Genetics-Epigenetics-Who is more vulnerable?

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In the acute to chronic pain transformation syndrome, most of the research has been conducted in the postsurgical setting, although any injury per se can be the sensitizer, such as any traumatic stress. Many risk factors have been identified including age, gender, the type of surgery, and pre-intra- and post-operation factors; genetic factors have been identified but at a level making it difficult to apportion the degree of contribution, although studies are quite difficult to conduct.

With respect to variants that alter the gene’s sequence, several variants have been identified within the COMT (catechol-O-methyl transferase) gene, the best-studied gene to date. This enzyme affects nociceptive and inflammatory pain and its variants, particularly the Val158Met variant, are associated with chronic temporomandibular joint pain. Gene variants in GCH1 (GTP-cyclohydrolase), which is involved in the synthesis of tetrahydrobiopterin, a modulator of peripheral and neuropathic pain, appear to affect cancer pain severity and the development of persistent neuropathic low back pain. More recently, a glucocorticoid receptor co-chaperone gene FKBP5 was identified in which several variants were associated with pain that had persisted for many weeks after a motor vehicle accident. As inflammation is a pivotal sensitizer in this syndrome, anti-and pro-inflammatory genes (TGFβ1 and IL-8) were associated with persistent temporomandibular pain. It is well recognized that one candidate gene will not be the major genetic factor, but rather a combination of genes (epistasis); a recent study showed that a combination of variants in COMT, GCH1 and ESR (oestrogen receptor 1) is highly associated with temporomandibular pain. Of concern overall is the lack of replication studies. All the genes described above contribute to loss- or gain-of-function of the resultant protein (enzyme, receptor etc).

Epigenetics deals with the environmental control of gene expression (up/down) through stress and other factors and is invariably tissue specific. That is, there is no change in the sequence of the gene. The most studied epigenetic modification factors involve DNA methylation and noncoding RNA, particularly microRNAs.

Epigenetic control of the genes involved in nerve injury is gaining increasing recognition. For example, the expression levels of inflammatory cytokines are under epigenetic control, glucocorticoid receptor function is modulated through DNA-methylation and mu opioid receptor regulation is also under DNA-methylation control. Recently, the promoter of the ligand gated ion-channel TRPA1 showed an association between its methylation status and experimental pain sensitivity.

Transiting from acute to chronic pain is a highly complex biochemical and biosocial process that is modulated by many factors, including genetics. Both genetics (gene sequence) and epigenetics (DNA-methylation and microRNA in particular) are likely to be key factors that with large and replication studies may provide one answer to “who is more vulnerable”.

References

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