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GENE NETWORK INVOLVED IN SEX DETERMINATION- A REVIEW

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ABSTRACT

Sex developmental disorders (SDDs) are inborn conditions where the changes of gonadal, or physiological sex is anomalous. A majority of the genes necessary for genital evolution were characterized through the investigation of disorder of sex determination mice.Nevertheless, the use of knockout and mutated mouse strains has greatly helped to explore the role and relationships of gonad genes within the network of the developmental genes. However, in recent years, the genetic help of defining and differentiating mammalian sex has progressed a lot. Here we study our current understanding of determining mice's sex based on observations from mouse models.

Key word: Chromosomes, LIM homeobox, Sex developmental disorders, Gonad genes.

INTRODUCTION

Genetic differences among sexes during embryo development are genetically resolute among the primates. These disparities affect human and physically physiological, sexual and social life significantly. Genetic differences among sexes throughout embryo development are genetically resolute among the primates. These disparities have massive psychological, cultural, and social effects on human and physical life. Sex creation can be categorized into two types of acts,' sex determination,' which is embryonic determination that governs the indistinct gonads that behave either ovaries or testicles, and' sex determination,' which occurs as the gonad develops and is determined to decide the phenotypical sex by the gonad outcome.Sex resolution, in primates, is equivalent to genital development. The factors that affect sex identification tend which regulate transcription, in which secreted hormones and their receptors are referred as factors affecting sex variations. Most of our knowledge of genes and their related proteins in sex-making comes from mouse models. There the raging understanding of gonad formation would be discussed, and how alteration of this dynamic growth network leads to the disorder of sex development. Gens that have participated in the development of embryonic mouse gonad need to be given special consideration.

Gonadal development in mice

Among rodents, both female and male are complemented by 19 sets of autosomal chromosomes but not similar among their sex chromosomes. Men contain one X and another Y (40, XY) among rodents, while females have two X chromosomes (40, XX). Two-sex embryos differ only by sex chromosomes at the time of conception. The first proof of dimorphism of sex in rodent embryos is significant at the time of the formation of bi-potential gonad to grow into either an ovary or a testis in XX and XY people.The commitment is produced in mice around embryonic day 10.5. Gonad distinction helps in ovarian and testicular hormone secretion and psychological activation.SRY's function in XY gonads is to tip the scale toward the route, which is unique to the testis **[1, 2].**

In mice, the SRY gene is located in the hetero-potential XY gonad **[3]**, and the SRY gene expression starts regulating SOX9 development. Sox9 has been expressed in mice to promote the production of Fgf9 and then both sox9 and FGF9 function together in +ve feedback loops, that are often postulated to repress wnt4 and are geared towards setting up testis-specific pathways.In the non-appearance of SRY in XX species, WNT 4 and RSPO1 are produced at high range and control cytoplasmic β-catenin, which is then moved into the nucleus, where it binds to the transcription factor / lymphoid enhancer-binding factor and turns on the transcription of the target gene. Both WNT4 and beta-catenin inhibit SOX9/FGF9's positive feedback loop, allowing for specific ovarian pathways to be formed.

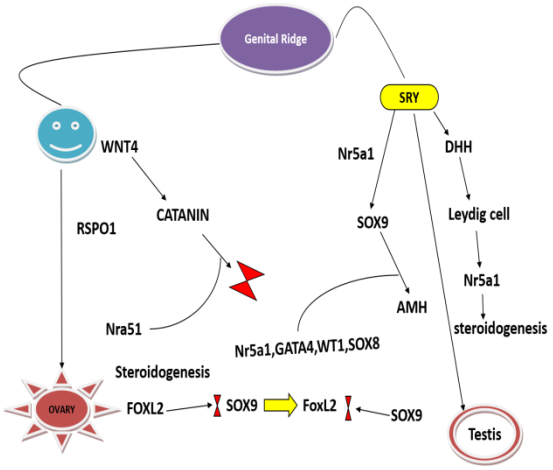

Fig1. Genomic cascade in sex determination.

