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Review

GENDER DYSPHORIA AND DNA

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SUMMARY

Gender dysphoria (GD) describes individuals for whom the native sex and expressed gender are not coincident and most of them self-identify as transgender women or men. It has been shown that genetic factors play an important role in GD and the presence of specific genetic variants in candidate genes could be correlated. On the other hand, twins studies have estimated its heritability. In this review, we collect and report the available data obtained by different molecular genetic studies.

Key words: *gender dysphoria - genetic factors – transgender - genetic influence*

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INTRODUCTION

Gender dysphoria (GD) refers to the suffering that can be generated by the incongruence between the gender expressed by an individual and the assigned gender. Suffering is not limited to the desire to belong simply to the opposite gender, but may include a desire to belong to an alternative gender as long as it differs from the individual's assigned gender. GD manifests itself differently in different age groups: pre-pubescent children prefer the clothing and hairstyles of the opposite sex, and may manifest a marked identification with the opposite gender in their choice of roles during play, in dreams and fantasies; adolescents and adults express a desire to get rid of primary and secondary sexual characteristics and to acquire those of the opposite gender. In addition, adolescents who come to clinical observation often want hormone treatment and many desire gender reassignment surgery. Several risk factors are involved in GD including temperamental, environmental and especially genetic and physiological factors (DSM-V 2013). In particular, genetic influence has been considered by different studies like for others psychiatric conditions (Juli et al. 2022). Here, we report genetic studies that identified candidate genes implicated in GD.

GENETIC STUDIES

In the last decades a number of research group have tried to analyze the genetic influence of GD although they have been limited by small sample sizes as well as a lack of replication. Recently, Theisen et al. using a Whole Exome Sequencing approach on the genomic DNA of 13 transgender males and 17 transgender females, identified 120,582 genetic variants that have been subsequently filtered using some criteria such as: a) variants not present in 88 in-house control exomes from non-transgender individuals represented by 17 males and 71 females, b) variants with frequency less than 0.01 in the databases ExAC, 1000 Genome, and Yale, c) variants not listed in the NCBI database of genetic variation dbSNP, d) The American College of Medical Genetics and Genomics (ACMG) Class 3 and 4 variants including frameshift, splice-site (intronic variants occurring 1-2 bps from the intron/exon junction), splice-region (exonic or intronic variants occurring 1-3 bps or 3-8 bps from the intron/exon junction respectively), nonsense variants as well as missense variants with Combined Annotation Dependent Depletion (CADD) score ≥20.

After filtering, 441 variants in 421 genes remained for further analysis and can be differentiated in 21 nonsense, 28 frameshift, 13 splice-region, and 225 missense variants. Among them, 19 genes were found to have associations with pathways of sexually dimorphic brain development and therefore were considered as candidate genes while 21 variants identified in these genes were confirmed with Sanger Sequencing (Theisen et al. 2019).

Regarding splice-region variants, there were identified 13 significative variants in different genes such as the transcription factor BACH2 that has been linked to a number of autoimmune diseases in humans, the cytochrome isoform CYP2D6 involved in the metabolism of different drugs, TBK1 gene that has an important role in the activation of interferon cascade, the Transmembrane Serine Protease 11E (TMPRSS11E) involved in cognition and predicted to be integral component of plasma membrane, the Dihydrouridine Synthase 1 Like (DUS1L) having tRNA dihydrouridine synthase activity, and others like RELN, PRRC2B, PIBF1, OR2H1, MRTO4, KDM6B, FBXO11, EPB41L1 genes (Theisen et al. 2019).

Frameshift variants identified by Theisen et al. were around 28 and all were heterozygous; the most representative genes with identified variants are BIRC6 that encoded for a protein involved in the apoptosis process, EPG5 gene that provides instructions for making a protein involved in a cellular process called

autophagy, NUMB encoding for a protein that determines cell fate as a result of its asymmetric partitioning at mitosis and Cytokeratin 19 (KRT19) a cytoplasmic intermediate filament protein which is responsible for structural rigidity and multipurpose scaffolds (Theisen et al. 2019).

Among missense variants, 225 variants were identified in 213 genes such as PATL1 of which protein is involved in mRNA storage, processing, regulation and degradation, RASA4B a GTPase-activating protein that inhibits cell growth, DSCAM gene that plays important roles in neural development including dendritic patterning and self-avoidance. Of interest, in transgender females were identified seven hemizygous variants noted in six genes located on the X chromosome: ASMT, CXORF57, GTPBP6, P2RY8, PLCXD1, RGAG1 while in transgender males four variants were identified in genes on the X chromosome like ATRX, GTPBP6, PPP2R3B, and ZXDA. There were no variants of genes located on the Y chromosome (Theisen et al. 2019).

