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Effects of sex steroids on the pattern of methylation and expression of the promoter region of estrogen and androgen receptors in people with gender dysphoria under cross-sex hormone treatment

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\textbf{A B S T R A C T}

Cross-sex hormone therapy (CHT) is critical for phenotypical and physiological transition in adults with gender dysphoria (GD). However, the impact of the CHT onto the molecular level/epigenetic regulation has not been comprehensively addressed. We postulate that CHT in GD could drive changes at the androgen receptor (AR), estrogen receptor alpha (ESR1) and estrogen receptor beta (ESR2), affecting their DNA methylation pattern and mRNA expression that may influence in the phenotypical changes associated to CHT.

We carried out a prospective observational study on individuals with a diagnosis of GD. 18 subjects (no previous CHT): 12 female to male (FtoM) and 6 male to female (MtoF). An Epityper Mass array TM method was used to study the DNA methylation and Real-time PCR quantitative reverse transcription PCR (qRT-PCR) was used to quantify the gene expression. The analysis of AR, ESR1 and ESR2 receptor was performed at baseline, 6 and 12 months after CHT. No differences in DNA methylation of ESR were found in MtoF, while DNA methylation was increased in FtoM at 6 and 12 months of CHT. The AR showed a significant increase of methylation in MtoF group after 12 months of estrogenic treatment. Regarding the expression analysis, AR expression was significantly decreased in FtoM upon CHT treatment. AR, ESR1 and ESR2 methylation were correlated with anthropometric, metabolic and hormonal parameters in FtoM and MtoF.

Our results support that CHT is associated to epigenetic changes that might affect the response to treatment with sex steroids.

\textbf{1. Introduction}

Cross-sex hormone therapy (CHT) is critical for phenotypical and psychological transition in adults with gender dysphoria (GD). CHT enables the development of the secondary sex characteristics of the desired sex, which is one of the cornerstones of sex reassignment [1–3].

Differences in the rhythm and acquisition of secondary sexual characters are observed in individuals using the same CHT and dosage [4]. Differences in both desired and non-desired effects induced by sex hormones could be related with the localization and action of sex hormones receptors. However, the impact of the CHT onto the molecular level/epigenetic regulation has not been comprehensively addressed nowadays.

Androgens act via the androgen receptor (AR) in multiple target tissues; we find them in gray matter as well as in subcortical structures and CHT are related with changes on brain cortical thickness [5]. At peripheral level, AR expression in all vascular cells could justify the effects on the phenotype and on cardiovascular risk as they are believed to increase the adhesion of monocytes to endothelial cells. Moreover, differences of AR expression in vascular tissues in relation to gender are described, with higher levels in men [6,7].

Estrogen receptors (ESR) are two; the estrogen receptor alpha (ESR1) is expressed in the uterus, prostate, pituitary, brain, skeletal muscle and blood cells among others, while the estrogen receptor beta

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(ESR2) is broadly expressed. The two ESR have distinct functions and act antagonistically in multiple pathways: ESR1 play an important role in growth and proliferation, while ESR2 exerts anti-proliferative, differentialiative and apoptotic actions in breast, prostate and colon cells [8]. Both receptors are required for the maintenance of glucose homeostasis with ESR2 predominating in the skeletal muscle and ESR1 in the adipose tissue [8,9].

DNA methylation is nowadays the best-defined epigenetic modification and involves inherent and acquired gene transcription changes, which occur independently of the DNA sequence [10,11]. AR, ESR1 and ESR2 promoter methylation are involved in the development of many diseases, such as atherosclerosis and tumorigenesis [12]. AR promoter methylation is implicated in the pathogenesis of prostatic cancer [13] and lung cancer [14], while ESR1 is involved in breast cancer [15], hepatocellular carcinoma [16], colorectal carcinoma [17] and stomach cancer, and ESR2 in endometriosis [8,18]. However, little is known about changes in the context of DNA methylation in these promoters upon CHT.

Changes in the AR expression associated to CHT may lead to changes in the sex hormones action in relation to the original sex and the desired sex. Sader’s study described in a short group of FtoM GD individuals the effects on AR expression [19].

Given these data, we postulate that CHT for sex reassignment in GD could drive changes at the AR, ESR1 and ESR2, affecting the DNA methylation and mRNA expression pattern of these receptors, that may influence in the phenotypical changes associated to CHT.

### 2. Material and methods

#### 2.1. Study design and subjects

We carried out a prospective observational study on individuals with a diagnosis of GD, who were attended in the Identity Gender Unit (UIG) of the Hospital Clinic from July 2012 to November 2013. All
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