High density profiling of the association of two-pore domain potassium ion-channel gene variants with pain.

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Members of the two-pore domain potassium (K2P) ion-channel family are unexploited therapeutic targets for pain. As regulators of the leak K^+ current in nociceptive sensory neurones, their pharmacological modulation could be used to reduce excitability within the pain-sensing pathway. A rationale that is robustly supported by knock-out mice who are highly sensitive to pain, familial genetic studies, and the in-vivo efficacy of selective agonists.

However, poor clinical translation within the pain field has impeded the development of novel analgesics, with many failing in the clinic. This challenge arises from the heterogeneity of the patient population, which is difficult to classify, with numerous types of pain and distinct biological mechanisms that are further influenced by sex, genetic, immune system, psychological and other environmental factors. Consequently, defining an appropriate clinical trial population is challenging, efficacy in rodents does not always translate into humans, and novel therapeutics fail to deliver on early promise.

One way to address this translational gap, is to turn towards large scale human genetic databases to validate targets and stratify patient populations using clinical data. This is exemplified by the fact that drugs that gain genetic linkage of a target to a disease are more likely to succeed in later clinical phases.

Here, we apply this approach to the K2P family using UK and Finnish Biobank GWAS statistics to compare the association of over 100,000 genetic variants identified within the 15 K2P ion-channel genes with 63 distinct pain phenotypes. We demonstrate that several K2Ps have strong suggestive associations with pain and that these results vary between the Finnish and UK populations. We provide this as an initial resource that we will build upon, highlighting the degree of pain-association of individual K2Ps within European populations.