The Influence of Sex on Brain Development Genetics and the Possible Relationship with Sex-Dependent Differences in Psychiatric Disorders

Cinsiyetin Beyin Gelişim Genetiği Üzerine Etkisi ve Psikiyatrik Bozukluklarda Cinsiyet Farklılıklar ile Olası İlişkisi

Arda Bağcaz¹, Yunus Kasım Terzi², Feride İffet Şahin²

¹Department of Psychiatry, Başkent University Faculty of Medicine, Ankara, Turkey
²Department of Medical Genetics, Başkent University Faculty of Medicine, Ankara, Turkey

ABSTRACT

There are sex-dependent differences in the prevalence, age of onset, and course of psychiatric disorders and cognitive abilities. Although it has been assumed that the direct effect of gonadal hormones in sensitive periods leads to sexually dimorphic brain development, current evidence suggests that another possible factor may be sex-specific regulations at the gene level. Understanding the sex differences at the gene level can be promising to identify the mechanisms that predispose or trigger psychiatric disorders, and may provide new prevention or treatment strategies. This paper aims to review the findings on the mechanisms that affect the sex-specific differences in brain development at the gene level and to discuss the relationship of these findings with different cognitive characteristics of the sexes and psychiatric disorders.

Key Words: Sex, developmental genes, psychiatric disorders, sex chromosomes, epigenetics, gene dosage

Received: 05.24.2021 Accepted: 08.31.2021

ÖZET

Psikiyatrik bozuklukların prevalansı, başlangıç yaş, seyirleri ve bilişsel beceriler açısından cinsiyete özgü farklılıklar mevcuttur. Gonadal hormonların beyin gelişiminin hassas dönemlerindeki direkt etkisinin cinsiyet dimorfizmine yol açtığı öne sürülmeye rağmen, güncel kantlar bir diğer olası risk faktörünün gen düzeyinde cinsiyete özgü düzenlemeler olabileceğini işaret etmektedir. Gen düzeyindeki cinsiyet farklılıklarını anlamak psikiyatrik bozukluklara yatkınlık oluşturan veya bu bozuklukların têtiklenmesine yol açan mekanizmaları ortaya koymak bakımından umut vadedebilir ve yeni önleme veya tedavi stratejileri sağlayabilir. Bu yüzden, cinsiyetin cinsiyete özgü farklılıklarını gen düzeyinde etkileyen mekanizmalar hakkında ortaya konulmuş bulgular derlenmiş ve bu bulguların cinsiyetlerin farklı bilişsel özellikleri ve psikiyatrik bozukluklarla ilişkisi tartışmıştır.

Anahtar Sözcükler: Cinsiyet, gelişimsel genler, psikiyatrik bozukluklar, seks kromozomları, epigenetik, gen dozaji

Geliş Tarihi: 24.05.2021 Kabul Tarihi: 31.08.2021
INTRODUCTION

Humans show sex-dependent differences in the prevalence, age of onset, and course of psychiatric disorders and cognitive abilities. Men are known to have higher visuospatial abilities whereas women have better verbal or social skills (1). Although the total brain volume is found to be higher in men, different structures have different volumes according to sex (2).

When examining the sex-dependent differences in psychiatric disorders, which are thought to be contributed by developmental processes in their etiology, it is seen that the typical age of onset of schizophrenia is between 15-24 years in men and 25-34 in women. (3). Although the lifetime prevalence is more common in women, the age of onset and the onset of manic episodes in bipolar disorders are earlier in men (4). Women are more prone to unipolar depression and anxiety disorders (5). Neurodevelopmental disorders such as autism, attention deficit and hyperactivity disorder (ADHD), intellectual disability (ID), dyslexia are more common in men, and their clinical manifestations vary according to sex (5).

Little is known about the molecular mechanisms of these structural and behavioral differences, called sexual dimorphism. The predisposition to neurodevelopmental disorders in men has been explained by the slower development of the male brain and its sensitivity to developmental problems for a longer time in the postnatal period. (6). It has been assumed that the direct effect of gonadal hormones is sensitive periods leads to sexually dimorphic brain development. Undoubtedly, this structural sexual dimorphism alone is not sufficient for the emergence of disorders. It seems that both the emergence of disorders and the level of cognitive skills are regulated by a multifactorial network that includes these biological factors that interact with environmental factors such as prenatal stress, diet, maternal infections, and early postnatal care.

When biological factors affecting brain development are examined, another factor discussed is the immune system response. As a matter of fact, it is known that the immune system response also shows sex-specific differences (7). Current evidence suggests that another possible factor may be sex-specific regulations at the gene level (8).

It does not seem possible to consider the genetic influence and gonadal hormone effects completely independent from each other. As it is known, when steroid sex hormones bind to their receptors in target cells, the ligand-receptor complex acts as a transcription factor in the nucleus and thus provides sex-specific gene expression. The contribution of sex hormones as transcription factors to sexual dimorphism can be found in another recent review (9).

