Influence of *CYP2D6*17* and **29* alleles on risperidone pharmacokinetics

Laura Ramsey, PhD

Section Chief of Individualized Therapeutics

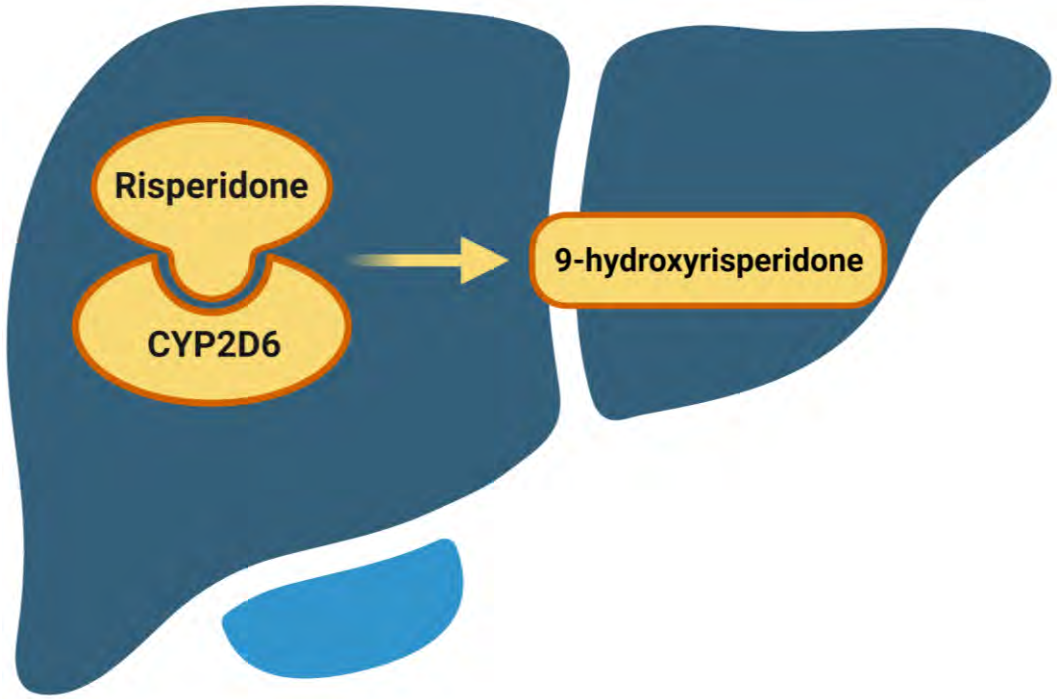
Associate Professor of Pediatrics

Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation

Children's Mercy Hospital

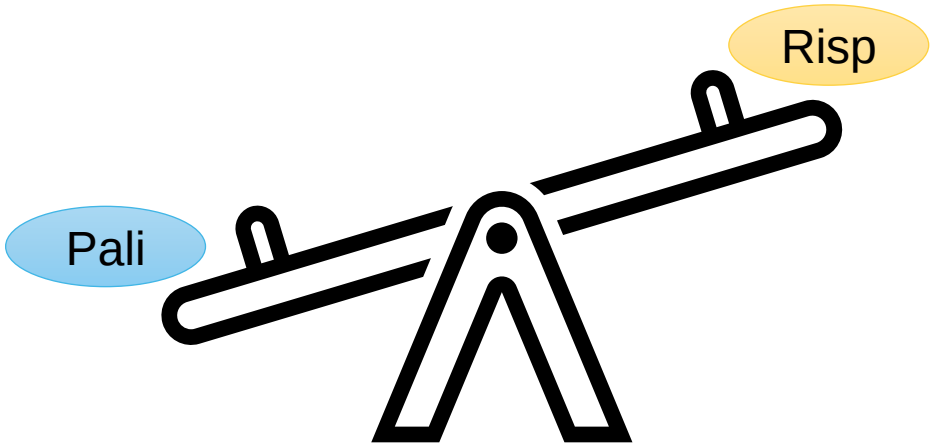
Risperidone Uses and Metabolism

- Indicated for treatment of schizophrenia, bipolar disorder, and irritability associated with autism in children and adolescents
- Also used to manage aggressive behavior and psychosis in patients with other mood disorders
- Metabolized by CYP2D6 into 9-OH-risperidone (paliperidone)
- Risperidone $t_{1/2}$: 3h in CYP2D6 NMs, 20h in PMs
- Paliperidone $t_{1/2}$: 21h in CYP2D6 NMs, 30h in PMs
- Side effects: extrapyramidal effects, weight gain, hyperprolactinemia



