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Table A. 東アジア人、欧米人、アフリカ人の代表的な CYP2D6 遺伝子多型 / 変異のアリル頻度

CYP2D6 Alleles	Enzyme Activity	Allele Frequencies (%)				
		Japanese (n=206)	Asian Korean (n=400)	Chinese (n=223)	Caucasian (n=589)	African American (n=154)
*1	Normal	43.00	33.25	37.90	36.40	34.70
*2	Normal	12.30	10.13		32.40	26.90
*3	None		0	0.00	2.04	0.30
*4	None	0.20	0.25	0.20	20.70	7.80
*5	None	4.50	6.13	7.20	1.95	6.20
*6	None		0.00	0.00	0.93	
*7	None		0.00		0.08	
*8	None		0.00	0.00	0.00	
*9	Decreased		0.00		1.78	
*10	Decreased	38.10	45.00	51.30	1.53	7.50
*11	None		0.00		0.00	
*12	None		0.00		0.00	
*13	None		0.00		0.00	
*14	None	0.70	0.50	2.00	0.00	
*15	None		0.00		0.08	
*16	None		0.00		0.08	
*17	Decreased		0.00			14.60
*18		0.20	0.00			
*21			0.25			
*27			0.38			
*35			0.13			
*39			0.63			
*41			1.88			
*47			0.13			
Duplication		1.00	1.13	1.30	1.93	1.90
*1×N		0.50	0.13		0.51	
*2×N		0.50	0.50		1.34	
*4×N			0.00		0.08	
*10×N			0.50		0.00	
Undetermined			0.25			

Table B-1. これまでに報告のある CYP2D6*10 多型ホモ保因者の経口投与後の薬物血漿中濃度の AUC 変化

薬剤	分類	野生型からの AUC 変化	引用文献
propranolol	β-遮断薬	2.3	[24]
carvedilol		1.5～2.1	[25]
metoprolol		3.5	[60]
tropisetron	制吐剤	6.3	[11]
tramadol	鎮痛剤	1.4	[27]
loratadine	抗アレルギー薬	2.2	[28]
risperidone	抗精神病薬	3.1	[29]
haloperidol		1.5	[22]
aripiprazole		1.6	[21]
paroxetine	SSRI	3.4	[26]
venlafaxine	SNRI	5.5 , 5.8	[10, 31]
nortriptyline	抗うつ薬	2.2 , 3	[32]
propafenone	抗不整脈薬	2.1	[33]
mexiletine		1.3	[34]

Table B-2. これまでに報告のある CYP2D6*10 多型による *in vitro* 薬物代謝活性の変化

代謝反応	*10 ミクロソーム	活性比	引用文献
Dextromethorphan O-demethylation	バキュロウイルス発現系	50, 100, 164	[12, 13, 17]
Codein O-demethylation		*10 定量限界以下	[12]
Fluoxetine N-demethylation		50	
MDMA demethylatin		123, 135	[13, 17]
p-Methoxy-amphetamine O-demethylation		34	
(-)-Methamphetamine N-demethylation		157	[13]
MPTP N-demethylatin		22	
Dextromethorphan O-demethylation	酵母発現系	16	[14]
Mexiletine p-hydroxylation		1.3	[35]
Mexiletine 2-methyl hydroxylation		1.1	
Bufuralol 1'-hydroxylation		3, 4.2	[14, 18]
Venlafaxine O-demethylation		2.1	[18]
(+)-Bunitrolol 4'-hydroxylation		4.1	
(-)-Bunitrolol 4'-hydroxylation		4.7	[36]
Debrisoquine 4'-hydroxylation		3	
Mexiletine p-hydroxylation	ヒト肝※	3.7, 5.2	[37]
Mexiletine 2-methyl hydroxylation		32	
Bufuralol 1'-hydroxylation		*10 定量限界以下	[14, 15]