Although the effect of gonadal hormones seems inevitable in the organization of the central nervous system, the first stages of this organization take place before the primordial gonads differentiate into the ovaries and testes where they will secrete hormones. While neural tube closure, which is a key point in early brain development in humans, occurs in the 4th week of gestation, the production of gonadal hormones begins at the 12th week. (7). At the early brain development process is independent of the effects of hormones, it seems reasonable that sex biases are primarily caused by the effects of imprinted X- and Y-linked genes. It was shown that X- and Y-linked genes are expressed in a sex-biased way in the mouse brain (11). The second trimester findings obtained in humans also showed that some of the Y-linked genes were expressed in this period in the male brain, while some X-linked genes had different expression levels according to sex (12). First trimester findings are more limited due to the difficulties of working the human brain in the early period. When the current evidence is examined, it is inferred that genes expressed in the brain as well as gonadal hormones during embryonal development can affect brain development, so there are differences in the expression of these genes by sex.

In this review, it is aimed to compile the findings on the mechanisms that affect the sex-specific differences in brain development at the gene level and to discuss the relationship of these findings with different cognitive characteristics of the sexes, sex-specific behaviors, and psychiatric disorders.

Effects of X-linked genes on brain development

The X chromosome is rich in genes expressed in the brain. These genes are expressed at different levels in different brain regions (2). It is known that regions with higher expression levels such as the cortex and hypothalamus are more associated with cognitive skills. When examined in connection with the clinical data, X-linked intellectual disability (XLDI) is 3.5 times more common than ID associated with autosomal genes, and this finding strengthens brain development and X chromosome connection. (13).

X and Y chromosomes contain some common genes. While most of these genes are located in pseudoautosomal regions, a small number of genes are X/Y gene pairs that are not found in the pseudoautosomal region. Two mechanisms have emerged to compensate for the haploinsufficiency of genes on the X chromosome compared to genes on autosomal chromosomes. The first is to balance the number by increasing the number of genes on the X chromosome, which is called dosage compensation, and the other is to silence a random X chromosome by X inactivation during female embryogenesis. A long non-coding RNA (IncRNA) called Xist is involved in X inactivation. The inactive X chromosome structure is observed as two large chromatin condensation regions separated by the DXZ4 locus, which is an IncRNA in the nuclei of cells, including the brain, and it is not clear whether there is a specific configuration for different cell types. This silencing mechanism is observed not only in the female sex but also in aneuploidy with excess X chromosomes such as XXY. It is known that changes in executive function and social skills or learning difficulties may accompany the phenotype in sex chromosome aneuploidies. (5). This patient group provides an important source of data for understanding the effect of the inactive X chromosome and gene dosage on sexual dimorphism in psychiatric and neurodevelopmental disorders. See another recent review for the detailed findings in sex chromosome aneuploidies (5).

Gene dosage effect

Up to 15% of X-linked genes escape from inactivation, expressing both alleles in women (14). While most of these genes are in pseudoautosomal regions, some of them are X homologs of X/Y gene pairs. Genes that are expressed at higher doses in females than males are mainly X homologs of the X/Y gene pairs. It is thought that these genes may be associated with sex-dependent differences due to the dosage effect (15). In addition, some other X chromosome genes may escape X inactivation even though they do not have a homolog on the Y chromosome.

It is known that changes in gene dosage that occur due to deletions or duplications in genomic DNA pose a genetic risk for cognitive, psychiatric, and neurological disorders. However, the increased risk created by gene dosage for different cognitive or behavioral disorders is not at the same level for every gene (16). In addition, neuroimaging studies indicate that gene dosage may have different effects on different anatomical regions in the brain and play a role in the formation of different phenotypes accordingly (17).

X/Y gene pairs

Among these gene pairs, there are members involved in the control of chromatin modifications, transcription, translation, RNA splicing, and protein ubiquitination. X/Y genes are highly dosage-sensitive (18). It has been determined that the X homologs of these gene pairs such as KDM6A, KDMSC, ZFX, RBPX are expressed more in males (21). In mice, Zfy1 and Zfy2 are expressed only in the testes, while Zfx is commonly expressed (22).

- **ZFX/ZFY**: Zinc finger transcription factor genes (ZFX/ZFY) have important roles in growth and reproductive system development. ZFX and ZFY are expressed in different tissues as specific to the species. While ZFX is expressed in the hypothalamus and cortex in the adult human brain, it is not expressed in the developmental process of the mouse brain (21). In mice, Zfy1 and Zfy2 are expressed only in the testes, while Zfx is commonly expressed (22).

- **RBMX/RBMY**: RNA binding motif proteins genes (RBXM / RBMY) express proteins with different functions in different tissues. It appears that the homologs of these genes are strongly dissociated functionally in both humans and mice. While RBMX/Rbmy are widely expressed and encode proteins that provide centromere cohesion, RBMY/Rbmy have testicular expression profile and functions (22). RBMX mutations are associated with XLDI (23).

