Editorial

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Pharmacogenomics

The effects of sex on pharmacogenetically-guided drug treatment

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"Assessing the different roles of genetic variants between men and women to justify the unequal sex response to drugs will be one of the future goals for a personalized and precision medicine."

Tweetable abstract: Sex-related pharmacogenetics is emerging area of research to better explain sex discrepancies in drug response. Sex pharmacogenetics should be considered an essential step for personalized medicine.

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Sex-based medicine is an emerging goal to improve care and treatment of men and women alike and to overcome the milligram/kilogram basis drug administration or the 'one size fits all' dose, leading to incorrect exposures. Overcoming the sex gap in the outcomes of treatments and toxicity is mandatory for precision medicine.

Sex-related biological differences have been reported to have a higher impact on drug pharmacokinetics (PK) and pharmacodynamics (PD): women are more frequently overdosed due to the smaller volume of distribution, the higher body fat (13.5 kg, 16.5 kg in female), the larger free fraction of drug and slower xenobiotic clearance. Even the sex-based differences in receptor number/binding could alter signal transduction pathway between sexes, leading to an imbalance in pharmacological effects. Plasma protein binding also varies between sexes, due to estrogen's influence in increasing the serum-binding globulins levels. Moreover, the secondary effect of sex hormones in the gene up- or downregulation contributes to enhance the sex disparities in the treatment outcomes [1].

Estrogens, by binding-specific nucleus receptors, could activate transcriptional processes and/or signaling events promoting the expression of absorption, distribution, metabolism and excretion (ADME) genes.

On this basis, oral contraceptives, pregnancy and menopause represent sex-specific conditions that impact treatment outcomes [2]. Concomitant medications/supplements intake, which has been observed to be greater in women than in men, can also impact differently between the sexes.

Notably, well-established evidence shows sociocultural aspects (i.e., alcohol intake, BMI, smoking, diet) as risk factors influencing different sex treatment outcomes and drug toxicity profile. Finally, the different microbiota compositions between males and females have been considered to explain sex differences in drug response [3].

A great deal of interest and attention is being placed on the genetic makeup that differentiates men and women and its role in drug toxicity and efficacy. The most noticeable difference between male and female are the sex chromosomes. Alteration in the X inactivation process, loss of the entire Y chromosome, gene mutation or deletion, epigenetic deregulation and miRNA effect have been correlated with altered drug response [4]. Many genes on the X-chromosome regulate the immune function (i.e., *TLR*, cytokine receptors transcriptional factors). The inactivation of X-chromosome leads to an upregulation of the immuno genes in women compared with men that could explain immunotherapy sex discrepancy. In particular, *IL-2*, *TLR-7*, *TRL-8*, *CD-40L* and e-*FoxP3* are X genes with a critical role in immune response. They could contribute to a higher expression levels of codifying protein in females, due to the X escape, with a higher resistance to immunotherapy in females [5].

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Besides the X–Y chromosomes, phase I and II enzymes have shown sex-related differences that could be affected by germline variants: CYP2B6, CYP2D6 and CYP3A4 exhibit higher activity in females while higher metabolic activity has been described in men for CYP1A. The phase II enzymes, UGTs and methyl-transferases, have been recorded to have a higher activity in males with respect to females. These different enzymatic activities led to sex-related different exposure to several drugs, such as clomipramine, clozapine and paracetamol metabolized by CYP1A, or codeine, encainide, flecainide and fluoxetine, metabolized by CYP2D6 and diazepam, fentanyl, lovastatin, simvastatin and tamoxifen metabolized by CYP3A. Regarding UGTs, sex variations in drug efficacy or toxicity have been reported for ibuprofen, paracetamol, azathioprine, dopamine, oxazepam and irinotecan [2]. A sex-dependent distribution volume of lipophilic/water-soluble drugs and a variable glomerular filtration could be affected by polymorphisms in the *ABC* genes in a different manner in men and women [6].

Several germline polymorphisms have been ascribed to the sex disparities in drug response. A specific gene–sex interaction was highlighted in analgesic therapy involving the *MC1R* gene. Specific genotype with two allelic variants of the *MC1R* gene has been correlated with better analgesia from pentazocine administration in red-haired, fair-skinned women compared with red-haired men and women who did not have the allelic variants [7].