※ヒト肝ミクロソームの活性比は、mg ミクロソーム蛋白当たりの CL_{int} 比 (*1/*1／*10/*10)で表している。

Table 1. EM、*10/*10 保因者、及び PM の肝ミクロソームを用いた *in vitro* 代謝実験から算出したキニジン非存在下及び存在下の固有クリアランス（CL_{int} 及び $CL_{int,quin}$）（μL/min/mg）

薬剤	EM [&]		*10/*10 [#]		PM [#]	
	CL_{int}	$CL_{int,quin}$	CL_{int}	$CL_{int,quin}$	CL_{int}	$CL_{int,quin}$
desipramine	34.4	4.15	5.97±3.95	ND	2.96±4.95	3.34±4.56
venlafaxine	7.51	1.83	2.80±0.61	1.28±0.33	1.74±0.83	1.68±1.40
propafenone	217	30.7	55.8±7.33	ND	ND[$]	ND[$]
risperidone	24.5	8.77	5.35±0.18	2.91±0.71	10.4[$]	11.4[$]
tropisetrone	2.58	1.13	0.17±0.66	ND	1.03[$]	0.97[$]
metoprolol	3.80	0.05	1.20±0.14	0.87±0.05	0.97±0.35	0.98±0.26

ND： not detected

&: プールド

#: 3 例の mean ± SD

$: 1 例

Table 2. ヒト肝ミクロソームを用いて算出した CYP2D6 の代謝寄与率（%）、及び EM に対する*10/*10 保因者 CYP2D6 相対活性の比較

薬剤	CYP2D6 寄与率 (%)	*10/*10 の CYP2D6 相対活性※1 (%, mean ± SD)
desipramine	88	24±8
venlafaxine	76	27±7
propafenone	86	26±11
tropisetron	57	20±11
risperidone	64	17±6
metoprolol	99	9±2
dextromethorphan※2	100	21±6
bufuralol※3	98	19±7

※1: 3 人の*10/*10 保因者から調製した肝ミクロソームを用い、CYP2D6 の選択的阻害剤である quinidine 存在下及び非存在下で測定した *in vitro* 代謝クリアランスより算出した。

※2: 代謝物 dextrorphan の生成速度より評価

※3: 代謝物 1'-hydroxybufuralol の生成速度より評価

Table 3. バキュロウイルス発現系の CYP2D6*1 及び*10 ミクロソームを用いて測定した固有クリアランス及びその活性比

基質	CLint,recCYP2D6 （μL/min/pmolP450）		CLint,recCYP2D6 活性比
	*1	*10	*1/*10
propafenone	10.3	0.775	13.3
risperidone	1.00	0.053	18.8
tropoisetron	0.14	N D	10.0
propranolol	8.55	0.161	53.2
paroxetine	8.40	0.576	14.6
nortriptyline	4.52	0.020	228
carvedilol	25.3	0.316	80.1
metoprolol	0.29	0.004	70.3
desipramine	1.25	0.014	90.9
bufuralol	2.24	0.057	39.2

(注)　bufuralol は代謝物 1'-hydroxybufuralol の生成速度（pmol product/min/mg）。

Table 4. 種々の異なるミクロソームを用いて算出した野生型に対する*10/*10 保因者における CYP2D6 相対活性の比較（%）

基質	バキュロ	ヒト肝	酵母
propafenone	4.0	26	—
risperidone	2.9	17	—
tropoisetron	<5.4	20	—
propranolol	1	—	—
paroxetine	3.7	—	—
nortriptyline	0.2	—	—
carvedilol	0.7	—	—
metoprolol	0.8	9	—
desipramine	0.6	24	—
bufuralol	1.4	19	12 , 17 [14, 18]
dextromethorphan	0.3, 0.5 , 1.1 [12, 13, 17]	21	3[14]

(注)　bufuralol, dextromethorphan は代謝物 1'-hydroxybufuralol, dextrorphan の生成速度。

酵母の各反応及びバキュロウイルスの dextromethorophan の反応は文献値を使用。

Table 5. 各薬剤の血漿中非結合率、及び in *vivo* より算出した肝固有クリアランス($CL_{h,int}$)と、*in vitro* 代謝実験で求めた $CL_{h,int}$ との比較

