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 Bozukluklardaki Cinsiyet Farklılıkları ile Olası İlişkisi

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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

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ÖZET

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

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

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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 disorder 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 in 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 testicles 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. (10). As 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, and 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 (XLID) 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 (lncRNA) 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 a lncRNA 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 aneuploidies 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 aneuploids (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, KDM5C, ZFX, RPS4X* show high expression differences depending on sex. (19). It is also observed that the severity of cognitive disorders associated with *KDM5C, KDM6A, DDX3X, USP9X, RBMX, NLGN4X, PCDH11X* genes differ in women and men. (13). It is seen that the X-linked homologs of these gene pairs are not sufficient for dosage compensation, but they are mostly expressed more than the Y-linked homologs. In addition to being expressed at different levels according to sex, they are expressed in different stages of development and different anatomical localization (20).

- *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 *ZFY* 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 (2).
- *RBMX/RBMY:* RNA binding motif proteins genes (*RBMX / 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*/*Rbmx* are widely expressed and encode proteins that provide centromere cohesion, *RBMY/Rbmy* have testicular expression profile and functions (22). *RBMX* mutations are associated with XLID (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 neuroligin. 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-amyloid 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 desulfatase enzyme responsible for the desulfation 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 lncRNA. *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 (*cbln4*), *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, XX*Sry*), 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 anteroventral 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. Later 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 (KRAB) superfamily with transcription-suppressing properties. SRY interacts with a repressor complex containing KRAB-associated protein-1 (KAP1), Mi2-associated nucleosome remodeling deacetylase (NuRD), histone 3 lysine 9 specific methyltransferase (H3K9me3) SETDB1, heterochromatin protein-1 (HP-1) proteins over KRAB. 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 KRAB protein, other KRAB family members and KAP1 are known to be expressed in the brain. It has been shown in the brain that KAP1 is needed for KRAB-mediated epigenetic silencing. KRAB-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-mRNA 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 transcript (*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 lncRNAs was expressed on the Y chromosome in the first trimester, and it was suggested that these lncRNAs 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.

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