Commentary

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Genetic findings related to pain and analgesics–why are they so inconsistent?

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The presence of interindividual variability in pain perception and efficacy of analgesics is known from human experimental studies and clinical practice. That this variability is partly caused by genetic dispositions is established in well-performed twin studies.[1] Multiple clinical studies have demonstrated relationships between specific genetic variations and pain or analgesic efficacy. A noncomplete list includes the genes coding for OPRM1 receptors, the COMT enzyme, MDR1 transporter proteins, the melanonocortin-1 receptors, GTP cyclohydrolase, enzymes that metabolize analgesics, and various genes encoding substances involved in the immune system.[2–8] However, findings are inconclusive, exemplified by the fact that the influence from one of the most studied genetic variants, the rs179971 in the *OPRM1* gene (A118G), which is widely believed to alter the efficacy of opioid analgesics, is not confirmed in meta-analyses or in large-scale studies that involve a validation sample.[9,10]

In this issue of PAIN, Cajanus et al.[11] present data demonstrating that variability in the gene coding for the fatty acid amine hydrolase (FAAH), an enzyme which metabolizes the endocannabinoid anandamide, is related to pain perception. In a cohort of 1000 women undergoing surgery for breast cancer, variability within the *FAAH* gene was related to both sensitivity to experimental pain and the need for opioid analgesics. This study included more patients compared to what is usually done in pain genetic association studies, the cause of the pain was one surgical procedure, the study had a plausible biological argument for the genetic association, and the study combined the assessment of experimental pain and clinical pain expressed by pain intensity and use of opioid analgesics. Thus, this study is one of the more comprehensive and well-designed studies performed in this research field. Still, similar to other studies, it runs a risk of being one of the many genetic association studies that will not replicate in other cohorts or will influence future clinical decision-making.

The reasons why even well-performed genetic association studies do not translate into robust associations, which can be implemented in clinical decisions-making, are numerous. Firstly, studies involving only one or a few SNPs may only capture some of the genetic variability. This is expressed by the frequent finding of relatively low explained variability in pain-related genetic association studies. Multiple biological systems involved in pain perception and opioid pharmacology together contribute to the patients' pain experience. These systems all consist of multiple factors, each encoded by a gene. Thus, pain is a true multigenetic trait, thereby minimizing the impact from each particular genetic variation. Involved genes may also include genes usually not considered as candidates in pain studies. A preliminary pooled DNA genome wide association (GWA) study for clinical pain and opioid efficacy suggested that genetic variability in pathways other than those most commonly studied were associated with pain intensity in patients treated with opioids for cancer pain.[12] However, as pointed out by Cajanus et al.,[11] GWA studies, due to the high threshold for reaching the genome wide level of statistical significance, can for a multigenetic trait fail to identify the genes with only a minor contribution to clinical variability. Genome wide association studies and candidate gene studies will also in many cases fail to identify genetic variants that are rare, but which may have profound effects in one or a few individuals.[13] Collectively, many such rare variants may still contribute to a larger part of the variability in the population.

Secondly, genetic variability can be caused by mechanisms other than SNPs. Animal studies have shown that alternative splicing of exons in the *OPRM1* gene during transcription to mRNA gives rise to multiple receptor variants. OPRM1 splice variants are present in the human brain[14] and may be responsible for varying analgesic response and adverse effects from opioids.[15] Moreover, variability can be the result of an interplay between genetic and environmental factors.

Thirdly, clinical studies often include different pain entities or include a mixture of pain entities. Intuitively, the influence from genetic variations can be specific for different pain etiologies. Often in studies of pain diagnoses, cancer pain being one example, different clinical conditions are collectively analyzed.[9] To include a more homogenous population, as done in the study by Cajanus et al.,[11] reduces the impact from potential confounders caused by differences in pain mechanisms. However, a strict selective study cohort also introduces some limitations, in that the potential identified predictors may be valid only for the particular population under study. Additionally, comparisons of studies are hampered by the use of multiple instruments to measure pain. Initiatives to standardize measurements of patient-reported outcomes within certain populations have been published and are welcomed.[16,17]

Finally, genetic variability not related to pain may indirectly influence the efficacy of analgesics or proxy outcomes for pain perception, such as the opioid consumption used by Cajanus

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et al.[11] Opioid consumption is related both to analgesic effect and to limitations of dose increments due to adverse effects. Genetic variation is related to adverse effects of opioids, such as nausea, constipation and cognitive failure.[18–20] Variations in opioid doses may therefore be caused not only by genetic variability resulting in poorer analgesic efficacy, but also by genetic variation putting the patients at higher risk for opioid-induced adverse effects.

In summary, performing genetic research in clinical pain is complex. Therefore, the research should involve a combination of basic research identifying potential pain mechanisms influenced by genetic variability, human and animal experimental research, clinical research in selected populations, and large-scale studies in more heterogeneous populations to address the clinical feasibility of genetic tests to guide pain therapy. Collectively, these different methodologies can drive this research field forward.

Conflict of interest statement

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