薬剤	血漿中非結合率% ※1	$CL_{h,int}$ (μL/min/mg micorosme)		
		in vivo ※1	*in vitro*	
			ヒト肝	バキュロウイルス ※2
propafenone	11	460	362 (1.3)	60.0 (7.7)
risperidone	11	38.5	34.2 (1.1)	7.79 (4.9)
tropisetron	42	39.4	2.58 (15.3)	0.92 (43)
propranolol	13	96.5	143 (0.7)	79.0 (1.2)
paroxetine	5	135	165 (0.8)	42.0 (3.2)
nortryptyline	8	70.5	51.2 (1.4)	48.5 (1.5)
carvedilol	5	136	213 (0.6)	174 (0.8)
metoprolol	89	13.2	3.80 (3.5)	1.66 (7.9)
venlafaxine	73	23.6	7.51 (3.1)	

（注）*in vitro* の列の（ ）内は、固有クリアランスの *vivo / vitro* 比

※1：経口投与後の AUC と血漿中非結合率の文献値はインタビューフォームあるいは Goodman & Gilman's the pharmacological basis of therapeutics (9th edition)を参照した。

※2：バキュロウイルス発現系ミクロソームは、CYP2D6 の発現量（5 pmol CYP2D6/mg microsome；文献値　）と寄与率を考慮して、mg ミクロソーム蛋白量当たりの肝固有クリアランスに直した。

Table 6. *In vitro*から予測した*10/*10 保因者の野生型に対するAUC上昇率と、*in vivo* 報告値

薬剤	*10/*10		*10/*10AUC 上昇率の vivo/vitro 比	PM
	predicted AUC 上昇率 (*vitro*)	observed AUC 上昇率 (*vivo*)		observed AUC ratio (*vivo*)
venlafaxine	2.8 ± 0.6	5.5 ± 1.7	2.0	2.3 ± 1.1
propafenone	3.9 ± 0.5	2.1 ± 0.7	0.5	NA
risperidone	4.6 ± 0.2	3.1 ± 1.4	0.7	8.7 ± 4.8, 5.0 ± 0.1
metoprolol	3.2 ± 0.3	3.5 ± 0.5	1.1	5.8 ± 1.0, 4.2 ± 1.0, 3.1 ± 0.8
tropisetron	5.6 ※1	6.3 ± 2.0	1.1	3.1 ※2
desipramine	8.8 ± 7.4	NA	—	6.8 ± 1.5