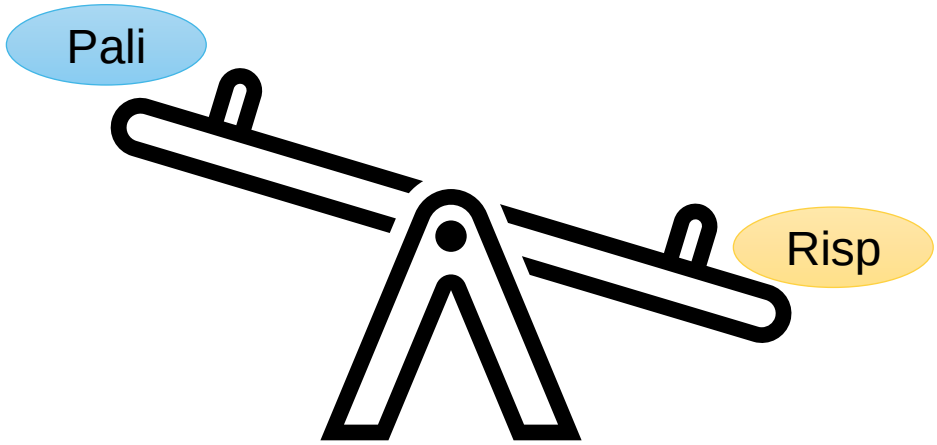
Risperidone metabolism & side effects

CYP2D6 PM



More weight gain
Less hyperprolactinemia

CYP2D6 UM



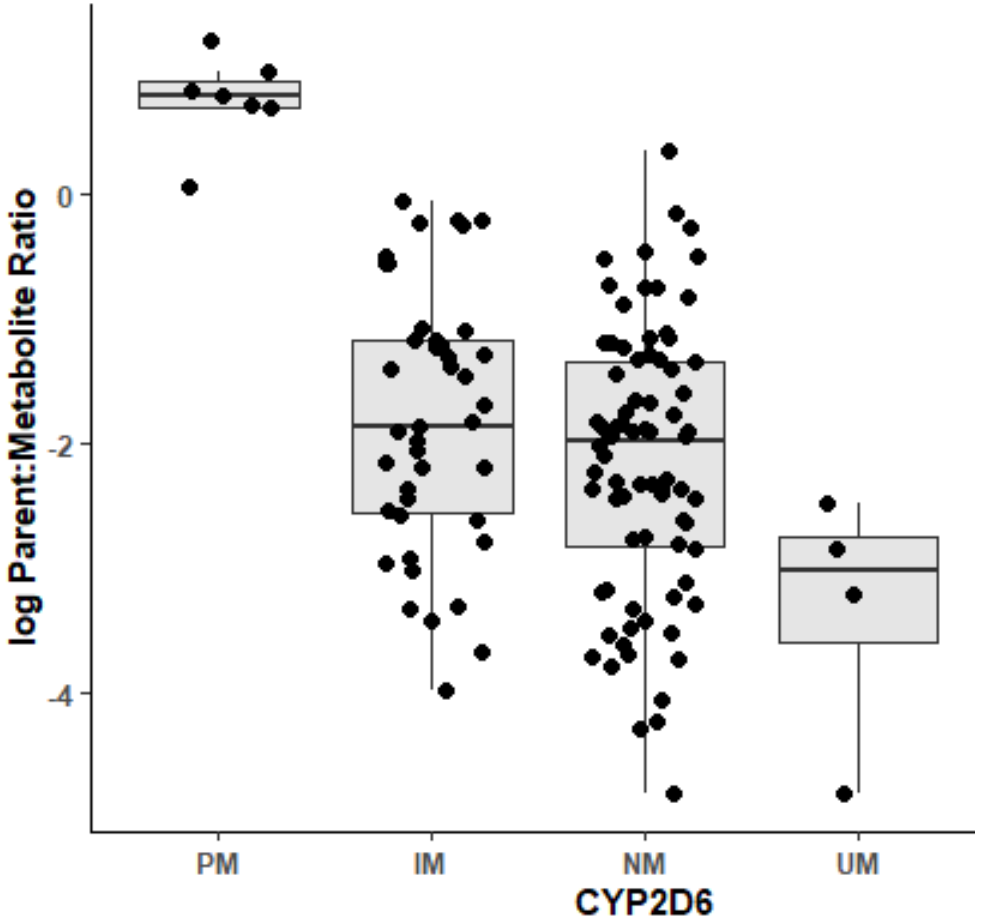
Less weight gain
More hyperprolactinemia

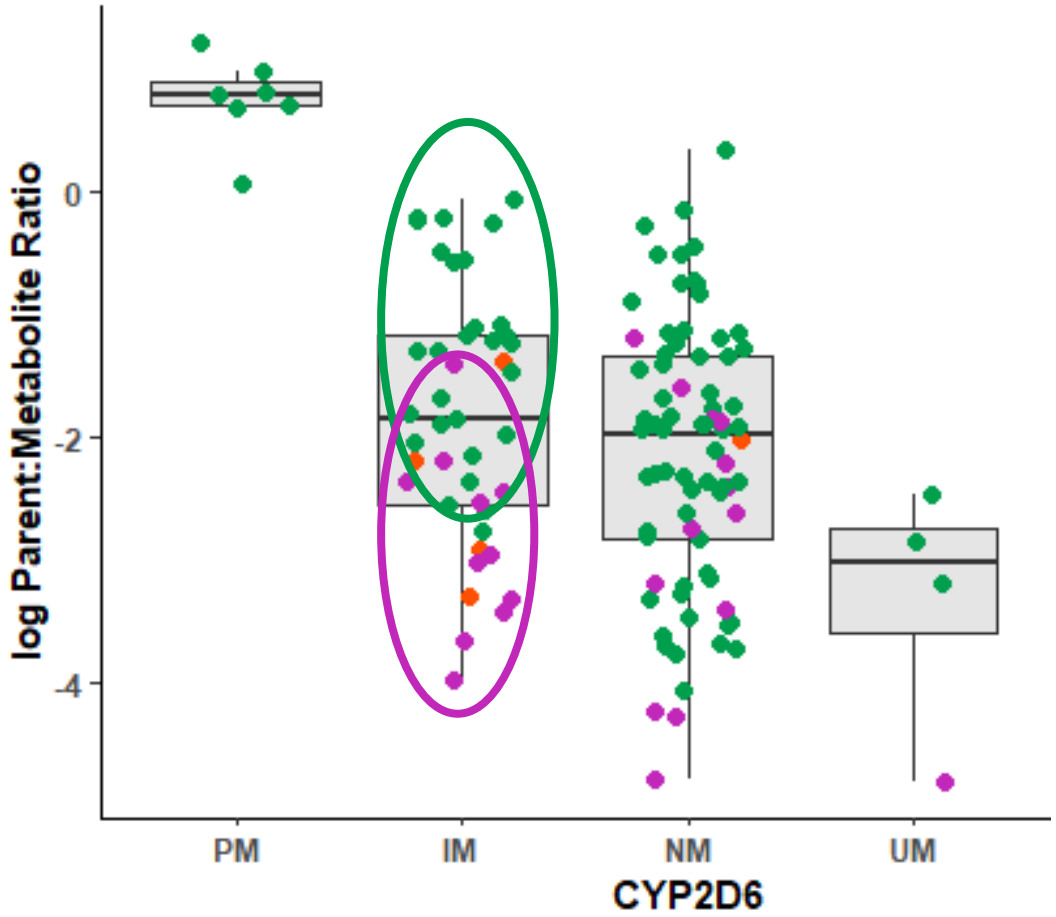
African study

- 211 patients, 64% male, 57% Yoruba, 26% Igbo, mean age 12 ± 5 years
- CYP2D6 genotype unresolved for 3 patients
- MAF of reduced function alleles: *17, 20% & *29, 12%
- CYP2D6 metabolizer phenotypes:
  - PM n=7, 3.4%
  - IM n=72, 35%
  - NM n=119, 57%
  - UM n=10, 5%
- Risperidone measurable in 133, 9-hydroxyrisperidone in 198 patients

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.70012
PMID: 40704440

CYP2D6 influences risperidone, metabolite & ratio





PM, poor metabolizer; IM, intermediate metabolizer
NM, normal metabolizer; UM, ultrarapid metabolizer

