Genetic biomarkers of pain states

The FDA Biomarkers, EndpointS, and other Tools (BEST) glossary of biomarker terms identifies a biomarker as a "defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions". Given the reported heritability for pain states of 16–50% (1,2), a substantial proportion of the risk of developing a chronic pain condition is driven by genetic background. For pain states, no robust genetic markers have been identified so far. However, multiple efforts of the pain research field have identified many genetic markers associated with several categories of pain states:

Genetic Markers for Rare Familial Disorders: In the case of specific rare familial single-gene disorders, genetic mutations can be strongly predictive for pain states. For example, mutations in the gene coding for sodium channel Nav1.7 produce either loss or gain of the function of the channel, leading to either inability to feel pain (3), or to enhanced pain sensitivity and spontaneous burning pain (4), respectively. Another example of the inability to feel pain due to a single-gene pain disorder is a disruptive mutation in the NTRK1 gene (5), which encodes neurotrophic receptor tyrosine kinase 1, and NGF (6), which encodes nerve growth factor beta, the binding partner of NTRK1. Although there are dozens of gene mutations identified today, severe mutations in which can either exacerbate pain or annul it, the prevalence of such familial disorders is extremely low. However, they have given great insight into the neurobiology of pain and therapeutic targets (7).

Genetic Markers for Common Diseases: In the case of common neuropathic, postoperative, and musculoskeletal pain disorders, each single genetic variant plays only a modest role, as such conditions are multifactorial and polygenic in nature, and a large network of pain genes (8) is important. These genetic variants are usually relatively common in the general population. Some of these polymorphic variants are found more often to be associated with chronic pain states and sometimes with multiple pain states, which have been shown to share genetic factors (9). Two examples of such polymorphic variants frequently implicated in chronic pain states are those in the mu-opioid receptor gene, *OPRM1*, and the gene coding for the non-selective cation channel, *TRPV1*. For example, cancer pain has been shown to be associated with genetic variability in *OPRM1* (10–12), which modulates opioid receptor's pharmacodynamics, affecting the efficacy of both endogenous opioids and analgesic opioid drugs. TRPV1 is involved in the transmission and modulation of inflammatory pain (13–15). Studies have shown evidence of increased TRPV1 levels in the environment of damaged nerve fibers and associated dorsal root ganglia (DRG). Polymorphisms in *TRPV1* are associated with pain states, for example, a variant rs8065080 (1911A>G) is associated with less capsaicin-induced warm hypoesthesia and heat pain sensitivity in healthy volunteers suggesting altered channel function (16).

Identification of new drug targets from genetic data: The identification of genetic variants contributing to chronic pain also leads to an understanding of the pathophysiology of human chronic pain states directly from the patients. This knowledge can ultimately be used to identify new approaches and drug targets to treat chronic pain. For example, the identification of the causal mutations in sodium channel Nav1.7 to familial pain disorders led to substantial efforts in the development of sodium channel blockers selective for this receptor subtype (17). The discovery of the critical contribution of the genetic polymorphisms within the human catechol O-methyltransferase *COMT* gene to pain perception and chronic pain through multiple genetic studies (18) led to new pharmacological approaches for chronic pain conditions through animal studies (19,20) and follow on clinical trials (21,22). These studies showed that propranolol, a nonselective β-adrenergic antagonist, which is widely used clinically for the treatment of hypertension and anxiety, is also clinically effective as a treatment for chronic facial pain.

Pharmacogenetics markers of drug efficacy: The genetic basis of the variability in therapeutic responses to various analgesics can be very substantial. In the pain field, the best example is probably the effect of polymorphisms of cytochrome P450 2D6 (*CYP2D6*) on the analgesic efficacy and safety of codeine. Codeine prodrug, which is metabolized by P4502D6 to morphine, has a little therapeutic effect in patients who are *CYP2D6* poor metabolizers, and have one or no copies of *CYP2D6* gene, whereas the risk of morphine toxicity is higher in ultrarapid metabolizers, who possess multiple copies of this gene in their genome (20). Another example is the association of A118G polymorphism in opioid receptor *OPRM1* with opioid requirements in postoperative (23) and cancer patients (24). The meta-analyses show that carriers of the G-allele (AG+GG) of the *OPRM1* A118G polymorphism reliably require higher opioid doses for pain management than those carrying the AA, although the dose difference is not large.

Pharmacogenetics markers of medication adverse effects: One of the most important pharmacogenetic findings for the adverse effects of analgesics is the discovery of the association between the genetic markers of human leukocyte antigens (HLA allele), HLA-B*15:02, and drug-induced severe cutaneous adverse drug reactions (SCARs), namely Stevens–Johnson syndrome or toxic epidermal necrolysis (SJS/TEN), from carbamazepine (25) and oxcarbazepine (26). Both drugs are recommended as first-line medications for certain neuropathic pain conditions such as trigeminal neuralgia. Moreover, the HLA-B*15:02 allele is the strongest genetic marker for the prediction of SJS/TEN induced by carbamazepine in some specific East and Southeast Asian ethnic groups due to high frequency of this allele found among these populations (27). Therefore, the US FDA issued a warning in 2007, which is still in effect today, for screening for HLA-B*15:02 allele prior to treatment of carbamazepine in all Asians and Asian ancestry patients (27). Moreover, a moderate association has been found between HLA-A*31:01 and the risk of developing SCARS to carbamazepine in the Japanese, Korean and northern European populations (28–30), demonstrating the usefulness of biomarkers to prevent adverse drug reactions in patients with specific ethnicity or ancestry.

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