（比較としてPMの野生型に対するAUC上昇率の*in vivo*報告値を右列に載せた）

*10/*10 保因者あるいはPM との比較, mean±SD

NA: not available

※1) 3例中のうち1ロットのクリアランスがN.Dであったので、*10/*10 の固有クリアランスは残りの2ロットの平均を使用

※2) 6時間後の血漿中濃度比

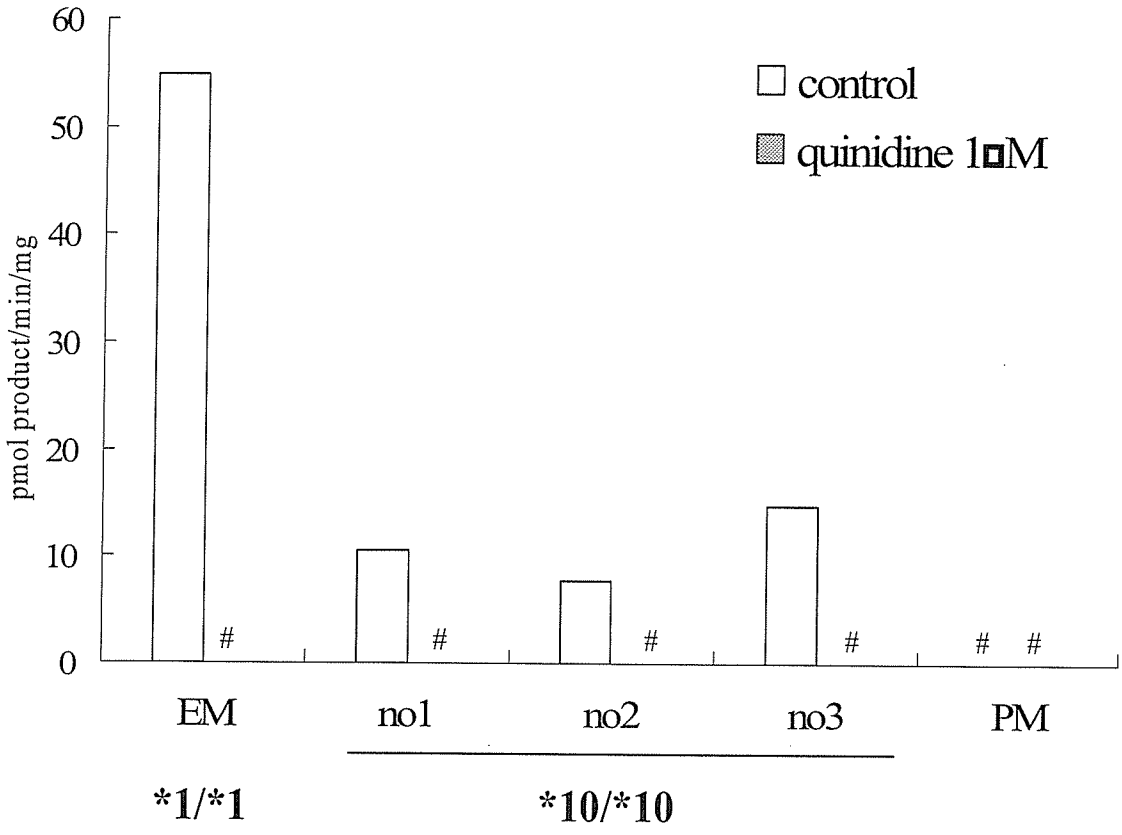


Fig. 1　ヒト肝ミクロソームにおける dextromethorphan O-demethylation 活性
#: quinidine 添加のサンプルの活性は全て検出されなかった。
duplicate のインキュベーションの平均を示す。