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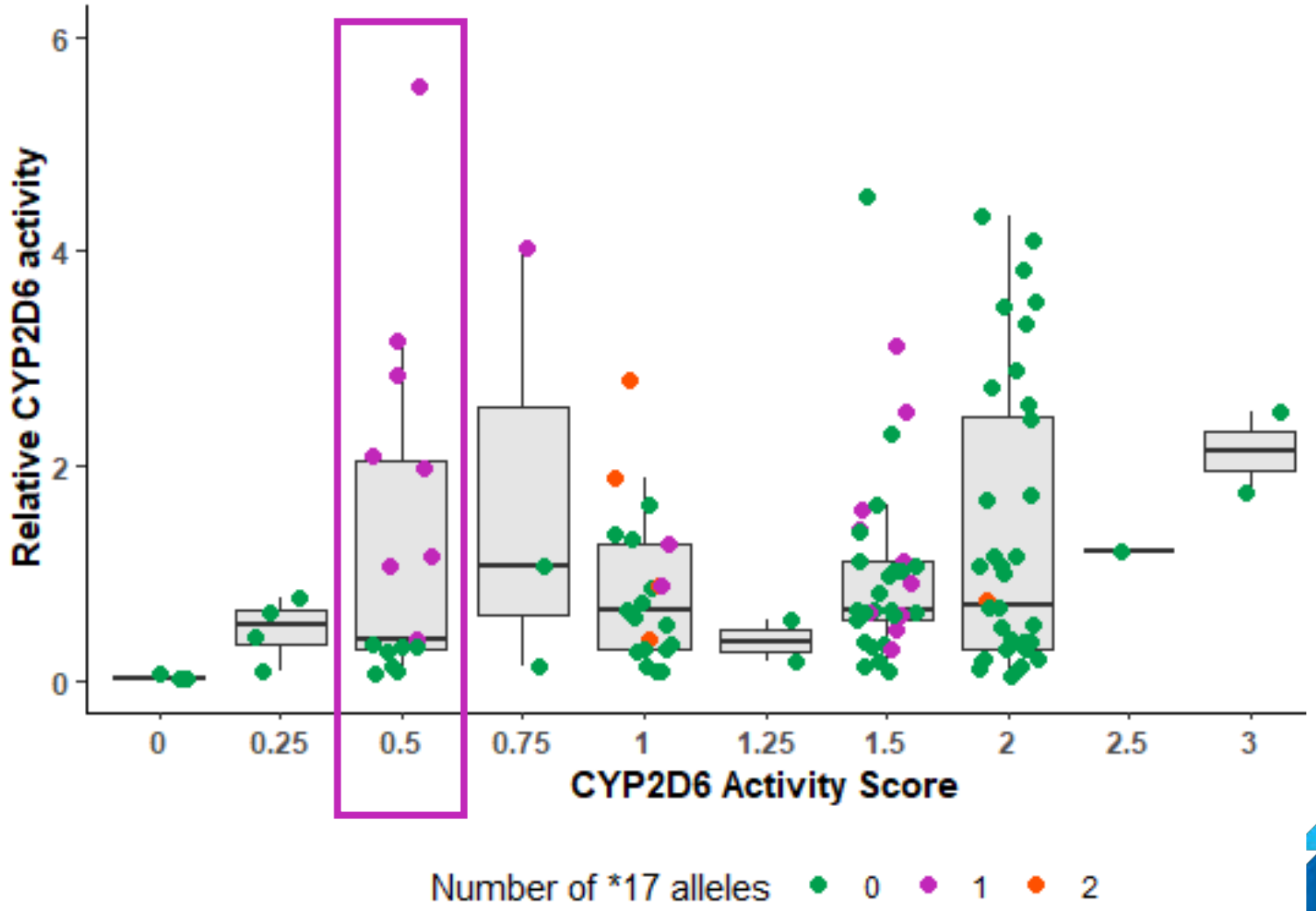
Calculating relative CYP2D6 activity

- Metabolic ratio: 9-hydroxyrisperidone/risperidone
- Requires both were measurable
- *1/*1 median = 100%
- PM (*4/*4, *4/*5, *5/*5) median = 0%



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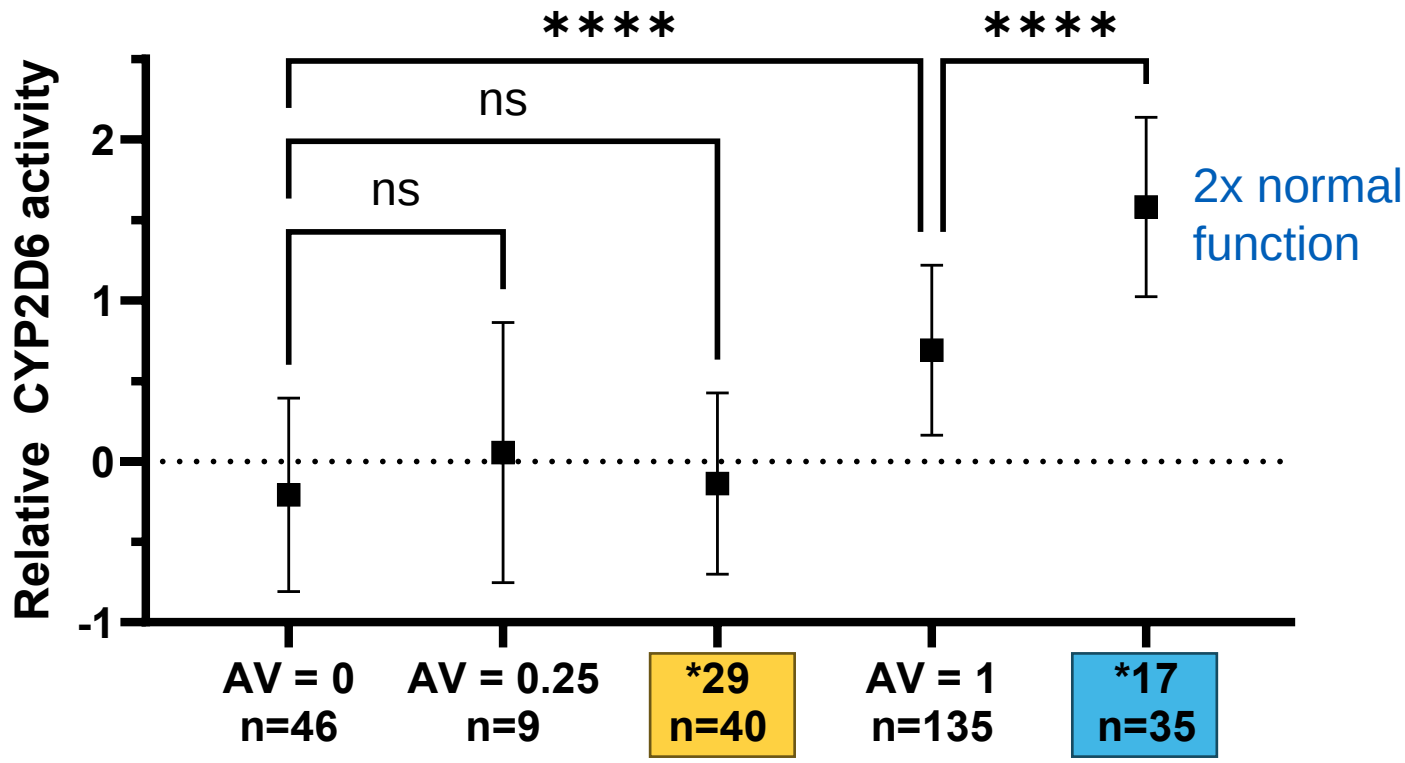
Does *17 have increased function for risperidone?