- **PCDH11X/PCDH11Y**: Different from other gene pairs, PCDH11X/Y, which encodes the protocadherin superfamily members responsible for cell-cell interactions in central nervous system development, is expressed more in males. (2, 24).
This gene pair is thought to have a key role in sexual differentiation, but which mechanisms in the brain they trigger are not known, while it has been suggested that it causes neuroendocrine tissue transdifferentiation by using classical Wnt signaling pathways in prostate cancer cell culture (25). The promoters of these two genes are in different regions (24). The cortex is the brain region with the richest transcripts of both genes, and they have also been detected in the amygdala, caudate nucleus, hippocampus, and thalamus (24). It has been shown that the PCDH11X transcript is preferred more in the cerebellum (24). The mutations of PCDH11X/Y have been shown in developmental dyslexia and speech retardation (26). PCDH11Y may play a role in disorders accompanied by cerebellar pathology such as ADHD and autism in men. This gene may cause changes in language skills, theory of mind, and problem-solving skills in men. As these features are affected in schizophrenia and autism, PCDH11Y is thought to be an important candidate gene to explain the predisposition of men to these disorders. However, there is no direct evidence on this subject (20).

- **NLGN4X/NLGN4Y**: It encodes a member belonging to the family of neuroligins. The cell adhesion molecules they encode interact with β-neurexin in the postsynaptic membrane during synaptogenesis (26). It has been shown that neuron differentiation, neurite formation, and cell-cell interaction decrease with the suppression of NLGN4X expression in neural stem cells (27). NLGN4X mutations have been reported in families with ID and autism spectrum disorder, but it is also known that this gene is intact in most cases of autism. NLGN4Y deletion was also reported in a boy with autism (2). As a result, it is understood that this gene pair contributes to the etiology of a small proportion of autism cases.

- **KDM6A (Utx/Uty)**: The Kdm6a / Utx found in mice encodes histone H3K27 demethylase. In the mouse brain, Utx is highly expressed in the amygdala, while Uty is highly expressed in the paraventricular nucleus of the hypothalamus but has largely lost its demethylase activity (28). In humans, KDM6A has important roles in the specialization of neural progenitors to cell lines, dendrite morphogenesis, and synapse formation, and it appears to be very important for neurodevelopment (2). KDM6A deficiency is associated with congenital disorders such as Kabuki syndrome and shows itself with a neurological and cognitive impairment phenotype (29). In addition, a moderate increase in Kdm6a gene dosage in a mouse model has been shown to result in decreased hAPP-derived β-amylloid peptide neurotoxicity and cognitive impairment (30). Therefore, it is thought that the KDM6A dosage may play a role in reducing the cognitive impairment in Alzheimer’s disease.

- **KDM5C/KDM5D**: Both genes encode histone H3K4 demethylase enzymes (31). KDM5C can play a role in various intracellular mechanisms by affecting gene expression in either activator or repressor directions by the way of H3K4me3 demethylation in the promoter regions of target genes (2). It is known that the decrease in KDM5C expression or encoded enzyme activity is associated with cognitive impairment in neurodevelopmental disorders. This effect is explained by the effect of KDM5C on the transcription of other genes such as SCN2A, SYN1, BDNF (32). However, the fact that KDM5C mutations cause severe mental disability in males suggests that the Y homolog (KDM5D) cannot compensate for the lack of X homologs, and the two homologs may not have the same function. KDM5C duplication may also cause neurodevelopmental impairment in men. Mutations in these genes in mice and humans resulted in neurite loss and shortening. In addition, the level of cognitive loss has been associated with Kdm5c dosage, and Kdm5c knock-out in mice increases aggression by reducing social interaction (31). However, this dose-dependent effect on cognition does not expand with further increase of the normal gene dosage. Ectopic transgenic Kdm5c copies in mice have also been shown to cause neurite shortening and loss (33).

- **DDX3X/DDX3Y**: Heterozygous de novo loss of function mutations in the DDX3X gene, which encodes the RNA helicase enzyme, are the most common causes of XLID in women (34). It has been demonstrated that the growth and differentiation of neural progenitor cells are impaired with DDX3Y knockdown (35).

**Other genes escaping X inactivation**

Another gene that has been studied in the brain is the STS gene, which expresses the steroid desulphatase enzyme responsible for the desulfuration of various neuroactive steroids. This enzyme is expressed in the placenta, liver, and cortex, thalamus, and hindbrain during embryogenesis. In mice, the STs pseudoautosomal region gene is expressed in both X and Y homologs. In mice, this gene has been associated with aggression, impulsivity, and attention (36). In rats, this gene does not have a Y homolog, and the X-linked Sts gene has been shown to affect learning, memory formation, and acetylcholine release in the hippocampus (37). It is observed that STS gene deletions in humans lead to X-linked ichthyocytosis and this disease is associated with autism and attention deficit dominant type of ADHD predisposition. The STs gene has also been directly linked to ADHD. The human STS gene does not have a functional Y-linked homolog, so it has been suggested that the expression of the enzyme in tissues may be higher in women than in men. It is thought that this difference may be associated with that the disorders such as ADHD, impulse control disorders, and pathological gambling occur more frequently in men (20).

