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Sexual Dimorphism in Humans-During Foetal Development, In Adult Metabolism

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Abstract: *According to recent findings both X and Y chromosome could have evolved from autosomal ancestors about 300 million years ago. In humans, the typical male has a diploid karyotype of 46 chromosomes i.e. 22 pairs of autosomes and XY pair of gonosomes(46,XY).A standard female karyotype is 46 XX.Thus humans are dimorphic: there is one type of humans who are males and the other type is female. The basis of sexual dimorphism in mammals derives from evolution of sex chromosomes (1). Probably a failure occurred in homologous recombination which resulted in the formation of a small area that was not identical to the two participating chromosomes. The presence or absence of this region coincided with a different pattern of development that altered androgen activity resulting in a sex determining role. In all living mammalians to day, this area in Y chromosome appears to retain the regulatory function and therefore described as the sex Determining Region of Y chromosome or SRY gene(2).But sexual Dimorphism is not just dependent on functioning of one chromosome(SRY).It is a gradual conversion process. According to this theory ,the X and Y chromosomes have experienced repetitive recombination failures through out time leading to micro and macroscopic specializations. This finally lead to the extensive differentiation in the current structure of gonosomes.(3)*

I. Introduction

Since Y chromosome is quite small in comparison to the X chromosome, it would simply not attribute to chromosomal recombinations. Each failed recombination could have been followed by some level of genetic instability which could have resulted partial deletion of Y chromosome ancestor. To day males carry a Y chromosome that almost entirely (95%) consist of non recombinant sequences .Combination is allowed only at polar regions ,the so called pseudoautosomal regions (PAR 1 and PAR 2).The non combinant region (NRY) has developed around SRY gene include a variety of genes and regulatory elements that co-operate to produce the main features of male phenotype. This male specific region of Y chromosome is called MSY(i.e. the NRY carrying the SRY and other genes).MSY has the ability to exchange DNA between its own two different regions,allowing some degree of variability. Palindromes present in Y chromosome facilitate Y-Y recombination. It has been argued that this could be the reason why Y chromosome retains its current length after millions of years of gradual deterioration(4).

Process of sex differentiation in brief:

- A sperm may contain either an X chromosome or a Y chromosome ,while the avum carries only X chromosome;these cells are haploid in nature.
- Sperm and ovum fuse to form a zygote which develops into a blastocyst and after several divisions and differentiation develops into an embryo.
- Primordial germ cells first appear in the proximal epiblast of the outer ectodermal layer of the embryo. From here they migrate through the primitive streak to the base of the allantois.
- The germ cells then migrate along the wall of the hindgut to the urogenital ridge-this is the site of the future gonads. Genital ridge contains four cell lineages that comprise the gonads:the germ cells,connective tissue cells,steroid producing cells(Leydig cells in testes and theca cells in ovary),and supporting cells(sertoli cells in testes and granulosa cells in ovary).(5)
- Fragilis and stella are the two genes that are unique to differentiating germ cells
  Fragilis belongs to an interferon –inducible family of transmembranous proteins ,involved in transducing antiproliferative signals and in adhesion;both these function may be important for coalescence of germ cells to the base of allantois.
- Fragilis is first detected in the proximal epiblast where its expression is influenced by BMP4 (Bone morphogenic protein 4) and then at the base of allantois. The protein from the gene Stella has a role in RNA

processing and chromatin modification.It maintains the pluripotent state of the migrating primordial germ cells by silencing transcription of genes specific for somatic cells.(1) Only the germ cells that reach the presumptive gonadal region differentiate;germ cells outside this region undergo apoptosis.However, if some escape ,they can later become germ cell tumours.

- Gonadal cells are bisexual.The presence of Y chromosome in sperm differentiate them to the male gonodal tissue ,while the presence of X chromosome in the sperm produces female gonadal tissue.
- Several genes are involved in differentiation of the bipotential gonad to one type of gonad.

o Nuclear Receptor subfamily 5 group A member gene 1(NR5A 1)and Wilm's tumour suppressor gene 1(WT 1) have very important roles.WT 1

Represents a transcription factor with tumour suppressor acticvity.It is
Expressed predominantly in the embryonic kidney and gonads.WT 1 protein mediates the mesenchymal-epithelial transition and differentiation by a)activating genes meant for epithelial cell differentiation. b)repressing genes meant for cell proliferation.WT 1 has two isoforms depending upon the presence of 3 amino acids such as lysine,threonine and serine.When these three are present it is KTS+ and in their absence it is called KTS- isoform. KTS-ve WT 1 isoform achieves synergy with a Steroidogenic factor 1(SF 1).SF 1 inturn promotes the expression of Mullerian Inhibiting Substance(MIS).The severity of the degree of gonadal abnormalities in 46 XY is determined by the degree of interruption of synergy between WT 1

and SF 1(6). However an intact WT 1 gene is not absolutely necessary for normal female development in 46 XX individuals. But they could have renal abnormalities with aberrant WT 1 expression.
Loss of KTS+ isoforms leads to:
1.Frasier Syndrome----Nephropathy,male pseudohermaphroditism,complete gonadal dysgenesis.
2.Mis-sense mutation of WT 1 leads to Denys-Drash syndrome---------: male pseudohermaphroditism, nephropathy,wilm's tumour.