- CYP2D6*17 activity value is currently 0.5 based on other substrates
- Cai et al found increased function for *17 allele with risperidone in 2006 (n=3)



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Among patients with detectable metabolite but not parent, over half were *17 allele carriers

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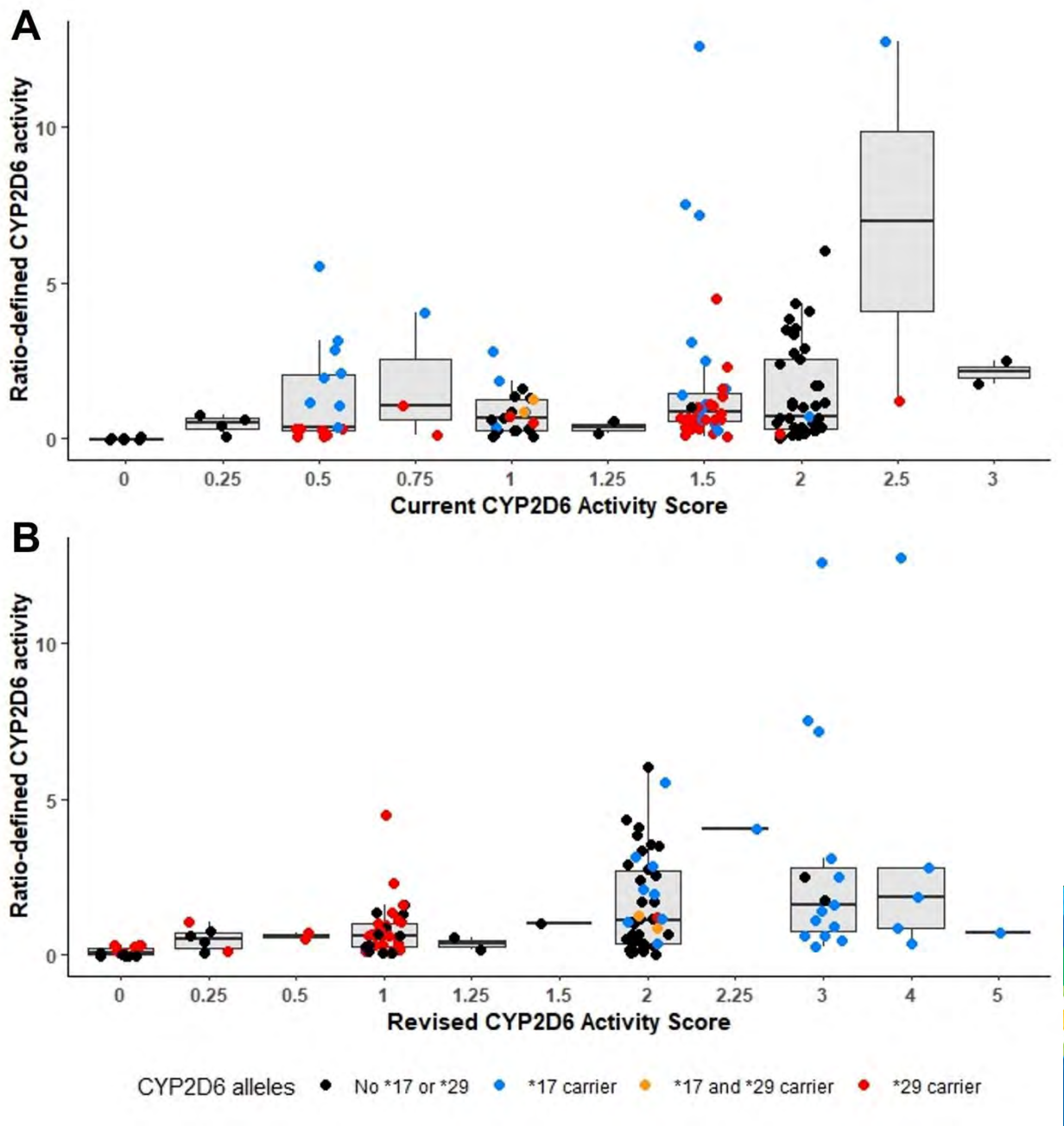
Revised activity score improves model fit

The current activity score explained 10% of the variability in the ratio-defined activity, while the revised activity score explained 23%

Revisions:

- *CYP2D6*17* AS 2 instead of 0.5
- *CYP2D6*29* AS 0 instead of 0.5



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Prior work by Jose de Leon

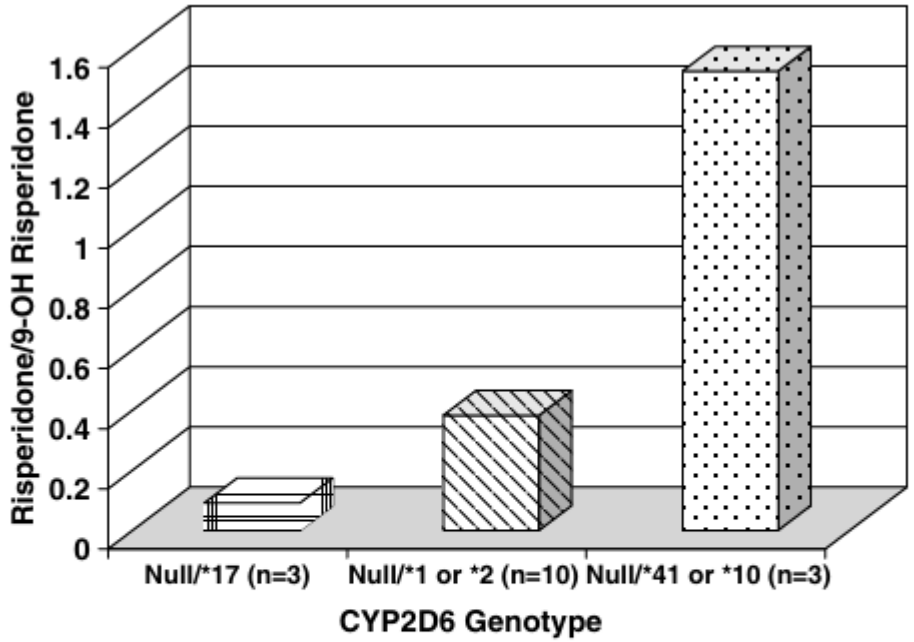

Figure 1 The ratio of risperidone/9-OH risperidone in three different groups of African-American patients stabilized on a fixed dose of risperidone/day. The average ratio was obtained from three African-American subjects who expressed only the *CYP2D6*17* allele, from 10 African-Americans expressing only the **1* or **2A* allele, and from three African-Americans expressing only the **10* or **41 CYP2D6* alleles. The typical ratio for *CYP2D6* poor metabolizers is >1.0, whereas ultrarapid metabolizers have ratios $\leqslant 0.10$.