Gene compulsory for establishment of Bi-potential gonad-

Mammalian gonads from bi-potential gonad or vaginal ridges are visible in both sexes **[4, 5, 6]**. In mouse, they first appear in specific region of mesonephros at around embryonic days E9.5, one day before the beginning of SRY speech, which is necessary to facilitate the formation of testis in XY individuals. Diverse genes have shown their significance in bi-potential gonad growth. The development of genital ridges takes place via coelomic epithelium and afterwards via split into fragments of underlie basement membrane, allowing separation into layers of proliferating coelomic epithelium into inner mesenchymal region of mesonephros **[7].**The rigidity ofurogenitalridges starts at E10.3, then at the anteroposterior axis. Urogenital ridges are filled by moving precursors of gamete cells, combined with stiffness **[8,9, 10, 11,12]**.The study of mutant mice has recognized numerous significant factors in both cell proliferation and consumption. To our information, GAT4 is preliminary factor of transcription expressed mainly inurogenitalridges.

GATA4 exists in coelomic epithelium cells of rostral part of genital ridges as soon as E10.0 and expression of it spread across rostro caudal axis till embryonic 10.2 **[7]**. There are following genes are involved in genital ridge formation.

Table 1.Summarization of some gene's importance for testis and ovary development

Testis		
Genes	**Gene product**	**Mutant type**
WT1	Factor in Transcription	Gonadal agenesis
SF1	Nuclear receptor	GR development block
GATA 4	Factor in Transcription	XY Reversal of Sex
SRY	Factor in Transcription	XY Reversal of Sex
Sox9	Factor in Transcription	XY Reversal of Sex
Fgf9	Signaling molecule	XY Reversal of Sex
Dax1	Nuclear receptor	XYhypogonadism
DHH	Signaling molecule	XY Gonadal dysgenesis
DMRT1	Factor in Transcription	XY female
AMH	Peptide hormone	Persistent Mullerian duct syndrome
Ovaries		
WNT4	Signaling molecule	Mullerian duct agenesis
FOXL2	Factor in Transcription	Premature ovarian failure
DAX1	Nuclear receptor	XY sex reversal

Nr5a1

super family of nuclear receptor adrenal 4 linking protein is also known as nuclear receptor subfamily 5, group A, category 1(Nr5a1), and transcription factor 1(Sf1) involved in sex determination was first defined as a gene coding a general transactivating factor linked to the steroid hydroxylase gene promoting it.Nr5a1+ve progenitor cells originate in adrenal glands and the coelomic epithelium somatic branch of gonads. Our adrenal glands are not well formed and exhibit fewer cell proliferation in mouse embryos **[13]**. Compound heterozygote study of six 1+/-, six 4+/- and Nr5a1+/-embryos reveals the disrupted development of progenitor gonadal cells depending on the expression level of Nr5a1 **[14]**. Embryos are those with homozygous deletion of Nr5a1express gonad regression by embryonic 12.5 with genetically programmed cell death of gonadal somatic cells **[15, 16, 17]**. Conversely, an enhanced amount of fetal Leydig cells **[18]** accomplishes an irregular production of Nr5a1 in Pod 1 lacZ / lac Z gonads.Therefore, over expression of Nr5a1 in Nr5a1 negative mice save compromised development of gonad and spleen. This difference in the rescue effect could convey partly the differential degree of expression of Nr5a1 between tissues and the distinctive responsiveness to the dosage of genes. **[19]**.Nr5a1works in gene cluster activation participate in steroidogenesis, such as cyp 17a1 and 3beta-HSD in testicular Leydig cells. However, Nr5a1 was first determined as a gene encoding a steriodogenic gene, agentthat increase rate of gene expression **[20, 21, 22]**. There are also numerous physiological processes in Nr5a1 **[23, 24]**. It could be proposed that Nr5a1 regulates the transcription of reference gene clusters involved in various physiological acts, including cell proliferation stimulation, metabolism, segregation and persistence that are critical for gonadal growth.The development of damaged gonadal and glands of adrenal in insulin / IGF signaling pathways in embryos is favored for this postulate. Insulin / IGF signaling mechanism is found to regulate the various physiological activities **[19]**.At a late stage, Nr5a1 controls the transcription of these important genes in XY gonad development for testicular differentiation, such as SRY-associated HMG box 9(Sox9) and anti-Mullerian hormone **[25, 26]**. A subset of larger population of coelomic epithelial cells expressing Nr5a1 and Gata4 is called the earlier population that belongs to genital ridge somatic lineages.

Such findings indicate that the creation of an exceptionally long narrow genital ridge concludes with Gata4 completing the anterior portion of the coelomic epithelium and Nr5a1 expression.

