EBioMedicine 2 (2015) 1280

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

# Sex-Specific Genetic Control of Diabetic Neuropathic Pain Suggests Subsequent Development of Men-only and Women—Only Analgesic Strategies

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In *EBioMedicine* Meng et al. (2015a) reported the results from their second genome-wide association study on neuropathic pain that aimed to identify novel genetic factors contributing to neuropathic pain in diabetic patients. The first study (Meng et al., 2015b) published earlier this year in the *European Journal of Pain* identified a cluster in the Chr8p21.3, next to *GFRA2* gene locus, associated with cases of neuropathic pain defined as diabetic patients with a prescription history of at least one of five drugs specifically indicated for the treatment of neuropathic pain and in whom monofilament test result was positive for sensory neuropathy in at least one foot. The narrow-sense heritability of this phenotype was 11.00%. That study confirmed that diabetic neuropathic pain is a genetically controlled trait. In the second study in a larger sample the authors found sex-specific loci for men (a cluster in the Chr1p35.1; *TLR12P-ZSCAN20*) and women (a cluster in the Chr8p23.1, next to *HMGB1P46*) associated with the same phenotype, and men had higher narrow-sense heritability than women (28.5% *vs.* 16.7%, respectively) (Meng et al., 2015a). This is the first evidence for the sex-specific contribution of genetic factors to diabetic neuropathic pain.

Although the association with newly-identified markers didn't reach conservative GWAS-level of statistical significance the data are still very interesting and worthy of further investigation in follow-up studies. Sex-specific genetic effects are of particular interest in the light of recently reported evidence of many "pain genes" influencing pain perception in men and women in different ways (Belfer, 2013). Some polymorphic alleles protect one sex from pain and predispose another to more severe or more chronic pain. For example, female carriers of minor allele of A118G genotype in *OPRM1* gene encoding mu opioid receptor had 2.3 times as much sciatic pain as male carriers of this allele twelve months after lumbar disc herniation demonstrating a slower recovery rate (Olsen et al., 2012). These data suggest that *OPRM1* G allele increases the pain intensity in women, but protects men showing sex-antagonistic effects. Other genes may contribute to pain phenotypes in both sexes but to the different degree having sex-biased effects. For instance, *COMT* gene encoding catechol-O-methyltransferase, the enzyme metabolizing catecholamine neurotransmitters, contributes to pain behavior in a sexually dimorphic way: it controls many experimental and clinical pain phenotypes much stronger in women than in men (Belfer et al., 2013; Belfer & Segall, 2011). Overall, low COMT activity (as determined by gene functional variants) leads to more severe pain in women predominantly. Furthermore, the particular gene × sex interaction may be pain modality-specific (Belfer et al., 2013).

These discoveries provide insight into biological mechanisms underlying the observed sex differences in pain prevalence, related behaviors, and analgesic response (Belfer, 2013; Bartley & Fillingim, 2013). Genetic effects may trigger specific aetiological and risk factors such as endogenous opioid functioning, sex hormones and psychosocial processes. These effects have high clinical relevance since they may explain the observed sex differences in responsivity to pharmacological and non-pharmacological pain interventions (Bartley & Fillingim, 2013). Therefore sex-specific genetic effects should be considered in pain pharmacogenetics studies since they may inform future efforts to develop novel sex-specific pain medicine.

All together the findings presented in Meng et al. (Meng et al., 2015a) advance our knowledge on genetics on human pain including neuropathic pain and painful diabetic neuropathy in particular. Further elucidation of genetic control of sex-specific vulnerability to more severe or more chronic pain is an essential step forward personalized (gender-specific) approaches to pain management.

## Disclosure

The author declared no conflicts of interest.

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DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.08.001.

http://dx.doi.org/10.1016/j.ebiom.2015.08.038