It is known that KDM5C, KDM6A, DDX3X genes can escape X inactivation in all tissues. Up to 10% of human genes can escape X inactivation in different tissues (14). For example, it has been shown that plp1 escapes inactivation only in the brain (38). The expression of genes that escape X inactivation in the brain is thought to be at a high level, and studies indicate that the expression of X-linked genes in the brain is higher in women (19). On the other hand, pseudoautosomal region genes show a male-biased expression pattern (39). In addition, transcription factors that regulate gene expression such as KDM5C and KDM6A may alter the expression of autosomal genes, leading to sex differences in brain development (2).

**Genomic imprinting**

Genomic imprinting is a mechanism that causes gene expression to be only or predominantly from a homolog inherited by a parent, as a result of epigenetically marking some genes in mammals according to their transmission from the mother or father (40). Some inherited alleles may prefer to be expressed when they are of paternal origin and some of them are of maternal origin. It has been reported that imprinted genes tend to be highly expressed in the brain, and these genes have effects on neurodevelopment, brain function, and behavior (40). The imprinted genes on the paternally inherited X are expressed only in the female brain, while the imprinted genes on the maternal X are expressed in both men and women. On the other hand, since some of the imprinted genes on maternal X will be silenced due to random X inactivation, it can be predicted that maternal origin genes will be expressed more in the male brain. Therefore, imprinting is one of the important candidates in explaining sex differences in terms of brain development and susceptibility to psychiatric disorders. For example, when individuals with Turner Syndrome were separated according to their X chromosome origins and compared in terms of cognitive skills, it was found that individuals with maternal X have lower verbal IQs and are more unsuccessful in behavioral inhibition. Researchers have interpreted this finding as paternal X is more important in terms of social cognitive skills (40). The fact that normal women have better social skills than men who do not have the chance to inherit the X chromosome from the father is consistent with other findings. As a result, different studies support the idea that the X-linked genomic imprinting effect may play a role in brain development and cognition (40).

**Non-coding RNAs**

Non-coding RNAs (ncRNA) are RNAs that have a regulatory role in many biological functions, including gene-silencing through histone modifications, and are classified into roughly two groups as short non-coding RNAs (sncRNAs) and long non-coding RNAs (lncRNAs). In genomic imprinting and X inactivation, it is seen that lncRNAs show different expression according to sex. Xist, which is required for X inactivation, is also a well-defined IncRNA. Xist is highly expressed from the X chromosome to be inactivated (Xi) and triggers Polycomb repressor complexes that mediate histone modifications. Heterochromatin spreading along the XI chromosome is seen as Barr body under the microscope (41).
One type of the sncRNAs are microRNAs (miRNAs) encoded by endogenous genes. miRNAs also have sex-specific expression patterns in a variety of tissues. It is known that some of the miRNAs are highly expressed in the mammalian brain and are associated with neurodevelopment (42). In mice, it has been shown that in chronic stress situations such as light cycle changes, noise, and malodor exposure during early gestation, more stress-sensitive male offspring emerge, and these traits can be passed on to the next generation (43). This paternal transition has been shown to be associated with the decrease in the levels of some miRNAs in the male brain. Findings suggest that ncRNAs are among the factors contributing to sexual dimorphism.

**Placenta and neurodevelopment**

Another hypothesis to explain the dimorphism in the male and female brains is the effect of sex-specific genes expressed in the placenta. Differences in the placenta based on sex may lead to sending different transplacental signals to the developing brain for each sex (6). Consequently, the male brain may be more sensitive to changes in the maternal environment such as infection, stress, and diet during development.

In a GWAS study about the sex-specific changes caused by early prenatal stress in the placenta, the X-linked O-linked N-acetylglucosamine transferase (OGT) gene has been shown to be important. It is stated that this gene has a sex-specific expression pattern and may be important for response to maternal stress (6). OGT stabilizes a histone H3K27 methyltransferase called EZH2 and thus leads to histone methylation (H3K27me3). It has been concluded that this pathway indicates global histone repression and possibly results in decreased placental transcription. Since OGT is less expressed in males, it has been suggested that the male placenta gives additional transcription response to maternal stress, in other words, it is in a more reactive state to stress (6).

**Effect of Y-linked non-recombinant region genes on brain development**

Since the genes in the non-recombinant region of the Y chromosome do not undergo recombination, they are generally transferred from father to son without change, resulting in sharing of a similar Y chromosome polymorphism profile over generations. Some of these genes are associated with testicular development and spermatogenesis and are mainly expressed in the testicles. Another group of genes are expressed in other tissues, including the brain. Postmortem studies indicate that approximately 20% of non-recombinant region genes are expressed in the brain (44). The high expression of these genes in the brain suggests that they may have a role in sex-specific differentiation of the brain. SRY is the most studied gene in this region, which is responsible for the differentiation of early gonads in embryogenesis towards ovaries or testicles.