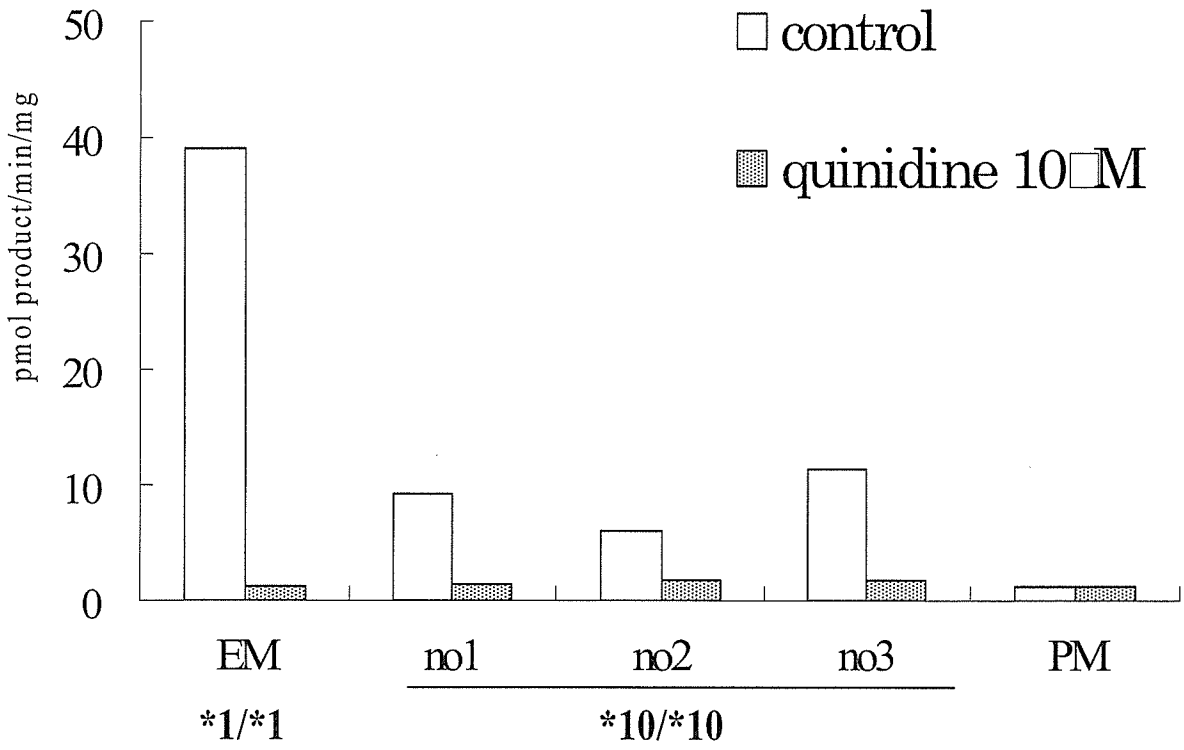


Fig. 2　ヒト肝ミクロソームにおける bufuralol 1'-hydroxylation 活性