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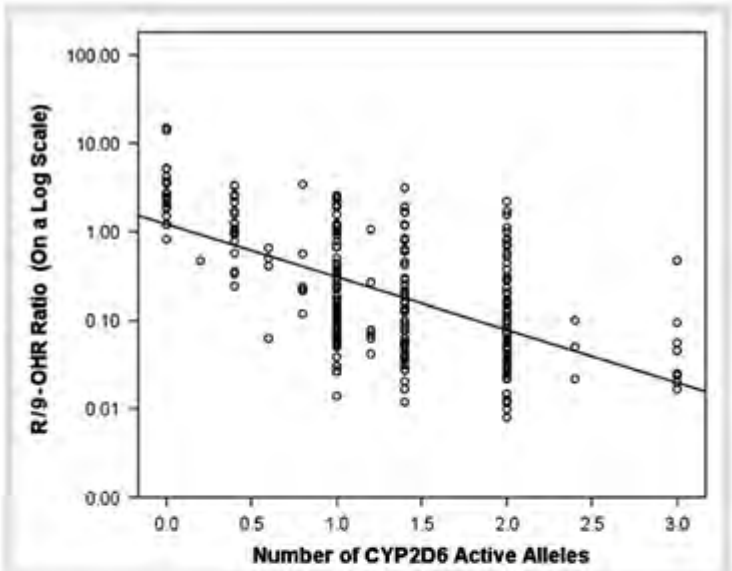

Fig. 1 Plot of plasma risperidone:9-hydroxyrisperidone (R:9-OHR) concentration ratio versus the number of CYP2D6 active alleles ($n = 277$). A regression line is also drawn. The significant and negative line slope suggests that the higher the number of active alleles in a patient, the higher the possibility that the patient has a low R:9-OHR ratio (using the natural log of the R:9-OHR ratio, slope = −1.4; 95% CI = (−1.6, −1.2); $t = 12.4$; $P < 0.001$). Although the information in this area is not definitive, we *a priori* assigned a CYP2D6 activity of 0 to *3, *4, *5, *6, *7, *8, *11, *15, *19, *20, *40, and *4xn; of 0.2 to *10 and *36; of 0.4 to *9, *29, *41, and *10xn; of 0.8 to *41xn; of 1 to *1, *2, *35, and *17, and of 2 to *1xn, *2xn, *35xn, and *17xn alleles. The literature suggests that allele *17 is associated with low CYP2D6 activity, but a visual inspection of the R levels in this study suggested that this was not the case for R [6]. Thus, *17 and *17xn were assigned an activity of 1 and 2, respectively. The activities of a patient's two CYP2D6 alleles were added to obtain the CYPD6 total activity for the patient (e.g., a CYP2D6 PM had an activity of 0, while a CYP2D6 UM had an activity of 3).

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Jose de Leon's risperidone-specific activity score proposal

A Provisional System for Approximation of CYP2D6 Activity for Alleles Identified by the AmpliChip CYP450 Test

For Most Drugs	*For Risperidone*
Inactive alleles (level of activity 0)	
*3,*4,*5,*6,*7,*8,*11,*15,*19,*20, *40 and *4xn	Same
Alleles with very low activity (level of activity 0.2)	
*10 and *36	Same
Alleles with low activity (level of activity 0.4)	
*9, *17, *29, *41 and *10xn	*9, *29, *41 and *10xn
Alleles with activity lower than normal (level of activity 0.8)	
*41xn and *17xn	*41xn
Alleles with normal activity (level of activity 1.0)	
*1, *2 and *35	*1, *2,*35 and *17
Alleles with increased activity (level of activity 2.0)	
*1xn, *2xn, and *35xn	*1xn, *2xn, *35xn, and*17xn

CYP=cytochrome P450.

de Leon J, Susce MT, Johnson M, Hardin M, Maw L, Shao A, Allen ACP, Chiafari FA, Hillman G, Nikoloff DM. *CNS Spectr.* Vol 14, No 1. 2009.

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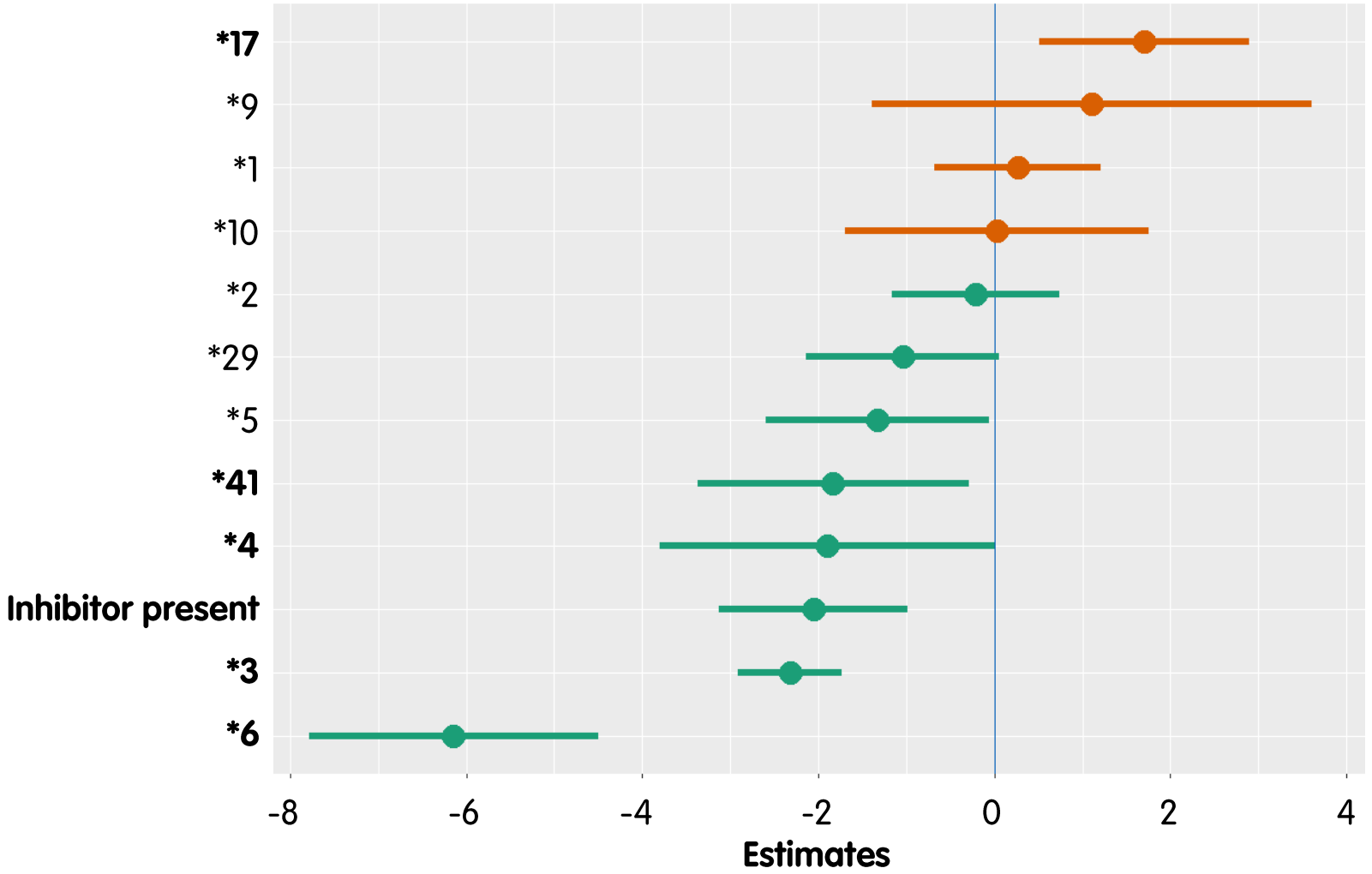
Validation study (published in March)