**The SRY gene**

SRY encodes a transcription factor containing the High Mobility Group (HMG) box as the DNA binding site (45). The molecular role of this transcription factor in testicular development is well-defined. It has been shown to activate Sry-related box 9 (Sox9), cerebellin 4 precursor gene (cbn4), pod1 and neurotrophin 3 (NT3) (8). However, data on SRY's role as a transcription factor in brain development are limited.

Sry-green fluorescent protein (GFP) mice have been shown to express Sry in the brain as well as the gonad on the embryonic 12th day (46). This finding indicates that the possible effects of Sry as a transcription factor on the development of the nervous system may play a role in differences between the male and the female embryo. In postmortem human studies, SRY protein was found in the medial rostral hypothalamus, frontal, and temporal cortex regions of the adult male brain (21). Sry has been described in catecholaminergic brain regions in male rats (47). In addition, Sry has been shown to be expressed in the medial mammillary body neurons of the substantia nigra and hypothalamus expressing tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis in mice (48). It is thought that these findings may indicate a mechanism that contributes to the male-biased conditions such as ADHD or addiction in which catecholaminergic mechanisms play a role (20). SRY protein was found in the tyrosine hydroxylase-positive substantia nigra pars compacta and ventral tegmental area neurons and GABAergic substantia nigra pars reticulata neurons in the human middle brain (49). In a male patient with ADHD, Yq deletion and Yp duplication including the SRY gene was detected and its possible relationship with the behavioral phenotype was discussed (50).

**To study sexual dimorphism in brain development, a mouse model with 4 different genotypes (XX with autosomal Sry transgene, XY with autosomal Sry transgene, and XX and XY without Sry gene) and Sry knockdown mice are used (20). Studies were conducted on postnatal behaviors, receptor expression profiles, cortical thickness, sexual behaviors, and cognitive differences of chromosomal and gonadal female (40, XX), chromosomal female-gonadal male (40, XXSry), chromosomal male-gonadal female (40, XY), chromosomal and gonadal male (40, XY) mice (20, 51). This model allows researchers to interpret that different features detected in two groups with the same gonads to be associated with sex chromosome effects other than the Sry gene or epigenetic effects, and the differences between two groups with different gonads can be explained by the effects of the Sry gene or gonadal hormones. For example, it was demonstrated by this model that vasopressin-positive fiber density in the lateral septum is genetically/epigenetically regulated, while sexual behaviors and the number of tyrosine hydroxylase-positive neurons in the anteroverentral periventricular nucleus of the hypothalamus are associated with the Sry transgene or gonadal sex hormones (51). However, since Sry expression also leads to testicular development and testosterone synthesis in the gonads, it is not possible with this model to distinguish whether the differences detected in groups with different gonads are caused by the Sry effect or the testosterone effect. After human neuroblastoma cell lines were used to study the isolated SRY effect.

In the human male neuroblastoma BE (2) C cell line, it has been determined that SRY activates the promoter of the gene encoding the monoamine oxidase A (MAO-A) enzyme, which is responsible for the oxidative deamination of monoamine neurotransmitters, including serotonin (52). MAO-A, one of the targets of SRY in the brain, is also responsible for dopamine breakdown. As a result of silencing Sry in catecholaminergic neurons with antisense oligodeoxynucleotides in mice, there is a decrease in tyrosine hydroxylase levels, which is the rate-limiting step in dopamine synthesis, without a decrease in the number of neurons (49). In the human neuroblastoma cell line, silencing SRY with siRNA leads to a decrease in the expression of more than one enzyme involved in dopamine synthesis, and SRY overexpression leads to an increase in the expression of these enzymes (49). The demonstrated effects of SRY on tyrosine hydroxylase and MAO-A as a transcription factor suggest that these mechanisms may contribute to men being more prone to dopamine disorders such as schizophrenia (53).

SRY is known to interact with many proteins in the testicles. Among these proteins, there are also members of the Krüppel-associated box (KRB) superfamily with transcription-suppressing properties. SRY interacts with a repressor complex containing KRB-associated protein-1 (KAP1), MIZ-associated nucleosome remodeling deacetylase (NuRD), histone 3 lysine 9 specific methyltransferase (H3K9me3) SETDB1, heterochromatin protein-1 (HP-1) post-transcription factor. Thus, it can silence target genes by histone modifications and chromatin remodeling. It is not yet known whether such an SRY-mediated mechanism is seen in the brain. However, although not the same KRB protein, other KRB family members and KAP1 are known to be expressed in the brain. It has been shown in the brain that KAP1 is needed for KRB-mediated epigenetic silencing. KRB-KAP1 complex triggers the spread of heterochromatin via H3K9me3 and HP1β (8). In summary, it has been revealed that SRY has epigenetic effects on the brain, but the effects of this regulation on brain development are not yet clear.

