Commentary

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From Galton to genome-wide association studies: evaluation of genetic and environmental factors predisposing to widespread pain

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Deep pain is classified into 2 general categories, ie, nociceptive and neuropathic, depending on the type of neural injury. In many cases, specific tissue damage, eg, due to chronic inflammation or latent trauma, may be a reason for the painful signs, thus sufficiently limiting the number of patients with "purely" neuropathic pain.[4,9] Despite diagnostic doubts in some individual cases, a population-wide search allows one to obtain informative pathogenetic correlations in sufficient groups of patients.

In this respect, Momi et al.[6] have performed a large-scale study in a sample from the TwinsUK Registry, which shows that widespread pain (WSP) is associated with neuropathic pain. This study also shows that WSP and neuropathic pain are clinical conditions that share common risk factors, both environmental and heritable ones, and highlights their relative contribution and interactions. The study by Momi et al.[6] included over 3800 subjects (90% of them are females), who range in age from 16 to 92 years (a mean of 59-64 years, for controls and cases, respectively).

Obviously, many persons from the older age groups have sufficient comorbidities, which may interfere with genetic effects registered in this study. The authors used the general methodology of classical twin studies, which has been applied in population genetics for many decades, since Galton's theories. The primary assessment of neuropathic pain syndromes was based on the well-validated painDETECT scale that evaluates pain quality, pattern, and irradiation mode.[4]

One should note that a special class of clinical conditions manifests with deep pains, including fibromyalgia, irritable bowel syndrome, or temporomandibular joint disorder (TMD).[2] Females are more prone to these syndromes, and also to chronic WSP in general.[10] Possible reasons for such sex-specific predisposal may depend on specific modes of brain limbic system activation, and also regulatory effects of gonadal hormones on these neural structures.

Twin studies have provided reliable support for the genetic background for various clinical conditions. However, for current in-depth studies, investigators typically seek specific gene variants predisposing individuals to develop neuropathic or nociceptive pain. The appropriate candidate genes may encode, eg, enzymes of neurotransmitter metabolism and specific membrane transporters or receptors. Of course, most functional genes exert their physiological effects within complex regulatory networks, thus showing significant associations with clinical features when screening large groups of patients. For example, such combined effects have been found by Smith et al.[8] who have studied a clinically relevant polymorphism (Val158Met) of catechol-O-methyl transferase (COMT), the key enzyme of catecholamine metabolism, among patients with musculoskeletal pain in TMD and healthy controls. This study revealed that the Met allele is associated with reduced COMT enzymatic activity and increased musculoskeletal pain. Moreover, these clinical and biological effects of the COMT polymorphism in the TMD patients proved to be modified by specific polymorphisms of estrogen receptor 1 and guanosine-5-triphosphate cyclohydrolase 1 genes. Hence, clinical expression and outcomes in pain syndromes may be subject to complex genetic regulation, from polygenic to more gene-restricted effects.

Painful symptoms similar to WSP have been commonly reported in women having premenstrual syndrome (PMS), a cyclic condition that is characterized by headache and various types of musculoskeletal pains, eg, arthralgia and bowel irritation in the days preceding menses. That suggests a sufficient dependence of these painful symptoms on the changing progesterone/estrogen ratio. We conducted a study that included 333 women in their reproductive age, of whom 233 females reported sufficient emotional or physical disturbances typical to PMS, as detected by prospective PRISM-based evaluations.[1] The entire group of women was subject to genotyping of well-known serotonin transporter gene polymorphism (*SLC6A4*, *5-HTTLPR* S/L alleles), dopamine transporter repeat numbers (*SLC6A3*, 9R/10R VNTR alleles), angiotensin-converting enzyme (ACE I/D), and estrogen receptor polymorphism (*ESR1*, exon 8, G594A). Of these four polymorphisms, only the S/S homozygosity for *SLC6A4* transporter proved to be associated with premenstrual headache, joint pain, and bowel irritation. Meanwhile, preceding studies have shown that the gene-specific effects of HTTLPR S/L polymorphism in PMS are not quite reproducible in other female cohorts with PMS.[3,5] Such uncertainty of results may be due to different ethnic and socio-economic factors changing expression of genetic traits in the patients, as presumed in appropriate dynamic model presented by Momi et al.[6]

Over last few years, special efforts have been dedicated to conducting genome-wide association studies to detect the genes potentially responsible for increased WSP risk. When studying a large cohort of WSP patients and healthy controls by means of next-generation sequencing, Peters et al.[7] have revealed the top 10 pain-associated candidate genes that were

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then subjected to more detailed studies of single-nucleotide polymorphisms. The rs13361160 and rs2386592 single-nucleotide polymorphisms have been mapped to the 5p15.2-region (CCT5 and FAM173B genes). Their association with WSP regulation is highly statistically significant, but their physiological significance for pain perception should be further assessed. The results obtained by genome-wide association studies screening and targeted studies of physiologically important genes may yield additional information on gene associations, because of different ideologies of genetic analysis.

In summary, studying genetic and environmental influences in large twin studies allows us to discover the general genetic, environmental, and social effects that affect the risks of developing WSP syndromes. The results of the study by Momi et al.[6] and similar studies will be useful in the future search for molecular drug targets for existing and novel analgetic compounds.

Conflict of interest statement

The author has no conflicts of interest to declare.

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