COMT haplotypes predict pain intensity and interference 6 weeks after motor vehicle collision

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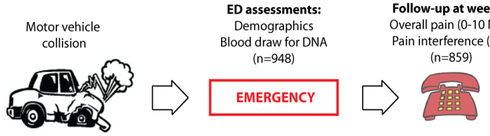
BACKGROUND

Catechol-*O*-methyltransferase (COMT), encoded by *COMT* gene, is the primary enzyme that metabolizes catecholamines. COMT exists in both soluble and membrane-bound (MB-COMT) isoforms. Three haplotypes in the central haploblock of the *COMT* gene code for different levels of COMT enzymatic activity and influence vulnerability to persistent pain.[1] However, two large population-based studies have failed to demonstrate an association between central haploblock haplotypes and chronic widespread pain.[2,3] In addition, other studies suggest that SNPs in the distal promoter P2 (controlling MB-COMT expression) influence transcription[4] and modify the effects of SNPs in the central haploblock on enzymatic activity.[5]

We hypothesized that interactions between three functionally important *COMT* loci (promoter P2, coding region, and 3'-untranslated region) affect vulnerability to persistent pain after motor vehicle collision (MVC).

METHODS

Study design: Prospective multicenter observational cohort study of individuals experiencing MVC



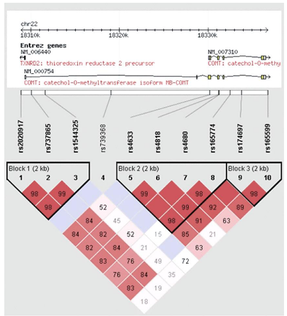
Study population: European Americans 18-65 years old presenting to the ED within 24 hours of MVC who did not have injuries requiring hospital admission: 1,416 individuals were eligible and 948 were enrolled. Sixty one percent were females.

Outcome measures: 1) Overall pain intensity was assessed via telephone interview or web-based questionnaire using a verbal 0-10 numeric rating scale (NRS); 2) Pain interference with life functions (general activity, walking ability, mood, relations with other people, sleep and enjoyment of life) was assessed using the Brief Pain Inventory (BPI), with each item scored on a 0-10 scale.

Blood collection and genotyping: Blood DNA was collected using PAXgene DNA tubes; genotyping was performed using the Sequenom™ platform.

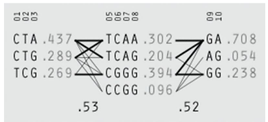
RESULTS

COMT polymorphisms were grouped in three haplotype blocks (promoter P2, coding region, and 3'untranslated region)



All SNPs were in Hardy-Weinberg equilibrium (p > .05).

Haplotypes and haplotype population frequencies were estimated using the expectation-maximization algorithm (below).



Haplotypes from the three *COMT* haploblocks were associated with pain outcomes after MVC

Haplotype	# alleles	Overall pain (SE)	F-value	P-value	Interference (SE)	F-value	P-value
	0	3.8 (0.1)			16 (1)		
A3 (TCG)	1	4.0 (0.2)	2.96	0.051	19 (1)	5.54	0.004*
	2	3.1 (0.4)			11 (2)		
	0	3.8 (0.2)			17 (1)		
LPS (CGGG)	1	4.1 (0.1)	4.26	0.014	19 (1)	3.69	0.024
	2	3.3 (0.2)			14 (2)		
	0	3.8 (0.1)			17 (1)		
B2 (AG)	1	4.2 (0.3)	1.73	0.175	17 (2)	3.85	0.021
	2	5.5 (1.2)			40 (8)		