Moreover, it is thought that RNA processing may also be an important mechanism in determining sex. SRY has been shown to facilitate alternative splicing of many well-defined pre-miRNA substrates in an in vitro experiment (54). In some cell lines, SRY coexists with β-catenin and splicing factors, and SRY physically interacts with β-catenin (55). Dax1, another X chromosome gene, works antagonistically with Sry in sex determination. Dax1 is a nuclear receptor that can migrate between the nucleus and the cytoplasm and binds to RNA, and in its overexpression, it changes the direction of sexual differentiation even in the presence of Sry (56). However, the role of these findings in sex differences of brain development is not yet known.

In addition, the Sry transcript can act as a regulator for ncRNA (57). The Sry gene is intronless in mammals. Mice have two different types of transcripts, one with transcription starting from the proximal promoter and the other from the distal promoter. The first type produces functional protein by complete translation. In the second type, a circular transcription (CircSry) is formed with an inverted repeat at the 5′ and 3′ ends. CircSry is highly expressed in the brain in the embryonic period and is destroyed in the postnatal period.
CircSry is thought to be a miRNA sponge that binds ncRNAs, thus attenuating the gene-silencing function. (57). For example, there are 16 binding sites for miR-138, which is common in neurons and has been shown to be involved in the growth of dendritic spines at synapses in hippocampal neurons (57).

Y chromosome non-coding RNAs

A recent study found that Y chromosome genes were expressed very early in the male brain and a group of IncRNAs was expressed on the Y chromosome in the first trimester, and it was suggested that these IncRNAs may have effects on early brain development (10). These findings remind that different molecules encoded by genes may have tissue, time, and sex-specific functions and suggest that ncRNAs encoded by the Y chromosome may contribute to sexual dimorphism.

CONCLUSION

Sex-specific regulation of brain development will be better understood with a new perspective alongside the classical sex hormones hypothesis. Future goals may include a better understanding of gene expression differences in different parts of the brain, revealing which genes are expressed or silenced at which developmental stages, and better defining the effects of transcription factors. For example, a recent study showed that genes associated with Alzheimer’s and Parkinson’s diseases are targets of different transcription factors by sex (58). By elucidating such sex-specific regulations, mechanisms that reduce susceptibility to diseases can be revealed, or many psychiatric disorders whose etiopathogenesis has not yet been clarified can be better understood.