duplicate のインキュベーションの平均を示す。

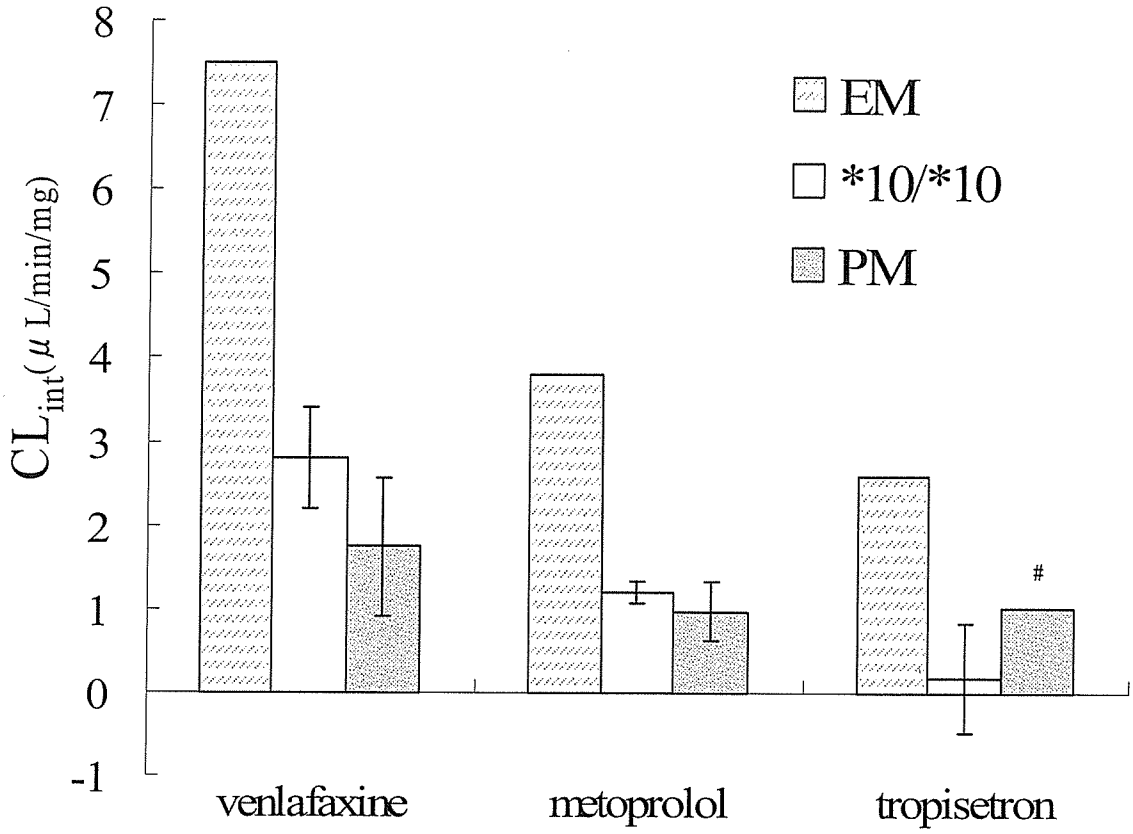
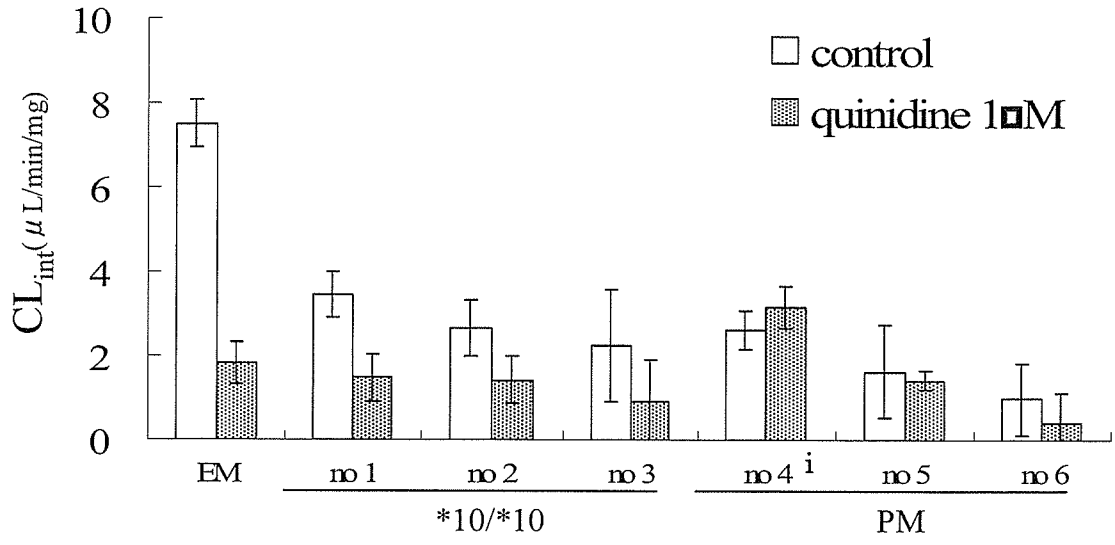