- Cincinnati Children's remnant blood samples collected in 161 patients admitted to psychiatry unit
- 63% male, mean age 12.5 (range 5-18), 26% Black, 67% White
- 46 patients on strong CYP2D6 inhibitor

http://dx.doi.org/10.1111/cts.70525

*17 allele has >4x normal function



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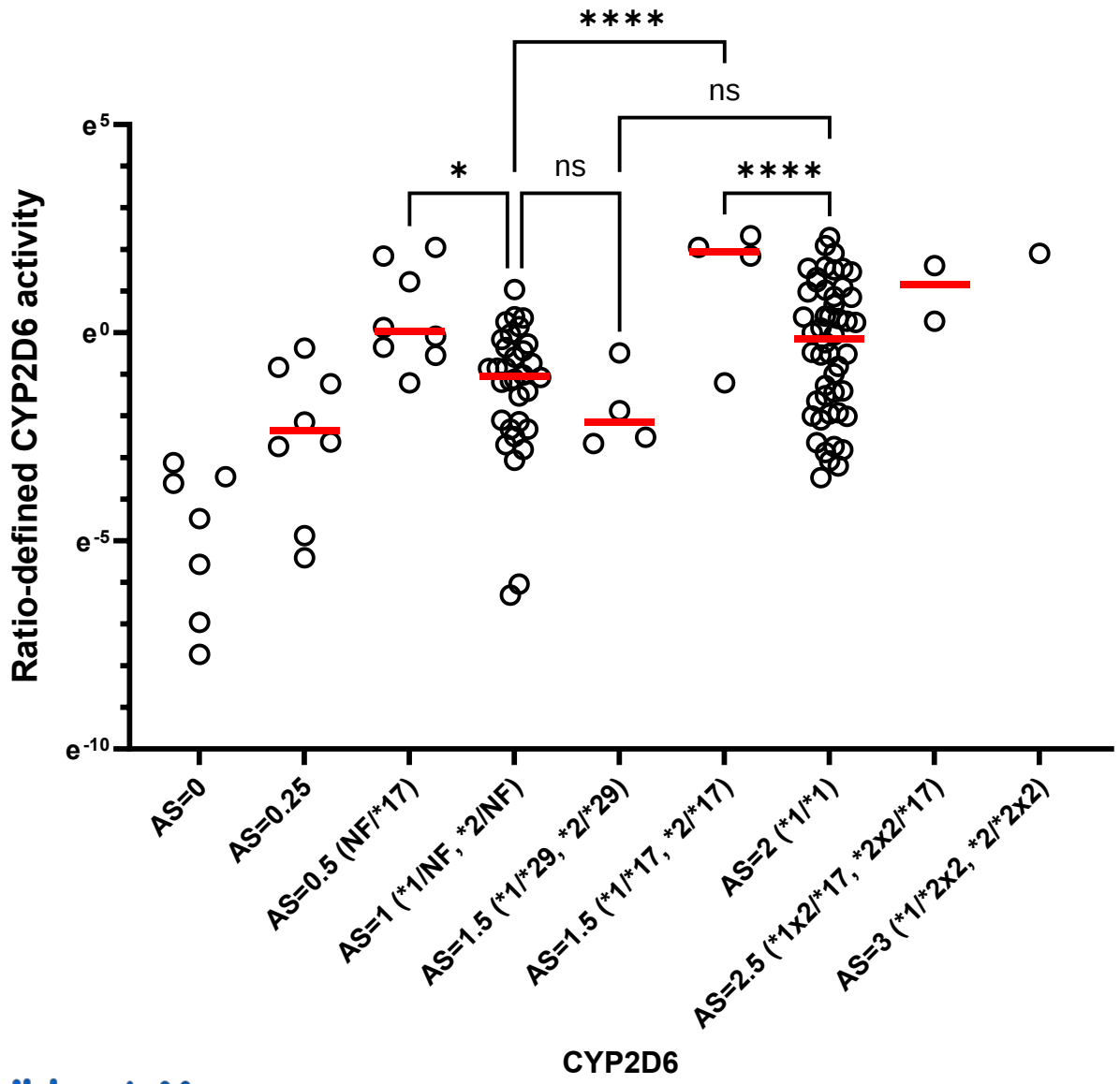
Estimated allele activity calculated from log-transformed ratio of 9-hydroxyrisperidone to risperidone in a multivariate linear regression model including concomitant inhibitor use. Those in bold have p<0.05 in the model. Estimates represent the exponentiated model coefficients.



*1/*17 have comparable activity to UMs, and significantly higher than AS=2 NMs
(will have more paliperidone than expected, potentially increasing risk for side effects)

NF/*17 have significantly higher activity than AS=1 IMs (may be undertreated with IM dosing)

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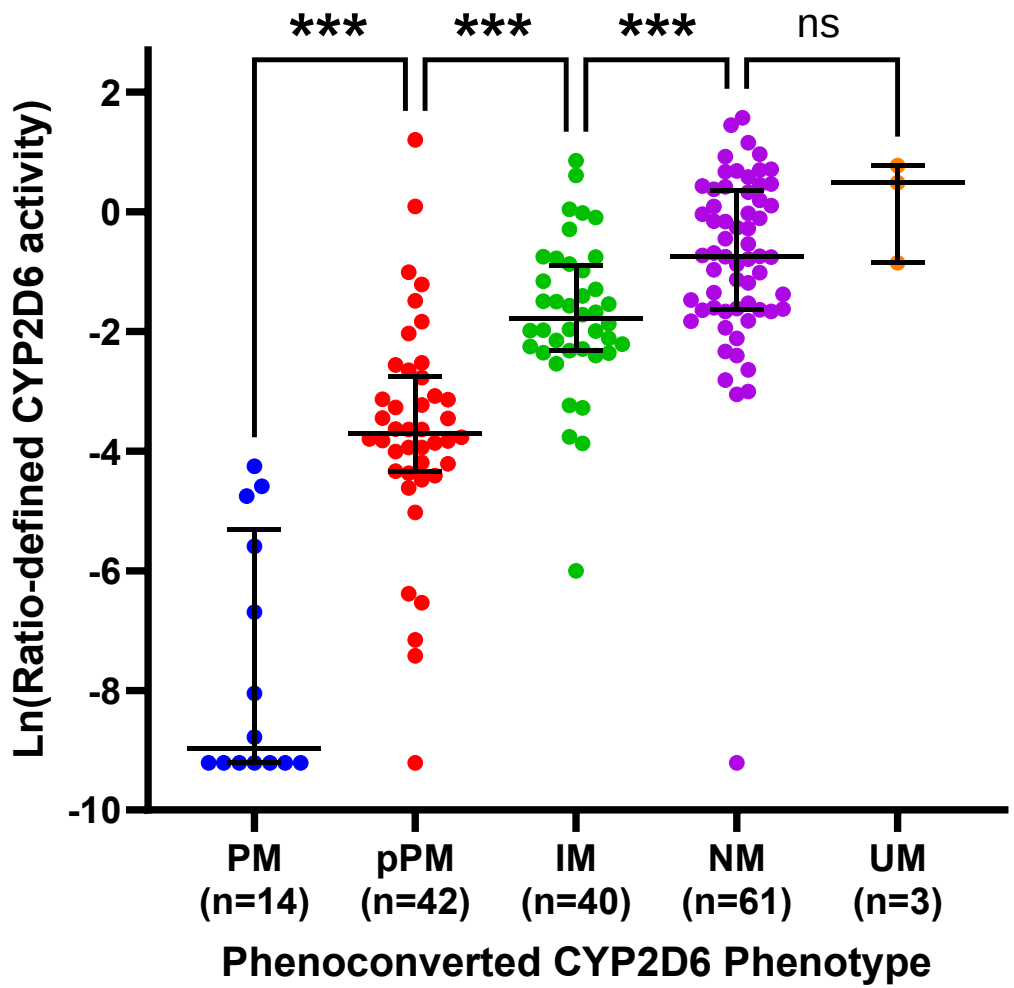
Phenoconversion is incomplete