SRY and Sox9

The fate of embryonic gonad is set on by dividing somatic cells into Sertoli cells or granulose cells. The proliferation of Sertoli cells in bi-potential gonads enhances the testicular differentiation strategy by enhancing the ovarian differentiation system. The function of the gene part Y linked gene SRY displaces the bipotential embryonic gonad to a testicular destiny to the greatest extent of the determination of mouse sex **[27, 28, 1]**. The immediate role of SRY is to cause pre-Sertoli differentiation of cells, which is necessary for the dedifferentiation of bipotential gonads from the testis. Spatiotemporal expression regulated in the Sertoli cells precursors SRY. In mouse genital ridges, SRY if initially expressed on E11.0, achieves high degree of expression at E11.5 and is lost shortly after E12.5. SRY's speech starts in the center of the genital ridges and becomes restricted to the posterior area before disappearing completely in the genital ridges. Sox9 is expressed in Sertoli cell precursors approximately 4 hours after SRY expression starts **[29, 30, 31, 32, 33]**. To activate the male development plan, the output of either sox9or SRY in bipotent gonad has been studied for transgenic mouse **[28, 34, 35, 36]**. Sox9 and SRY are transcription factors with a known amino acid sequence as the domain HMG **[37, 38]**. This HMG motif appears to grab DNA sequences (A / T) ACAA(T / A) with high avidity of sox family proteins **[39]**.In the highest degree SRYdeficient find human patients showing male to female sex transfer that affects SRY's ability to bind and bend DNA **[39, 40].**SRY's deficient analysis of its C terminal domain suggests that SRY C terminal domain could contribute to SRY conformation and could affect SRYfunctions **[41]**. Nuclear localization signal at the north end of the SRY HMG box and SRY disabled in this NLS contributes to the elimination of nuclear imports, which explains only a few cases of human sex reversal **[42, 43].**

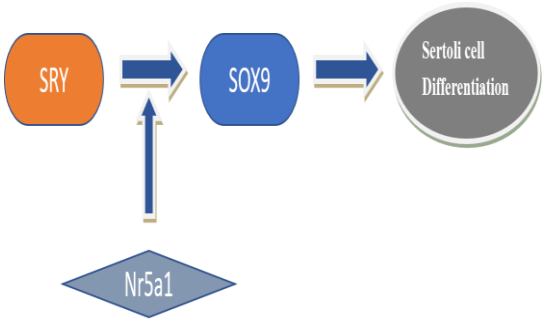

Fig 2.SRY and the transcriptional network that controls testis determination. In mice, having one specific genetic source, the Y-linked gene SRY, induces differentiation of pre-Sertoli cells. SRY Directly transactivates Sox9 via the core element of the sox9 (Tesco) testis-specific enhancer region, together with Nr5a1. Sox9 itself, along with Nr5a1, also leads to Tesco's protection of the Sox9 expression.

Instead of SRY, Sox9 transgene was accomplished to improve the technique of the method of testicular differentiation **[44, 45].** Hence the important action of SRY in deciding the testis can only be over sox9 voice. Another risk is that the sox9 transgene drug promotes not only endogenous sox9, but also other SRY target genes that are required to facilitate the test growth.

WT1

Wilms ' tumor 1(WT1) is a gene that encodes the transcriptional factor of the zinc finger, was first noticed as the wilms tumor responsible gene. Especially in children, kidney cancer is caused by human WT1 mutation **[46].**WT1 contains two isoforms with additional three amino acids (threonin, lysine, serine) between the third and fourth zinc digits. WT1 is mostly found in mesodermal developmental tissues such as the urogenital slope, gonads Armstrong et al. 1993. The gonadal phenotype is replicated in other disorders where improvements in WT1 such as Densys-Dars syndrome (gonadal defects and renal failure) have been made **[47, 48]** and Frasier syndrome **[49]**. The Frasier sufferer was shown toundergo modifications leading to loss of isoform WT1 + KTS. In these isoforms, these three specific amino acids exist between the third and fourth zinc fingers of WT1, lysine, threonine, and serine. The 2 distinct isoforms –kts and+ kts were expressed in the embryogenesis process in order to play different functions. It was shown that the –KTS isoforms fastened to the SRY promoter region which led to SRY transactivation **[50].** In fact, the-ktsWT1isoforms were manifested within the promoter Nr5a1 to fasten sequences **[51]**.