SE=standard error of mean; * significant after multiple testing correction

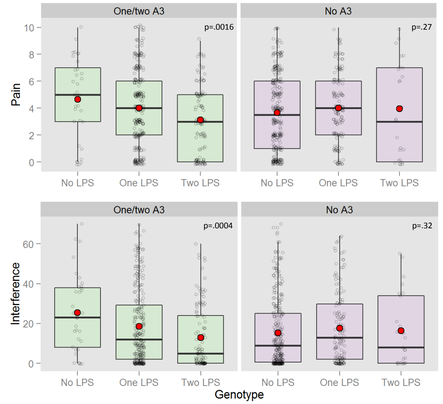
Multivariate regression analysis revealed significant haplotype × haplotype and haplotype × sex interactions

		Overall pain			Interference		
Model term	DF	Type III SS	F Value	P Value	Type III SS	F Value	P Value
A3	1	49.5	6.63	0.0102	3942.9	12.55	0.0004
LPS	1	8.9	1.19	0.2759	548.8	1.75	0.1866
A3*LPS	1	73.3	9.8	0.0018	4957.7	15.78	<.0001
B2	1	66.3	8.87	0.0030	5657.5	18.01	<.0001
B2*Sex	1	54.5	7.29	0.0071	5263.1	16.75	<.0001
Sex	1	143.6	19.21	<.0001	1465.3	4.66	0.0311
Site	7	106.6	2.04	0.0480	5611.1	2.55	0.0133

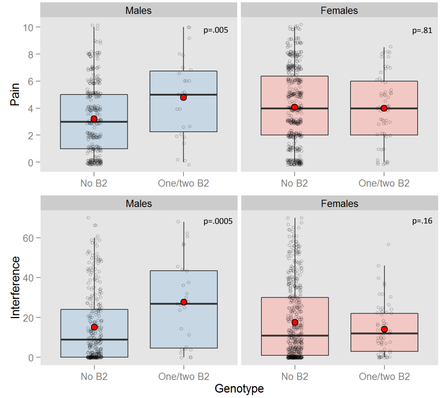
df=degrees of freedom, SS=sum of squares

RESULTS (Cont.)

Low pain sensitivity (LPS) haplotype had a protective effect on pain and pain interference only among individuals with one or two copies of the A3 allele (left panels)



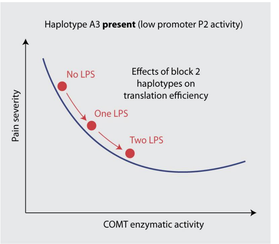
B2 haplotype was associated with increased pain and pain interference only among men (left panels)



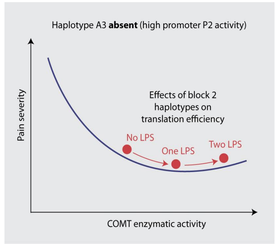
Boxplots indicate minimum, maximum, median, lower and upper quartile. Red dots indicate the mean.

COMMENTARY

Hypothesized mechanistic explanation for the interacting influence of haplotypes in the promoter P2 and *COMT* coding regions on pain outcomes after MVC: U-shaped dose-response curve between COMT activity and post-MVC pain vulnerability



a) In presence of the promoter P2 haplotype associated with low levels of *COMT* transcription, the effect of the haplotypes covering the coding region of *COMT* is prominent because of the steep dose-response curve.



b) In absence of the "low transcription" P2 haplotype the total enzymatic activity is shifted to the right so that the effect of the haplotypes in the coding gene region is reduced because of the flattened dose-response curve.

CONCLUSIONS

Results of this study suggest that the potential influence of *COMT* polymorphisms on pain outcomes is best evaluated using a haplotype-based approach that takes into account interactions between distal promoter, coding, and 3'-untranslated region haploblocks and sex differences in these interactions. Further studies are needed to investigate the biological substrate for these interactions.

REFERENCES

[1]Diatchenko et al. (2005) *Hum Mol Genet*, 14, 135-143. [2]Hocking et al. (2010) *Pain*, 149, 143-151. [3]Nicholl et al. (2010) *Ann Rheum Dis*, 69, 2009-2012. [4]Bray et al. (2003) *Am J Hum Genet*, 73, 152-161. [5]Shifman et al. (2002) *Am J Hum Genet*, 71, 1296-1302.

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