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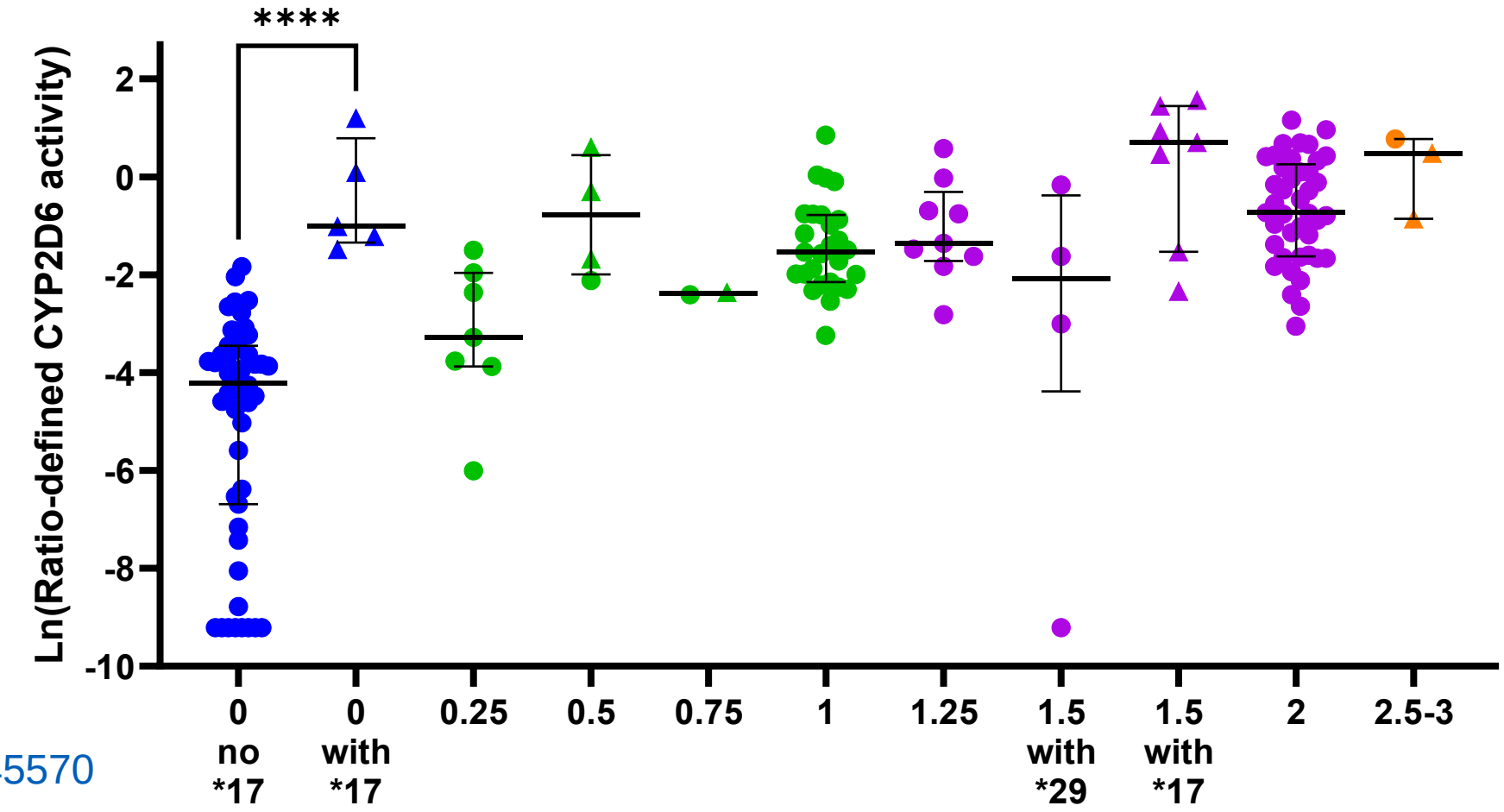
Outliers in phenoconversion often have *17 alleles



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In vitro data demonstrates substrate specificity for *CYP2D6*17*

*CYP2D6*17* contains four SNPs: 1023C>T in exon 2; 1661G>C in exon 3 (a silent SNP); 2850C>T in exon 6; and 4180G>C in exon 9, resulting in three substitutions: T107I; R296C; and S486T, respectively.[199] Compared with *CYP2D6*2*, *CYP2D6*17* contains one more substitution (T107I). This change occurs in a region of the β′-helix that is conserved across species, and residue 107 may be involved in substrate recognition. The *17 allele has been associated with decreased debrisoquine hydroxylation *in vivo*.[199] Expression of the cDNAs in COS-1 cells revealed that the CYP2D6.17 enzyme displayed only 20% of the wild-type activity, whereas the T107I substitution alone had no significant effect on enzyme function.[202] Allozymes containing both T107I and R296C showed a 5-fold higher K_m for bufuralol than the wild-type enzyme, whereas the S486T mutation showed no impact.[202] In contrast, when codeine was used as a substrate, the T107I substitution alone was sufficient to cause a significant increase in the apparent K_m,[202] indicating a differential effect for this substitution depending on the CYP2D6 substrate. The apparent K_m for codeine was 5- to 10-fold higher for CYP2D6.17 than for the wild-type enzyme.[202] These findings indicate that CYP2D6.17 displays an altered affinity for substrates and that a combination of the T107I and R296C substitutions are required for altered catalytic properties of the enzyme towards bufuralol.