In conclusion, sex-dependent development of the brain depends on very complex processes including gene effects before gonadal hormone secretion, the effects of gonadal hormones at sensitive prenatal, perinatal and postnatal periods, the effects of different transcription factors, ncRNAs, other epigenetic factors, and gene-gene interactions. Technological developments facilitate to reveal of sex-biased genes and their effects on brain development. To investigate the sex differences can be promising to identify the mechanisms that predispose or trigger psychiatric disorders, and to develop strategies that may provide prevention, and developments in this area can provide a turning point for the treatment of these disorders.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Craig IW, Harper E, Loat CS. The genetic basis for sex differences in human behaviour: role of sex chromosomes. Ann Hum Genet. 2004; 68:269–84.
2. Raznahan A, Distech CM. X-chromosome regulation and sex differences in brain anatomy. Neurosci Biobehav Rev. 2021;120:28–47.
3. Hafner H, Riecher-Rossler A, An Der Heiden W, Maurer K, Fatkenheuer B, Loffler W. Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. Psychological Medicine. 1993;23:925–940.
4. Kennedy N, Boydell J, Kalidindi S, Fearon P, Jones PB, van Os J et al. Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. The American Journal of Psychiatry. 2005;162:257–262.
5. Green T, Flash S, Reiss AL. Sex differences in psychiatric disorders: what we can learn from sex. Neuropsychopharmacology. 2019;44:9–21.
6. Bate T. The placenta and neurodevelopment: sex differences in prenatal vulnerability. Dialogues Clin Neurosci. 2016;17:459-464.
7. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol. 2008;8:737–44.
8. Sekido R. The potential role of SRY in epigenetic gene regulation during brain sexual differentiation in mammals. Adv. Genet. 2014;86:135–165.
9. Gegenhuber B, Tollkuhn J. Signatures of sex: sex differences in gene expression in the vertebrate brain Wiley Interdiscip Rev Dev Biol. 2020;9(1): e348.
10. Johansson MM, Pottmeier P, Suciu P, Ahmad T, Zaghloul A, Halvardsson J et al. Novel Y-Chromosome Long Non-Coding RNAs Expressed in Human Male CNS During Early Development. Front. Genet. 2019; 10:891.
11. Reinius B, Johansson MM, Radomksja KJ, Morrow EH, Pandey GK, Kanduri C et al. Abundance of female-biased and paucity of male-biased somatically expressed genes on the mouse X-chromosome. BMC Genomics. 2012;13:607.
12. Reinius B, Jazin E. Prenatal sex differences in the human brain. Mol. Psychiatry. 2009; 987: 988–989.
13. Neri G, Schwartz CE, Lubs HA, Stevenson RE. X-linked intellectual disability update 2017. Am. J. Med. Genet. 2018; A176:1375–1388.
14. Posnyick BJ, Brown CJ Escape from X-Chromosome inactivation: an evolutionary perspective. Front. Cell Dev. Biol. 2019;7:241.
15. Distech CM. Dosage compensation of the sex chromosomes and autosomes. Semin. Cell Dev. Biol. 2016; 56:9–18.
16. Moreno-De-Luca D, Moreno-De-Luca A, Cubells JF, Sanders SJ. Cross-dosage comparison of four neuroepithelial CNV regions. Curr Genet Med Rep. 2014;2(3):151–161.
17. Dennis EL, Thompson PM. Typical and atypical brain development: a review of neuroimaging studies. Dialogues Clin Neurosci. 2013;15(3):359–384.
18. Raznahan A, Parikshak NN, Chandran V, Blumenthal JD, Clasen LS, Alexander-Blath AF et al. Sex-chromosome dosage effects on gene expression in humans. Proc. Natl. Acad. Sci. U. S. A. 2018;115:7398–7403.
19. Oliva M, Munoz-Aguirre M, Kim-Hellmuth S, Wucher V, Gewirtz ADH, Cotter D et al. The impact of sex on gene expression across human tissues. Science 2020;369.
20. Kopsida E, Stergiakouli E, Lynn PM, Wilkinson LS, Davies W. The Role of the X Chromosome in Brain Function. Open Neuroendocrinol J. 2009;2:20–30.
21. Mayer A, Lahr G, Swaab DF, Pilgrim C, Reisert I. The Y-chromosomal genes SRY and ZFY are transcribed in adult human brain. Neurogenetics. 1998;1:281–288.
22. Matsuana S, Takata H, Morimoto A, Hayashiha K, Higashi T, Akatsuchi K et al. RBMX: a regulator for maintenance and centromeric protection of sister chromatid cohesion. Cell Rep. 2012;1:299–308.
23. Shashi V, Xie P, Schoch K, Goldstein DB, Howard TD, Berry MN, et al. The RBMX gene as a candidate for the Shashi X-linked intellectual disability syndrome. Clin. Genet. 2015;88:386–390.
24. Blanco P, Sargent CA, Boucher CA, Mitchell M, Affara NA. Conservation of PCDHx in mammals; expression of human X/Y genes predominately in brain. Mammm Genome. 2000;11:906–14.
25. Yang X, Chen MW, Terry S, et al. Complex regulation of human androgen receptor expression by Wnt signaling in prostate cancer cells. Oncogene. 2006;25:3436–44.
26. Johansson MM, Lundin E, Qian X, Mirzaadeh M, Halvardsson J, Darji E et al. Spatial sex dimorphism of X and Y homolog gene expression in the human central nervous system during early male development. Biology of Sex Differences. 2016;7:5.
27. Shi L, Chang X, Zhang P, Coba MP, Lu W, Wang K. The functional genetic link of NLGN4X knockdown and neurodevelopment in neural stem cells. Hum Mol Genet. 2013; 22(18): 3749–60.
28. Xu J, Deng X, Watkins R, Distech CM. Sex-specific differences in expression of histone demethylases Ltx and Utx in mouse brain and neurons. J. Neurosci. 2008;28:4521–4527.
29. Wang YR, Xu NX, Wang J, Wang XM. Kabuki syndrome: review of the functional link of NLGN4X knockdown and neurodevelopment in neural stem cells. Hum Mol Genet. 2013; 22(18): 3749–60.
