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Topical review

Candidate gene approach in genetic epidemiological studies of osteoarthritis-related pain

Anna Bratus [a,b,*], Andre Aeschlimann [c], Giancarlo Russo [b], Haiko Sprott [a]

[a] University Hospital Zurich, Division of Rheumatology, Center of Experimental Rheumatology, Zurich, Switzerland
[b] University of Zurich/ETH Zurich, Functional Genomics Center Zurich, Zurich, Switzerland
[c] RehaClinic (Bad Zurzach), Bad Zurzach, Switzerland

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1. Introduction

Osteoarthritis (OA) is a common degenerative joint disease often accompanied by chronic pain and characterised by articular cartilage degeneration, subchondral bone changes and synovial membrane inflammation [30]. Familial studies, initiated more than 70 years ago, revealed a strong genetic influence on this disease [31]. Subsequent genome-wide linkage and association studies performed in OA cohorts identified multiple loci involved in the risk for OA [29,35]. Moreover, it is accepted that genetic variants can also affect sensitivity to pain in patients with OA [35]. However, because the correlation between the severity of pain and the degree of radiographical changes observed in the joint is low [18], it is likely that factors other than radiological abnormalities contribute to interindividual variations in OA-related pain experiences. Indeed, the aetiology of chronic OA pain is complex and difficult to understand. Arthritic pain reflects changes in both the periphery (sensitization of nociceptors in the setting of inflammation) and the central nervous system (central sensitization) [18]. Chronic pain in the joint is also influenced by genetic factors, with a 44% heritability estimate in a sib-pair study [39]. In this review, we summarise and discuss recent genetic epidemiological studies that identified 4 known functional genetic variants in pain candidate genes that influence pain experiences in patients with OA: *SCN9A* (sodium channel, voltage-gated, type IX, alpha subunit); *COMT* (catechol-O-methyltransferase); *TRPV1* (transient receptor potential cation channel, subfamily V, member 1); and *P2X7* (purinergic receptor P2X, ligand-gated ion channel, 7).

2. Genetic Polymorphism

2.1. Genetic polymorphisms in SCN9A

SCN9A encodes the $Na_v1.7$ protein, 1 of 9 isoforms of the voltage-gated sodium channel. The critical role of $Na_v1.7$ in pain sensation has been described previously in a number of genetic studies [9,27]. Several single nucleotide polymorphisms (SNPs) in *SCN9A* have been identified in the carriers of 3 different inherited severe human pain disorders. Primary erythromelalgia and paroxysmal extreme pain disorder are caused by numerous missense mutations linked with increased $Na_v1.7$ activity leading to abnormal attacks of severe pain. In contrast, channelopathy-associated insensitivity to pain is caused by various nonsense mutations linked to a loss of function of $Na_v1.7$ and a loss of pain sensation. More common *SCN9A* polymorphisms also exist that might contribute to variability in chronic pain sensitivity. The latter was assessed using the Western Ontario and McMaster Osteoarthritis Index (WOMAC score; WS) on a 1 to 20 scale.

Reimann and coworkers [28] performed genetic studies in a cohort of 578 subjects with radiographically confirmed OA. Of the 27 *SCN9A* SNPs tested, rs6746030, in which an arginine replaces tryptophan at codon 1150 of $Na_v1.7$ (R1150W), was significantly associated with OA-related pain perception (Table 1). Subjects with the tryptophan variant were more pain sensitive than individuals with the arginine variant (mean WS for individuals carrying *SCN9A* 1150 W/W, W/R, and R/R genotypes were 11.64, 9.83, and 9.21, respectively). The same association was also found in other pathological pain conditions, including sciatica, postamputation phantom limb pain [28], and multiple regional pain [36] as well as in the sensitivity to C-fibre–mediated heat stimulus–evoked pain in healthy European females [28]. The exact mechanism by which the tryptophan variant $Na_v1.7$-1150W enhances pain sensitivity is not clear; 2 separate experiments testing the electrophysiological properties of $Na_v1.7$ channels in human cells (HEK293) have shown some discrepancies [11,28]. However, expression of the tryptophan variant

* Corresponding author. Address: University of Zurich/ETH Zurich, Functional Genomics Center Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland. Tel.: +41 44 63 53970.
E-mail address: Anna.Bratus@uzh.ch (A. Bratus).

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Table 1
Variations in sensitivity to OA-related pain caused by the genetic polymorphisms in 4 pain candidate loci determined in genetic population studies.

Gene symbol (gene ID)[a]	Protein coded by the gene	Biological function of protein	Chromosomal location	SNP-reference ID[a]/allele variants/codon variants	Genotype-phenotype association in pain	Clinical variant of the disease/ethnic population	Sample size (n) (cases vs controls)	Women% (cases vs controls)	*P* value[b]	Effect size	References
SCN9A (6335)	Voltage-gated sodium channel $Na_V1.7$ protein type 9 subunit alpha	Nociception signalling	2q24	rs6746030/G>A/R1150W	AA: reduced channel susceptibility to voltage dependence slow inactivation/greater experience of pain	OA hip and OA knee/self-reported as Caucasian	n = 578 (cases)	64	0.0158	0.76 (0.14–1.38)[d]	[28]
COMT (1312)	Catechol-O-methyl-transferase	Degradation of catecholamine neurotransmitters such as norepinephrine and dopamine	22q11.21-23	rs4680/G>A/V158M	AA: lower enzyme activity (threefold reduction in enzyme thermostability)/higher pain sensitivity	Hip OA/Caucasian	n = 288 (radiographic OA) n = 171 (female radiographic OA)	59 100	0.02 0.005	2.9 (1.2–6.1)[e,f] 4.9 (1.6–14.8)[e,f]	[37]
TRPV1 (83810)	Transient receptor potential cation channel, subfamily V, member 1	Transducer of painful thermal stimuli	17p13.3	rs8065080/G>A/V585I	AA: lower risk for painful OA; No association found	Symptomatic knee OA/Caucasian; Asymptomatic knee OA/Caucasian	n = 7122 (3270 vs 3852); n = 4950 (1098 vs 3852)	63 (54 vs 71) 70 (67 vs 71)	0.00022[c] 0.93[c]	0.74 (0.64–0.87)[e,g,h]; 0.99 (0.81–1.22)[e,g,h]	[34]
P2X7 (5027)	$P2X_7$ purinoceptor	ATP receptor-transducer of pain with neuropathic and inflammatory origin	12q24	rs7958311/G >A/R270H	AA: the hypofunction of receptor: lower risk for developing chronic pain	OA hip and OA knee/African American and Caucasian	n = 1329 (743 vs 586)	58 (66 vs 55)	0.015	0.79 (0.65–095)[e,i]	[32]

[a] ID gene number and ID SNP number refer to NCBI database.
[b] *P* value for rare allele association.
[c] *P* value obtained in meta-analysis.
[d] mean effect size: mean difference in pain score per additional rare allele, calculated from the linear regression analysis (lower and upper 95% confidence interval); trend test.
[e] OR (95% CI), OR = odds ratios, 95% CI = 95% confidence interval.
[f] OR refers to a dominant model (OR refers to the pain risk of individuals carrying the *COMT* 158 M/M and M/V compared with the carriers of the V/V genotype).
[g] OR refers to a recessive model (OR refers to the pain risk of individuals carrying the *TRPV1* 585 I/I compared with the carriers of V/I and V/V genotypes).
[h] OR obtained in meta-analysis,
[i] OR from logistic regression using sex, age, BMI, collection site, and genotyping batch as covariates.