The nonsense variants found were 21 and included genes such as DIAPH2 that is the unique located on sex chromosome X of three transgender males and one transgender female. Other examples of genes are AIM1 an actin-binding protein that suppresses cell migration and micrometastatic dissemination, C1R that acts as a mediator in the innate immune response by ultimately triggering phagocytosis and inflammation, CTC1 gene that provides instructions for making a protein that plays an important role in telomeres which are found at the ends of chromosomes (Theisen et al. 2019).

In addition to 441 variants described above, 21 variants in 19 genes were found to have associations with previously described estrogen receptor activated pathways of sexually dimorphic brain development. Several studies analyzed these pathways in rodents identifying four key areas of the brain: the ventromedial nucleus, the medial preoptic area, the anteroventral periventricular nucleus and the arcuate nucleus (McCarthy et al. 2017, Mong et al. 2001, Perrot-Sinal et al. 2003, Perrot-Sinal 2007, Speert et al. 2007, Wright et al. 2010). In each of these regions, the identified dimorphic pathways are initiated by neuronal estrogen receptor (ER) activation and result in sex-specific regional differences in dendritic density or volume. Hereafter, we summarize data obtained from whole exome sequencing analyses. In the anteroventral periventricular nucleus only one variant has been identified in BOK gene that is involved in the apoptosis process togheter with the modulation of other two factors BAK and BAX (Theisen et al. 2019, Einsele-Scholz et al. 2016). In the medial preoptic area, nine candidate genes with variants have been identified such as TNN involved in repulsive properties on neurites and neurons, EGF, a regulator of sex differences in neuronal morphology, CDH8 involved in dendritic arborization, DNER that mediates neuron-glia interaction, SPHK1 regulating COX2 acetylation in neurons, CTNNA2, DSCAML1, EFHD2 and SYNPO (Theisen et al. 2019, Abe et al. 2004, Borger et al. 2014, Deller et al. 2003, Eiraku et al. 2005, Friedman et al. 2015, Yamagata et al. 2008, Lee et al. 2018, Neidhardt et al. 2003).

In the ventromedial nucleus, 4 confirmed variants have been evaluated and found in genes that are implicated in the activation of NMDA receptors i.e. MAP kinase MAP4K3 that controls the maintenance of dendritic spines, GRIN1, RIMS3 and RIMS4 belonging to the presynaptic machinery for neurotransmitter release (Theisen et al. 2019, Hsu et al. 2005, Wang et al. 2003, Fagerberg et al. 2014). Like anteroventral periventricular nucleus, also in the arcuate nucleus only one variant has been found in KCNK3 neuronal genes that is important in chloride channels and Cl- influx into the neuron (Theisen et al. 2019, Brickley et al. 2001).

TWINS STUDIES

To determine heritability, several studies evaluated concordance rates of GD in monozygotic and dizygotic twins. It has been shown that in adolescents the heritability is around 38-47% in natal females and 25-43 in natal males and in adults 11-44% or 28-47% respectively (Polderman et al. 2018). Coolidge et al. identified heritability at 62 % (Coolidge et al. 2002) while Sasaki et al. observed a heritability of 41% for adolescent assigned females and 11% for adult assigned females (Sasaki et al. 2016). Heylens et al. reported a concordance of 39.1% in monozygotic twins and 0% in dizygotic pairs (Heylens et al. 2012). On the other hand, Diamond found that the concordance among same-sex Dizygotic pairs was 33% for assigned males and 23% for assigned females (Karamanis et al. 2022). Recently, Karamanis et al. performed a register-based study to analyze the prevalence of GD between twins and non-twin siblings of individuals with GD in Sweden population over the period 2001-2016. The data were collected from the Statistics Sweden and the National Board of Health and Welfare. In a total of 2592 full siblings to GD cases were registered and 67 of them were twins. The age at first GD diagnosis for the probands was around 11.2-64.2 years. It has been found that the proportion of different-sex twins both presenting with GD was 37%, higher than that in same-sex twins that was 0% and in non-twin sibling pairs 0.16% (Karamanis et al. 2022).

CONCLUSIONS

Although different works analyzed the genetics influence in gender dysphoria, most of them have been restricted by limited sample size and absence of replicability. In any case, the genetic variants identified so far in candidate genes may represent preliminary data for further studies that will help to better understand how genetic factors may impact an individual's tendency to manifest gender dysphoria.

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Contribution of individual authors:

Giada Juli: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, validation, writing original draft, writing review & editing, supervision.

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