In addition, isoforms with + kts also play an important role in regulating SRY transcript. Removal of this+ kts of WT1 isoforms leads to reduced SRY degree in all probability driven by binding affinity to RNA.In fact, the-ktsWT1 isoforms were manifested within the promoter Nr5a1 to fasten sequences **[51].** In addition, isoforms with + kts also play an important role in regulating SRY transcript. Removal of this+ kts of WT1 isoforms leads to reduced SRY degree in all probability driven by binding affinity to RNA **[52].**

Emx2

The gene, analogous to empty spirals from the Drosophila head gap gene, is Empty Spiracles homeobox 2. Lacking Emx2 in mouse embryos leads to deformation or agenesis of ureters, kidneys, and gonads, and genital tract, while normal bladder and adrenal gland development. **[53]**Coelomic epithelium cells are lowering their cell polarity by forming Emx2-/genital ridges. The number of migrated Emx2-/-coelomic epithelial cells in the mesenchymal compartment also decreases, leading to the formation of damaged gonads **[54].**

LIM Homeobox 9

The LIM homebox 9 (LHX9) is a member of the LIM homeobox gene family. The germ cells usually move in mice that lack LhX 9 gene but the genital ridge somatic cell was unsuccessful in being able to proliferate and produce separate gonad. Typically, male genetically engineered mice, lack of antimuller hormone and testosterone, develop as phenotypic females **[15, 55]**.In the Lhx9 negative genital ridge, the effect of steroidogenic factor 1, a nuclear receptor necessary for gonadogensis, is reduced to a minimum level, indicating that Lhx9 may remain upstream of Nr5a1 in an evolving mouse cascade **[55].** Analysis therefore showed that LHX9 would fasten and transactivate the promoter Nr5a1 in competition with WT1 **[51]**. Nevertheless, LHX9 mutation review did not reveal any mutations in a number of patients with human sex determination disorder **[56].**

Desert Hedgehog

Desert hedgehog belongs to the class of signalling hedgehog molecules which include sonic hedgehog and Indian hedgehog **[57]**.

The Desert hedgehog is unique among the three members of the family, represented in the development of the XY mouse gonad somatic cell community from embryo 11.5(E11.5) and continuing to seretoli cells. Even no expression is shown in XX ovaries at either time **[58, 59, 60].** Desert hedgehog fasten to its patched 1 receptor (PTCH1), soon after DHH. Patched 1 receptor is linked to Leydig membrane and peritubularmyoid cells, and its level of expression increased with DHH **[61,62].**DHH appears to be essential in Leydig cells for over-expression of sf1 **[62].** Some DHH modifications have been rendered in patients with full or partial gonadal dysgenesis levels 40, XY.

Fibroblast growth factor 9

FGF9 codes the cell survival, cell proliferation, cell differentiation, cell migration, fibroblast growth factor 9 that plays a role in various processes of evolution. Fgf9 is regulated in the bi-potential gonad, just after the presentation of SRY. Mice lacking in Fgf9 demonstrate reversal of male to female sex along with impaired cell growth of the sertoli. Although this is evident on some inherited cases but not on another **[63, 64].** Because of the lack of Fgf9, sox9 activity is not controlled, Sertoli cells do not distinguish, testis development is stopped and somatic cell genes instead express ovarian growth and female pathway. There is a research in support of the idea that SRY and Nr5a1 start positive feedback loop by over-expression sox9, that is, turn up regulates FGF9 and further enhances the expression of sox9 **[65]**. FGFR2 is integrated in progenitor Sertoli cells plasma membrane and interprets the developmental check for Sertoli cell proliferation and differentiation **[66].**

CONCLUSION

After the discovery of SRY in 1990, our understanding of genes and its expression was indulging in genitalprogress and Sex-determination causative agents has been greatly enhanced. Comparative genomic hybridization (CGH)/SNP chip arrays continue to analyze ideal gene rearrangements and engage in differentiating and evaluating gonads with the development of better protocols.However, even mysterious DSD situations, more split in the testis and ovary production network shows us that there is still much to perceive.

Such 2 array-based methods require rearrangements to be assessed in presumed regulatory elements that, if changed, would contribute to Disorder of Sex Determination. The usage of microarrays to test Copy Number Variation has had some favorable results in the identification of causative mutations in mysterious DSD situations. This method, though, is restricted to determining significant rearrangements and may fail to notice small genomic rearrangements or point mutations. Next-generation sequencing (NGS) and whole-genome sequencing can have a higher purpose for mutation identification and should help to overcome mysterious DSD events. Whole genome sequencing, which encompasses all other methods, is an important tool for evaluating.

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