Contribution of the COMT Val158Met variant to symptomatic knee osteoarthritis

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Main text

There is extensive literature reporting discordance between the presence and severity of symptoms and the degree of radiographic structural osteoarthritis (OA).[1-5] Genetic differences may account for some of this discordance. Indeed, certain genetic variants implicated in pain sensitivity have been shown to be significantly different between asymptomatic radiographic cases of OA and symptomatic cases.[6-9]

The catechol-O-methyltransferase, encoded by the *COMT* gene, is a major degrading enzyme in the metabolic pathways of catecholaminergic neurotransmitters.[10] Genetic variation at the *COMT* gene has been shown to result differential pain sensitivity.[10-12] Carriers of the Val158Met *COMT* variant have been reported to have a higher risk (odds ratio (OR)=2.9, 95% CI 1.2–6.1) of hip pain as compared with carriers of the Val/Val genotype among those with hip OA.[9] This result has not been replicated in independent cohorts, nor for OA in other joints. We assessed whether the Met allele in the *COMT* gene is involved in increased risk of symptomatic knee OA in seven cohorts: five cohorts from the UK, one from Australia and two from the US were included (**Table 1**). Assembly of the cohorts was approved by the local research ethics committees and all study participants gave fully informed consent to participate in genetic studies.

The association between the Met+ genotype at COMT position 158 and knee OA was evaluated using logistic regression adjusting for age, sex, and BMI. The ORs were meta-analyzed using the methods described in [8]. For the symptomatic versus asymptomatic knee OA comparison, we also adjusted for KL grade. We also evaluated sex-specific associations. Robust variance estimation was used for the TwinsUK and FOA studies with regards to relatedness. Given the sample size available, the study is powered to detect with $p<0.05$ and 80% power an

OR of 1.245 for the 158COMTMet+ genotype comparing symptomatic with asymptomatic knee OA and an OR of 1.14 for symptomatic knee OA vs. controls.

The association between this genotype and the presence of knee OA, irrespective of symptoms, was close to the null for most cohorts, as was the association with asymptomatic knee OA versus controls (**Table 2).** The effect estimate was suggestive of a 10% increased prevalence of symptoms in those with knee OA compared with those without the polymorphism (adjusted OR 1.10 (95% CI 0.95-1.27), p=0.2), but did not reach statistical significance and is much lower than the original report on symptomatic hip OA.[9] Similar results were seen in sex-stratified analyses (**Table 2**).

Despite biologic plausibility and demonstration of an association in other musculoskeletal pain conditions we did not find an association between the 158COMTMet+ genotype and the knee OA phenotypes studied. The *COMT* variant may contribute differentially in knee and hip OA pain with the effect being smaller in knee OA. Additionally, while the original finding in hip OA was driven primarily by an association among women, we found no evidence for a stronger effect in women in our data. There are some study limitations: some of the included cohorts contributed only a small number of cases and the definition of asymptomatic OA used may further reduce the power to detect a genetic association. Other variants of this gene, or a haplotype approach[11] may provide additional insight for the importance of *COMT* in the pain experience of OA. Other factors that contribute to the pain experience (e.g. catastrophizing, affect) may need to be accounted for.

As with the structural disease, the experience of pain in knee OA is multifactorial. Identification of genetic variants in large, well-phenotyped cohorts may provide much-needed rational therapeutic targets for the substantial unmet clinical need of pain management in OA. [596 words]

