of the pharmacokinetic dimension (e.g., CYP450 isoenzymes). It is difficult to reach a stable therapeutic window to assess pharmacodynamic effects and variations in response to a specific drug in the midst of side effects and drug switching.

There is not a consistent phenotypic conversion for the *35 allele of CYP2D6 in the literature. Databases maintained by the Clinical Pharmacogenetics Implementation Consortium,[43] the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB),[44] and the Human Cytochrome P450 Allele Nomenclature Committee[45] refer to the *35 allele functionality as normal. It may be appropriate to consider the *35 phenotype to be on the upper boundary of extensive metabolizers. Given this placement in the functional range, we assign *35 a metabolic reserve of 1.5 and classify only the *35/*35 homozygous diplotype as ultrarapid, with a metabolic reserve of 3. Concerning the *17 allele of CYP2C19, there has been inconsistency as well, to the extent that some laboratories had classified

the allele as ultrarapid on its own. CPIC has published guidelines that only the *17/*17 homozygote be categorized as ultrarapid, whereas it has recommended the descriptor "rapid" for the *1/*17 carrier. We believe that there are similar issues with regard to the regulatory polymorphisms of both *CYP2D6* and *CYP2C19* genes, and that only the respective homozygotes *35/*35 and *17*17 should be classified as ultrarapid metabolizers, as is the case in this patient.

Toxicology

Toxicology data were available only for three selected patient presentations: two prior to referral and one after. Certainly, the urine drug screens are routine and valuable for monitoring prescribed and illicit drugs and determine the patient's compliance or addiction. However, even when performed at high resolution with mass spectrometry, urine toxicology will not be useful for phenotype-to-genotype correlations until the toxicology and genetic data are integrated into a clinical decision support system. It is noteworthy than in the first report, when the patient was taking hydrocodone, the toxicology was negative for both the parent drug, hydrocodone, and its active CYP2D6 metabolite, hydromorphone, but positive for its inactive CYP3A4 metabolite, norhydrocone. In the second report, when the patient was taking hydromorphone itself, the test was positive for the drug. In a CYP2D6 ultrarapid metabolizer, immediate breakdown of hydrocodone to hydromorphone is expected, which could lower the parent drug below detection levels and alter the ratio of the metabolites. This case illustrates how a compliant patient who is a CYP2D6 ultrarapid metabolizer could test negative for hydrocodone because of metabolizer status. In contrast, hydromorphone, which is not a CYP2D6 substrate, can achieve therapeutic levels and pain relief and should be a preferred alternative in such patient.

Implications of common CYP2D6 and CYP2C19 nonexpansion rapid alleles

The case presented represents an extreme of coincidence, a double homozygous status for *35 for *CYP2D6* and *17 in *CYP2C29*. However, given that *35 is not rare and *17 is common, there will be combinations of these alleles where the patient inherits not four, but three or two copies, or even one copy, of these alleles.

If the other alleles are normal, it raises the possibility of a range of clinically significant suprafunctional patients. Such individuals are suprafunctional in CYP450 metabolic routes, which could compensate for single-gene deficiencies in the same genes or buttress overlapping pathways in drug metabolism. The metabolic overcapacity may reduce specificity and break down nonsubstrate drugs, with risk to the patient of adverse reactions with several pharmaceuticals.[3] That patients may be substantially enhanced for CYP450 drug metabolism indicates the importance of combinatorial genotyping in medical practice.

The ultrarapid status presents unique risks for opioid treatments. Some opioid prodrugs, such as codeine and oxycodone, become immediately metabolized upon administration, which results in a bolus of morphine or oxymorphone, which in turn presents a risk of respiratory depression. For opioid drugs, the ultrarapid status results in immediate breakdown, which prevents the attainment of therapeutic, steady-state drug concentrations. These patients will register drug and urine levels of the opioid drugs significantly below range, even when the patient is compliant with the regimen.

It is likely that, depending on the metabolites or their vulnerability, suprafunctional patients may evidence unusual symptoms of opioid intoxication. Unusual central nervous system (CNS) manifestations after codeine, hydrocodone, or oxycodone include nervousness, restlessness, confusion, hallucinations, or paradoxical stimulation.[46] Pain management patients reporting unusual adverse psychiatric symptoms after treatment with codeine, hydrocodone, or oxycodone may benefit from CYP450 combinatorial genotyping. Dosage adjustments in suprafunctional patients are possible but difficult, since a dosage depends on the relative activity of metabolite to precursor. Alternative treatments with medications not dependent on these pathways may be preferable.

Psychological aspects

Patients at either extreme of CYP450 metabolic function are lost in the health care system because they are difficult to manage empirically. Unfortunately, prevailing and repeated therapeutic failures may imply fault with the patient, who may become suspected of malingering, noncompliance, or nocebo effects. Patients obtain validation and a boost to self-esteem

after the molecular diagnosis afforded by combinatorial genotyping. This information itself is therapeutic, as it determines innate pharmacological phenotypes of the person. Unfortunately, there remains a knowledge gap in the medical profession about the value of the CYP450 genotyping, which some uninformed physicians may disregard or even dismiss.

As shown by the disbelief from the psychiatrist, the present is a difficult time for physicians and other health care providers to implement pharmacogenetics in their practice. Conflicting or inconsistent evidence in the field is coming from commercial marketing, scientific literature, and peer experience. This case may serve to highlight the clinical scenarios where pharmacogenetic information is relevant and useful for directing drug therapy.

There have been various reports linking the combined *CYP2D6* and *CYP2C19* "ultrarapid" metabolizer phenotype to suicide attempt.[47] The neurobiological mechanism has been attributed to a very rapid breakdown of endogenous, pharmacologically active CYP2D6 ligands. The suicidal attempt by the patient may be consistent with this possible risk.

Future prospects

This case demonstrates the clinical value of combinatorial CYP450 genotyping of drug-metabolizing genes in the evaluation of patients with histories of adverse reactions and sensitivities to multiple drugs. The clinical history and outcome of the patient reported here are extraordinary with regard to management of pain and psychiatric medications at the highest extreme of metabolic function. We foresee the routine combinatorial CYP450 genotyping before medication prescription to diagnose adverse drug reactions and treatment resistance and to guide future drug therapy.

Declaration of interest

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