30. Davis EJ, Broestl L, Abdulai-Saiiku S, Worden K, Bonham LW, Minones-Mayoano E et al. A second X chromosome contributes to resilience in a mouse model of Alzheimer’s disease. Sci. Transl. Med. 2020;12.
31. Iwase S, Brookes E, Agarwal S, Badeaux AI, Ito H, Vallianatos CN et al. A mouse model of X-linked intellectual disability associated with impaired removal of histone methylation. Cell Rep. 2016;14:1000–1009.
| Page | Reference |
|------|-----------|
| 32.  | Poleta L, Padula A, Attianese B, Valentino M, Verrillo L, Filosa S et al. Histone demethylase KDM5C is a SAHA-sensitive central hub at the crossroads of transcriptional axes involved in multiple neurodevelopmental disorders. Hum. Mol. Genet. 2019;28:4089–4102. |
| 33.  | Wei G, Deng X, Agarwal S, Iwase S, Disteche C, Xu J. Patient mutations of the intellectual disability gene KDM5C downregulate netrin G2 and suppress neurite growth in Neuro2a cells. J. Mol. Neurosci. 2016;60:33–45. |
| 34.  | Snijders Blok L, Madsen E, Juusola J, Gillissen C, Baralle D, Reijnders MRF et al. Mutations in DDX3K are a common cause of unexplained intellectual disability with gender-specific effects on wnt signaling. Am. J. Hum. Genet. 2015;97:343–352. |
| 35.  | Vakilian H, Mirzaei M, Sharifi Tabar M, Pooyan P, Habibi Rezaee L, Parker L et al. DDX3Y, a malespecific region of Y chromosome gene, may modulate neuronal differentiation. J. Proteome Res. 2005;14:3474–3483. |
| 36.  | Davies W, Humby T, Kong W, Otter T, Burgoyne PS, Wilkinson LS. Converging pharmacological and genetic evidence indicates a role for steroid sulfatase in attention. Biol Psychiatry. 2009;66(4):360–7. |
| 37.  | Johnson DA, Wu TH, Li PX, Maher TJ. The effect of steroid sulfatase inhibition on learning and spatial memory. Brain Res. 2000;865:286–90. |
| 38.  | Berletch JB, Ma W, Yang F, Shendure J, Noble WS, Disteche CM, Deng X. Escape from X inactivation varies in mouse tissues. PLoS Genet. 2015;11:e1005079. |
| 39.  | Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R. Landscape of X chromosome inactivation across human tissues. Nature. 2017;550:244–248. |
| 40.  | Davies W, Wilkinson LS. It is not all hormones: Alternative explanations for sexual differentiation of the brain Brain Research 2006;1126:36–45. |
| 41.  | Maenner S, Blaud M, Foullien L, Savoye A, Marchand V, Dubois A et al. 2-D structure of the A region of Xist RNA and its implication for PRC2 association. PLoS Biology. 2006;8:e1000276. |
| 42.  | Arvanitis DN, Jungs T, Behar A, Davy A. Ephrin-B1 reverse signaling controls a posttranscriptional feedback mechanism via miR-124. Molecular and Cellular Biology. 2010;30:2508–2517. |
| 43.  | Morgan CP, Bale TL. Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. J Neurosci. 2011;31(33):11748–11755 |
| 44.  | Vawter MP, Evans S, Choudary P, et al. Gender-specific gene expression in post-mortem human brain: localization to sex chromosomes. Neuropsychopharmacology. 2004;29:373–84. |
| 45.  | Hacker A, Capel B, Goodfellow P, Lovell-Badge R. Expression of Sry, the mouse sex determining gene. Development. 1995;121:1603–1614. |
| 46.  | Wang H, Hu YC, Markoulaki S, Welstead GG, Cheng AW, Shivalila CS et al. TALEN-mediated editing of the mouse Y chromosome. Nature Biotechnology. 2013;31:530–532. |
| 47.  | Milsted A, Serova L, Sabban EL, Dunphy G, Turner ME, Ely DL. Regulation of tyrosine hydroxylase gene transcription by Sry. Neurosci. Lett. 2004;369:203–207. |
| 48.  | Dewing P, Chiang CW, Sinchak K, Sim H, Fernagut PO, Kelly S et al. Direct regulation of adult brain function by the male-specific factor SRY. Current Biology. 2006;16:415–420. |
| 49.  | Czech DP, Lee J, Sim H, Parish CI, Vilain E, Harley VR. The human testisdetermining factor SRY localizes in midbrain dopamine neurons and regulates multiple components of catecholamine synthesis and metabolism. Journal of Neurochemistry. 2012;122:260–271. |
| 50.  | Mulligan A, Gill M, Fitzgerald M. A case of ADHD and a major Y chromosome abnormality. J Atten Disord. 2008;12(1):103–5. |
| 51.  | De Vries GJ, Rissman EF, Simerly RB, Yang LY, Scordalakes EM, Auger CJ et al. A model system for study of sex chromosome effects on sexually dimorphic neural and behavioral traits. Journal of Neuroscience. 2002;22:9005–9014. |
| 52.  | Wu JB, Chen K, Li Y, Lau YF, Shih JC. Regulation of monoamine oxidase A by the SRY gene on the Y chromosome. FASEB Journal. 2009;23:4029–4038. |
| 53.  | Rosenfeld CS. Brain Sexual Differentiation and Requirement of SRY: Why or Why Not? Front. Neurosci. 2017;11:632. |
| 54.  | Ohe K, Lalli E, Sassone-Corsi P. A direct role of SRY and SOX proteins in pre-mRNA splicing. Proceedings of the National Academy of Sciences of the United States of America. 2002;99:1146–1151. |
| 55.  | Bernard P, Sim H, Knowler K, Vilain E, Harley V. Human SRY inhibits betacatenin–mediated transcription. International Journal of Biochemistry & Cell Biology. 2008;40:2889–2900. |
| 56.  | Lalli E, Ohe K, Hindelang C, Sassone-Corsi P. Orphan receptor DAX-1 is a shuttling RNA binding protein associated with polyribosomes via mRNA. Molecular and Cellular Biology. 2000;20:4910–4921. |
| 57.  | Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495:384–390. |
| 58.  | Lopes-Ramos CM, Chen CY, Kuijjer ML, Paulson JN. Sex differences in gene expression and regulatory networks across 29 human tissues. Cell Rep. 2020;31:107795. |