Table 1. Descriptive characteristics of study subjects

Cohort name	Genetics of Osteoarthritis and Lifestyle	Hertfordshire Cohort Study	Nottingham Case-Control Study	TwinsUK Study	Chingford study	Tasmanian Older Adult Cohort	Health ABC study	Framingham study
Cohort acronym	GOAL	HCS	Nott	TwinsUK	Chingford	TASOAC	Health ABC	FOA
Reference for cohort details	8	8	8	8	8	8	13	14
Country of origin	UK	UK	UK	UK	UK	Australia	USA	USA
Knee OA								
Symptomatic[a]	n=1199	n=86	n=1703	n=45	n=127	n=86	n=361	n=327
age yrs mean (SD)	68.4 (7.2)	65.3 (2.8)	68.7 (8.9)	57.5 (7.2)	65.7 (5.8)	65.0 (7.2)	75.1 (3.0)	73.1(8.5)
F gender %	46.88%	44.3%	55.3%	100%	100%	58.50%	62.6%	62.1%
BMI kg/m^2 mean (SD)	31.2 (5.4)	29.7 (5.4)	29.7 (5.4)	27.9 (4.5)	26.7 (3.4)	31.3 (6.3)	30.4 (5.3)	30.3(6.2)
K/L≥3 %	89.7%	38.6%	80.8%	29.0%	44.1%	42.6%	65.9%	56.3%
TKR %	94.8%	9.3%	90.3%	26.7%	23.5%	0%	16.9%	13.8%
COMT Met+%[b]	77.6%	67.2%	75.9%	74.4%	81.9%	72.7%	64.0%	78.6%
Asymptomatic[a]	n=376	n=44	n=0	n=235	n=58	n=136	n=88	n=222
age yrs mean (SD)	69.0 (6.7)	65.2 (6.4)	N/A	58.1 (7.8)	65.7 (5.9)	65.8 (7.6)	75.1(2.9)	75.5(7.6)
F gender %	43.9%	31.8%	N/A	100%	100%	43.80%	61.4%	55.4%
BMI kg/m^2 mean (SD)	28.9 (4.9)	28.4 (4.0)	N/A	26.7 (4.9)	26.2 (4.4)	28.1 (4.3)	30.1(5.0)	27.9 (5.1)
K/L≥3%	49.5%	15.9%	N/A	34.0%	26.4%	24.8%	55.7%	37.8%
TKR %	0%	0%	N/A	0%	0%	0%	0%	0%
COMT Met+%	76.4%	73.8%	N/A	72.6%	70.7%	77.9%	55.7%	75.2%
unaffected	n=743	n=542	n=728	n=978	n=401	n=329	n=631	n=1,270
age yrs mean (SD)	62.6 (8.4)	64.8 (2.7)	66.3 (7.4)	52.9 (7.2)	62.9 (5.7)	61.8 (7.5)	74.4 (2.8)	67.9 (9.9)
F gender %	49.9%	50.1%	57.4%	100%	100%	47.9%	58.9%	58.2%
BMI kg/m^2 mean (SD)	27.1 (4.4)	26.2 (3.8)	26.6 (3.9)	24.5 (4.0)	24.7 (3.6)	27.4 (4.4)	26.8 (4.3)	27.4 (4.8)
COMT Met+%	74.4%	77.5%	74.1%	73.7%	77.0%	76.9%	67.0%	76.4%

TKR= total knee replacement, KL= Kellgren-Lawrence

COMT Met+ = frequency of carriage of a Met (either Met-Met or Met-Val) at codon position 158 of the COMT gene

(a) Subjects were considered to have symptomatic knee OA if they had at least one knee with radiographic knee OA (as defined by Kellgren and Lawrence (KL) grade ≥2) and if they had pain in the same knee. Symptoms were considered present in a knee if pain (or in some cohorts, pain, aching, or stiffness) was present in the knee for most days of the month during the prior year, or most days of the prior month. Those with a total knee replacement were classified as symptomatic regardless of current pain status. Because the Nottingham Case-Control Study did not have any asymptomatic subjects and the Hertfordshire Cohort Study had very few symptomatic subjects, and these two UK study cohorts comprised participants of similar ages, data from these two cohorts were pooled.

(b) Genomic DNA was extracted from peripheral blood. For GOAL, Chingford, HCS, TASOAC and Nottingham samples, the rs4680 SNP genotyping was carried out by Kbioscience Ltd, Hertfordshire UK. The TwinsUK samples were genotyped with the Infinium HumanHap 300 and 610 assay (Illumina, San Diego, USA). FOA Study samples were genotyped using the Affymetrix GeneChip® Human Mapping 500K array set (Santa Clara, California). Health ABC samples were genotyped on the Illumina Human1M-Duo BeadChip array. For both TwinsUK and HABC, rs4680 was directly typed. The SNP was imputed in FOA and had MACH_RS = 0.963006, average MACH-QUAL=0.981084. The polymorphism was in Hardy-Weinberg equilibrium in controls for all cohorts ($p>0.05$). A dominant effect model was used.

Table 2. Association between the 158COMTMet+ genotype and symptomatic or asymptomatic knee OA in 7 independent cohorts adjusted for co-variates. Odds ratios (OR) are shown for B=both genders, F= females only, and M=males only.