- Deletion of several closely linked genes can cause WAGR:-

Wilm's tumour
Aniridia
Genital abnormality
Mental retardation

- Steroidogenic factor 1 (SF 1)is the product of the gene NR 5A 1.The mRNA of this gene product is produced in the urogenital ridge which forms the gonads and adrenals.

a)SF 1 binds to upstream regulator units of Anti Mullerian factor (AMF) gene and promotes its expression.
b)Both SF 1 and another transcription factor called GATA 4 promote AMH(Anti mullerian hormone) production(product of AMF gene).(6)

- Another cotranscriptional factor of AMH regulation is SRY related SOX 9.SOX 9 acts through a protein – protein interaction with SF 1.

SF 1 also activates the receptor of the sertoli cell specific hormone(AMH) by binding to Mullerian inhibitory substance II(MIS II) receptor. Mutation in SF 1 results in primary gonadal insufficiency and male hermaphroditism in 46 XY individuals. But in 46 XX females development of ovary is not affected by mutations in SF 1.(4) Homolox A genes (HOX A) are expressed in the craniocaudal axis of the mullerian ducts and specify the identity of developing structures.Expression of LIM class of proteins(transcription factors) in the epithelium of wollfian and mullerian duct highlight the initial sexual duality of the forming reproductive systems.

SRY(Sex determining region on Y chromosome) is expressed for very short time.It is an one axon gene in Y chromosome .This gene triggers testes formation from the indeterminate gonads.SRY's main and only function is to activate the transcription factor SOX 9(SRY –type HMG box-9) which in turn initiates the male differentiation programme.SOX9 promotes sertoli cell differentiation from bipotential supporting cell precursors.The early testes also prduces Prostaglandin D2. PGD 2 recruits cells of the supporting cell lineage to a sertoli cell fate.The gene encoding for Prostaglandin D synthase is regulated by SOX 9 expression.SRY also down regulates WNT4 genes and upregulates FGF 9 genes which facilitates male sex differentiation.(7)

Mutations in SRY gene cause pure gonadal dysgenesis with XY male to female sex reversal(Swyer syndrome) or true hermaphroditism.(4)

For females there are the presence of two X chromosomes. Hence there is a dosage difference and potential imbalance in expression of genes in females. Random X inactivation is the process by which one X chromosome is silenced in female embryos in order to avoid X hyperexpression..This mechanism leads to dosage compensation of the large majority of X linked genes. Random X inactivation silences either the paternal or maternal X chromosome at the blastocyst stage and persists into adulthood.X inactivation has three steps-

initiation,spreading,and maintenance. Each X chromosome has a X inactivation centre(Xic).In the Xic domain there is an element called Xist(X inactive specific transcript)which encodes a RNA .This RNA recruits a protein and coats the X chromosome and promotes compaction beginning at the Xic,mostly paternal X chromosome is inactivated in females..Finally this compacted X chromosome is called the barr body.However some genes escape gene inactivation and allowed for their differentiated role in females.(8)The absence of a Y chromosome and hence SRY gene allows formation of ovary in female embryo.DSS-AHC critical region of X chromosome gene 1(DAX 1 also called NR0 b 1) achieves the feminization of genital structures ,a process described as dosage sensitive sex reversal. NR0 b 1 is - Nuclear Receptor subfamily O, group B,member 1.DAX 1 begins to be expressed at the same time as SRY,but DAX levels rapidly fall as testes cords begin to appear;but in females in the absence of SRY, DAX 1 continues to be expressed. DAX 1also represses the activity of SF1 gene. It also forms heterodimers with SF1 to ensure repression of SOX 9 which is necessary for ovary development.DAX 1 also down regulates AMH.(9) DAX 1 gene is expressed in human ovarian tissues,ventromedial nuleus of hypothalamus,gonadotropic cells of pituitary gland and in the adrenal cortex.A small amount of DAX 1 gene product in males is also required for the initial organization of seminiferous tubules.(8)

The steroid producing cells of ovaries are present in the inner and outer theca.The SF 1 protein is the key regulator of androgen production in these cells also,but it also helps to limit p450 aromatase activity, thus achieving an optimal androgen and oestrogen ratio.

In the absence of SRY/male hormones the wolffian ducts degenerate.Mullerian duct persists and differentiates into female reproductive tract including fallopian tube,uterus,cervix and upper portion of vagina.(4)

Although the chromosomal basis of sex is determined at the moment of conception ,the internal structures are indifferent till 6 weeks of gestation.

Wolffian ducts in males become male internal genitalia(Epidedymis,vas deferens and seminal vesicles).Internally the process results in the ejaculatory system for sperm and completed by 14^{th}. week of gestation.External structures are initially indifferent and consist of urogenital tubercle,urogenital swellings and the urogenital folds which develop into male external genitalia.All these occur by 14^{th}. week of gestation.