An analysis by genotype of patients with chronic noncancer pain treated with opioids, antiepileptic and antipsychotic demonstrated a different type of adverse drug reactions (ADRs) in men and women based on genetic variants: *OPRM1-G* allele and *COMT*-GG polymorphisms were associated with vomiting and depression in men respect to dizziness and dry skin in women. Conversely, the incidence of sexual dysfunctions were the same in both sexes [8].

In bipolar patients, Eugene *et al.* analyzed the transcriptome-level gene signatures in males and females, highlighting two genes (*RBPMS2* and *LILRA5*) selective for male lithium responders and three genes (*ABRACL*, *FHL3* and *NBPF14*) selective for female lithium responders [9].

Regarding cardiovascular disease therapy, *ACE* gene insertion/deletion polymorphisms have been correlated with a sex-based different response to ACE inhibitors (ACEIs). Women with D/D genotype, ACEIs are more renoprotective compared with D/D men. Furthermore, ACEIs are more effective in D/D men than in those with the I/D than the I/I genotype [10]. The same ACE polymorphism also affects hydrochlorothiazide response in a sex-specific manner with a higher response rate in I/I females and D/D men [11]. Among patients with high cholesterol levels treated with atorvastatin, a significantly weaker triglycerides reduction effect was observed in men carrying *ABCC2*-24C >T variant with respect to women carrying the same polymorphism [12].

Four SNPs near the *IL28B* gene have been associated with, HCV therapy response in a sex-dependant manner. A higher rate of therapy outcome and also spontaneous HCV clearance was observed in females than men [13].

In the context of solid tumors, a case in point is 5-fluorouracil (5-FU): sex difference in its clearance increases ADR risk in women [14]. Nevertheless, preliminary data reported a high incidence of ADRs in men carrying *DPYD**2A polymorphism compared with women [15]. Further studies in larger female populations with equal representation are needed. Despite the role of *TYMS* polymorphism in predicting severe ADRs is controversial, *TYMS*-TSER 3R/2R in patients treated with 5-FU/capecitabine was associated with a higher incidence of ADRs in female cancer patients with respect to men, potentially linked to ER regulation of TS expression [16]. A higher prevalence of 2R/2R *TYMS* genotype was also reported in female African–American patients developing ADRs compared with men [17].

Regarding somatic aspect, tumor mutational burden (TMB), together with PD-L1 expression, DNA mismatch repair deficiency cytotoxic T-cell infiltration have been reported as predictive biomarkers of immune checkpoint inhibitor effectiveness. Particularly, a higher TMB, single-nucleotide variation neoantigen load and PD-L1 were observed in male melanoma patients than in female patients. Moreover, male patients reveal a higher relative abundance of immune cells, a higher mRNA expression of immune checkpoints, which could explain a higher response rate with respect to female patients [18]. Conversely, TMB has been correlated with immune checkpoint inhibitors response for female lung cancer patients than for male patients [19]. How genetic variants affect this scenario remaining an intriguing issue to be addressed.

Pharmacogenomics (PGx), is developing a pivotal role in clinics and specific PGx recommendations have been made by several consortiums for genotype-based drug prescription. However, sex-related PGx recommendations, involving both genetic and sex aspects, have yet to be formulated. The literature data reported a 40% difference in PK between the two sexes due to several factors, including the well-known sex differences in *ADME* genes activity. It has been demonstrated that women have a nearly twofold greater risk than men of developing ADRs and are more likely to be hospitalized [20]. Some evidence supports the role of genetic polymorphisms in such sex discrepancies

but only paucity and anecdotical data derived from clinical trials are available. To overcome these limitations, adequate representation of the two sexes should be ensured in the clinical studies recruitment. Regulatory agencies constantly performed periodic analysis to assess the correct enrollment of the two sexes but, generally, primary and secondary end points do not include separate sex-specific analysis, especially the PGx sex-related disparities. In the last years, plenty of genetic variants have been associated with drug efficacy and safety. Assessing the different roles of genetic variants between men and women to justify the unequal sex response to drugs will be one of the future goals for a personalized and precision medicine.

Author contributions

All authors contributed to the writing of the manuscript.

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