Fig. 3 各種ヒト肝ミクロソームの固有クリアランス　（低クリアランス薬物）
Triplicate のインキュベーションの平均±標準偏差
n = 1



i) PM lot no1 : 3A5 plus

Fig. 4 ヒト肝ミクロソーム代謝実験における venlafaxine の固有クリアランス
各ロットのインキュベーションの平均±標準偏差

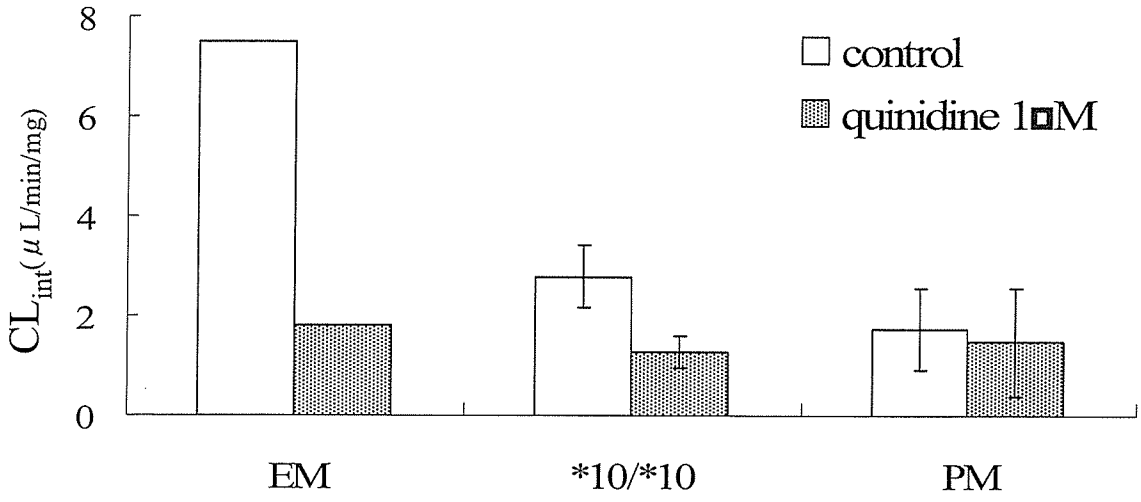


Fig. 5 ヒト肝ミクロソーム代謝実験における venlafaxine の固有クリアランス
*10/*10 , PM ともに 3 ロットの平均±標準偏差

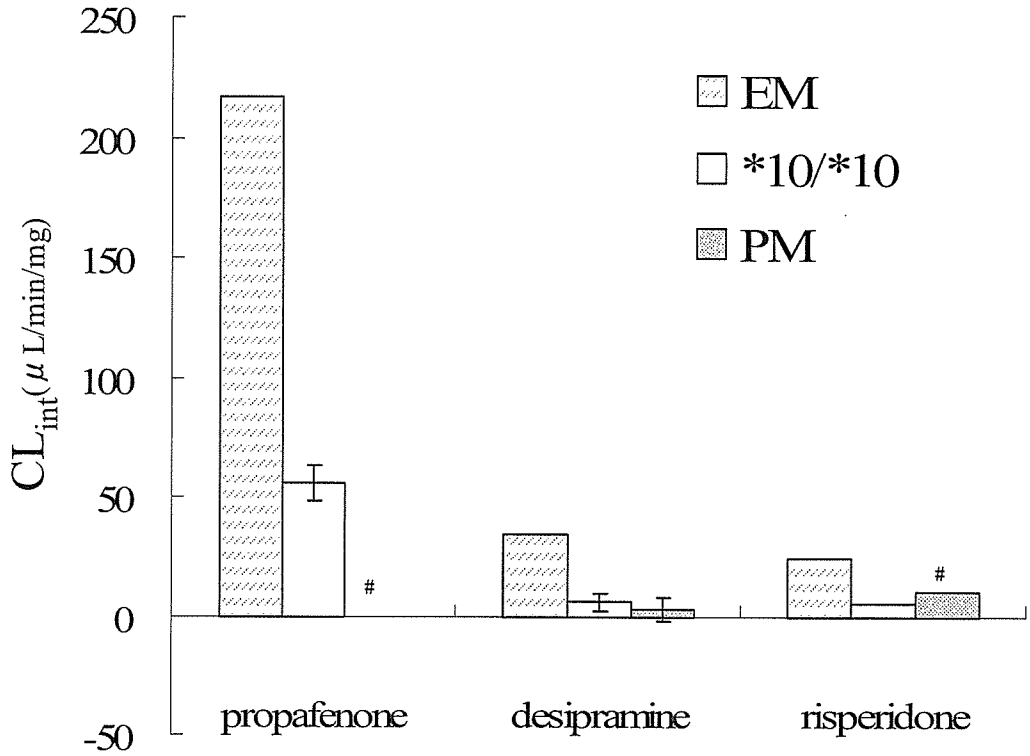


Fig. 6 ヒト肝ミクロソーム代謝実験における固有クリアランス　（高クリアランス薬物）
Triplicate のインキュベーションの平均±標準偏差
n = 1