Cohort Study	Adjusted OR (95% CI), p-value			
	Any knee OA vs controls*	**Symptomatic knee OA vs controls***	**Asymptomatic knee OA vs controls***	**Symptomatic knee OA vs Asymptomatic knee OA†**
Chingford (only F)	F=1.09 (0.70, 1.69)	F=1.38 (0.82, 2.34)	F=0.66 (0.35, 1.26)	F=1.38 (0.82, 2.34)
Framingham	B=1.13 (0.87, 1.47) M=1.33 (0.89, 1.99) F=1.00 (0.72, 1.34)	B=1.22 (0.89, 1.67) M=1.65 (0.97, 2.80) F=1.02 (0.69, 1.50)	B=1.02 (0.72, 1.45) M=1.04 (0.62, 1.74) F=1.00 (0.62, 1.60)	B=1.10 (0.72, 1.68) M=1.63 (0.81, 3.27) F=0.88 (0.50, 1.52)
GOAL	B=1.06 (0.84, 1.34) M=0.89 (0.65, 1.21) F=1.33 (0.92, 1.93)	B=1.11 (0.87, 1.43) M=0.97 (0.69, 1.35) F=1.38 (0.92, 2.07)	B=0.96 (0.71, 1.3) M=0.94 (0.72, 1.23) F=1.01 (0.73, 1.39)	B=1.03 (0.78, 1.36) M=1.31 (0.86, 1.99) F=0.70 (0.43, 1.14)
Health ABC	B=0.95 (0.72, 1.25) M=1.25 (0.81, 1.92) F=0.80 (0.56, 1.14)	B=1.03 (0.76, 1.40) M=1.27 (0.80, 1.01) F=0.89 (0.61, 1.31)	B=0.69 (0.43, 1.11) M=1.26 (0.57, 2.77) F=0.48 (0.26, 0.88)	B=1.43 (0.88, 2.32) M=0.95 (0.42, 2.17) F=1.84 (0.99, 3.40)
HCSNott	B=0.99 (0.88, 1.11) M=0.90 (0.68, 1.18) F=1.01 (0.77, 1.33)	B=1.00 (0.89, 1.13) M=0.93 (0.71, 1.23) F=1.00 (0.76, 1.32)	B=0.74 (0.48, 1.15) M=1.12 (0.44, 2.81) F=0.61 (0.20, 1.84)	B=1.31 (0.85, 2.02) M=0.80 (0.31, 2.04) F=1.55 (0.51, 4.74)
TASOAC	B=0.88 (0.70, 1.09) M=1.17 (0.66, 2.05) F=0.48 (0.26, 0.91)	B=0.92 (0.70, 1.22) M=0.74 (0.48, 1.15) F=1.14 (0.72, 1.8)	B=1.00 (0.81, 1.24) M=1.09 (0.70, 1.69) F=1.41 (0.89, 2.24)	B=0.94 (0.72, 1.24) M=0.47 (0.18, 1.19) F=0.52 (0.20, 1.37)
TwinsUK (onlyF)	F=0.98 (0.71, 1.35)	F=1.03 (0.51, 2.11)	F=0.96 (0.68, 1.36)	F=1.11 (0.53, 2.37)
Summary fixed effects by gender	M=1.02 (0.87, 1.20) F=0.98 (0.86, 1.12)	M=1.00 (0.85, 1.19) F=1.08 (0.92, 1.25)	M=1.01 (0.83, 1.22) F=0.93 (0.78, 1.1)	M=1.12 (0.84, 1.51) F=1.04 (0.82, 1.33)
overall summary fixed effects (95% CI) Met+ carriers	0.99 (0.92, 1.08) p=0.88	1.04 (0.95, 1.13) p=0.42	0.93 (0.82, 1.06) p=0.28	1.10 (0.95, 1.27) p=0.21
Intra-study heterogeneity I^2 (95% CI)	0% (0%,36%)	0% (0%,48.6%)	0% (0%,62.4%)	0% (0%,55.5%)
Sample size	5093 OA, 5622 controls	3934 Sx OA, 5622 controls	1159 nonSx OA, 5622 controls	3934 Sx OA, 1159 nonSx OA

*adjusted for age, sex and BMI

†adjusted for age, sex, BMI and KL grade

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