TABLE 1

Comparison of enzyme kinetic parameters for CYP2D6.1-, CYP2D6.10-, and CYP2D6.17-mediated metabolite formations

All reactions were run in duplicate. Error estimates are based on the best fit of the average values obtained at each point to the Michaelis-Menten equation using nonlinear regression analysis.

Biotransformation	K_m	V_{max}	CL_{int}	CL_{int} ratio
	μM	*pmol/min/pmol P450*	*μl/min/pmol P450*	*% CYP2D6.1*
CYP2D6.1				
Bufuralol 1′-hydroxylation	10.2 ± 0.6	6.29 ± 0.12	0.617	
Dextromethorphan *O*-demethylation	2.97 ± 0.39	3.49 ± 0.10	1.18	
Debrisoquine 4-hydroxylation	73.7 ± 7.0	1.32 ± 0.04	0.0179	
Atomoxetine 4-hydroxylation	2.73 ± 0.23	19.1 ± 0.4	6.99	
(*S*)-Fluoxetine *N*-demethylation	0.834 ± 0.111	0.414 ± 0.012	0.496	
Nortriptyline 10-hydroxylation	4.07 ± 0.36	0.96 ± 0.02	0.236	
Tramadol *O*-demethylation	286 ± 44	12.9 ± 0.5	0.0451	
Codeine *O*-demethylation	1079 ± 307	3.68 ± 0.33	0.00341	
CYP2D6.10				
Bufuralol 1′-hydroxylation	12.9 ± 1.1	0.29 ± 0.01	0.0225	3.65
Dextromethorphan *O*-demethylation	9.14 ± 0.59	0.57 ± 0.01	0.0624	5.31
Debrisoquine 4-hydroxylation	94.5 ± 7.8	0.20 ± 0.01	0.00212	11.8
Atomoxetine 4-hydroxylation	3.45 ± 0.45	2.07 ± 0.07	0.600	8.58
(*S*)-Fluoxetine *N*-demethylation	0.455 ± 0.076	0.017 ± 0.001	0.0374	7.54
Nortriptyline 10-hydroxylation	48.1 ± 8.0	0.15 ± 0.01	0.00312	1.32
Tramadol *O*-demethylation	331 ± 107	1.03 ± 0.09	0.00311	6.90
Codeine *O*-demethylation	1206 ± 239	1.14 ± 0.07	0.00095	27.9
CYP2D6.17				
Bufuralol 1′-hydroxylation	9.47 ± 1.54	1.33 ± 0.07	0.140	22.8
Dextromethorphan *O*-demethylation	17.3 ± 1.0	3.41 ± 0.05	0.197	16.8
Debrisoquine 4-hydroxylation	108 ± 8	1.24 ± 0.03	0.0115	64.2
Atomoxetine 4-hydroxylation	8.33 ± 0.40	12.8 ± 0.18	1.53	21.9
(*S*)-Fluoxetine *N*-demethylation	2.57 ± 0.50	0.104 ± 0.005	0.0405	8.17
Nortriptyline 10-hydroxylation	18.5 ± 4.0	0.32 ± 0.02	0.0173	7.33
Tramadol *O*-demethylation	209 ± 52	3.36 ± 0.21	0.0161	35.7
Codeine *O*-demethylation	1470 ± 253	4.03 ± 0.24	0.00274	80.4

PMID: 17470523

Mutations in substrate binding pocket and increased stability

variant	amino acid mutations[a]	enzyme activity[b]
CYP2D6*2	R296C, S486T	normal
CYP2D6*4	P34S, L91M, H94R, S486T	none
CYP2D6*10	P34S, S486T	decreased
CYP2D6*17	T107I, R296C, S486T	decreased
CYP2D6*53	F120I, A122S	increased

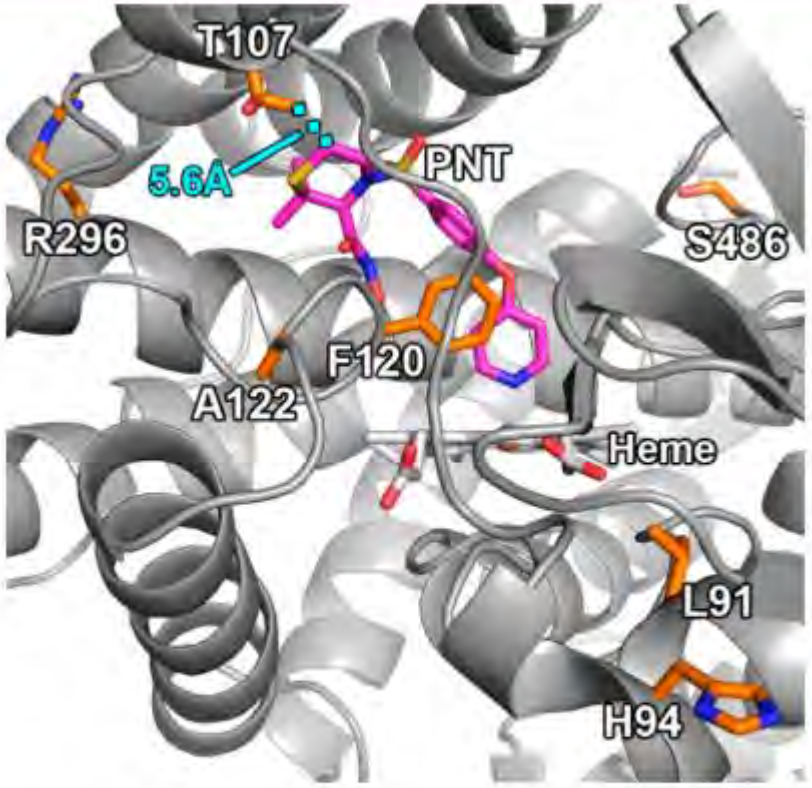

Figure 8. Active site and nearby regions in the native crystal structure of CYP2D6. The mutated amino acids are shown in orange, while the ligand prinomastat (PNT) is shown in pink color. The closest distance between two heavy atoms of T107 and the ligand is shown in cyan.

structure (cf. Table S11). The mutation at position 486 is known to have no significant impact on the enzyme activity in CYP2D6*17.[57] Additionally, all mutations in CYP2D6*17 are located at substrate recognition sites (SRS) providing another indication for the substrate-dependency of the observed effects.[57,58] Contrary to previous observations in the absence of the membrane,[12] our data shows that CYP2D6*17 reached its RMSD equilibrium faster than any other system. Other groups previously discussed that CYPs with faster equilibration times display higher stability in vitro.[12] This points toward a more stable structure of this variant in comparison to others.

PMID 30126275

Conclusions

- *CYP2D6*29* allele had very little activity
- *CYP2D6*17* allele had increased activity
- Validated Nigerian findings in Cincinnati Children's population
- Significant harm could be done by continuing to use current activity score system for risperidone (underdosing in IM with *17, increased production of 9-hydroxyrisperidone which has ↑ hyperprolactinemia risk in NM with *17)

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