In the absence of testes ,the mullerian duct differentiates into fallopian tubes,uterus,cervix and upper portion of vagina.The urogenital tubercle,urogenital swellings and the urogenital folds develop into female external genitalia.

Estrogen stimulates formation of female external genital parts.(6)

Androgen together with AMH and insulin like growth factor 3(Ins I 3) are involved in testicular descent to the scrotum,via the action of the transcription factor LIM 1.In females,there is no androgen and the associated Ins I 3.Thus the suspensory ligaments hold the ovary inside the abdomen.(4)

- **Sexual dimorphism in metabolism:**

Females have the unique function of child bearing and feeding. Hence the energy metabolism in males and females should differ to meet the distinct sex specific function.

In humans sex specific specialization is associated with distinct body fat distribution and energy substrate utilization i.e, females store more lipids and have higher whole body insulin sensitivity than males and males tend to oxidize more fat than females.(10).Women have higher percent body fat ,less visceral fat and more subcutaneous adipose tissue both in abdomen and gluteofemoral region giving the gynoid body shape Upper body subcutaneous adipose tissue is more lipolytically active than lower body subcutaneous adipose tissue in both men and women. Non oxidative FFA clearance through re-esterification is higher in women than in men, suggesting that women tend to store where as men tend to oxidize circulating FFA. .(11)

Men are less sensistive to antilypolytic effects of insulin i.e, the release of post prandial FFAs from upper body subcutaneous adipose tissue is less suppressed in men and FFA release from visceral fat is less suppressed in women.(12) After a meal ,systemic FFA flux is more suppressed by insulin in women suggesting that women have higher risk of fat gain. The contribution of visceral fat lypolysis to hepatic FFA delivery is greater in women, they are more susceptible to hepatic insulin resistance.(13) It has also been shown that a greater portion of post prandial FFA(primarily by LPL) enters upper subcutaneous adipose tissue both in men and women, but a greater portion is stored in subcutaneous fat in women while storage occurs more in men in visceral fat. The menstrual cycle has no apparent effect on FFA tissue uptake in healthy women.(14)

During exercise women oxidize more lipids and less carbohydrate despite less muscle glycogen and exhibit lower hepatic glucose production.This preferential substrate selection is attributed to estrogen.It has also been stated that eostrogen can directly suppress TG synthesis by reducing lipogenesis in liver and increasing lipolysis in adipocytes.In both males and females oetrogen promote β oxidation of FFA and reduce storage of TG acting via PPAR δ and by activating AMPK.(7)

Estrogens exert their physiological effects through two estrogen receptors(ER) subtypes.ER-α and ER-β which belong to the nuclear receptor family of ligand activated transcription factors. ER-α is expressed mostly in reproductive tissue,kidney,bone,white adipose tissue and liver. ER-β is expressed mainly in CNS, ovary, prostate ,lungs ,G I tract and bladder.The major physiological eostrogen -17 β oestradiol(E2) has similar affinity to both types of receptors.(15)

Hypothalamus is the key regulator of food intake and energy homeostasis.

Hypothalamus processes afferent signals from the gut and brainstem and sends efferent signals that modulate food intake and energy expenditure. Hypothalamus is subdivided to a)interconnecting nuclei including Arcuate nucleus(ARC),b)paraventricular nucleus(PVN),c)ventromedial nucleus(VMN),d)Dorsomedial nucleus and lateral hypothalamic area. In experimental animals direct injection of 17 β oestradiol into the PVN area reduce food intake.,reduce body weight and increase running activities.Food intake in women is lowest during periovulatory period when the estrogen levels are the maximum.(15)

Both ER-α and ER-β are expressed in hypothalamus.In experimental animals ER-α silencing on VMN of hypothalamus increased food intake and reduced energy expenditure.

In experimental animals E2 treatment suppressed the expression of Fatty acid synthase,Steroyl-coenzyme desaturase 1 enzyme.Further, ER-β negatively regulates PPAR γ which is a key lipogenic factor.The mechanism behind inhibition of PPAR γ by ER-β is suggested to be a competition between PPAR γ & ER-β for the common co-activator PPAR γ coactivator 1.Thus both isoforms of estrogen receptor participate in antilipogenic action of estrogen.

Leptin is an adipokine secreted by subcutaneous adipocytes and transfers a catabolic signal to the hypothalamus,to inhibit food intake and increase energy expenditure.Leptin levels are higher in females than males.In addition, raised levels of estrogen have been associated with increased leptin sensitivity in brain. (15)

Estrogen regulates pancreatic β cell function. It has been suggested that long term estrogen exposure increases insulin levels, insulin target gene expression and insulin release in experimental models. Men with Aromatase deficiency, cannot produce estrogen from testosterone ,these subjects display impairmrnt in glucose metabolism and insulin resistance.

It has also been stated that estrogen augments intestinal cholesterol absorption leading to overproduction bile , induce cholesterol supersaturation of bile and consequent bile stone formation, a condition more common in women. Estrogen decreases plasma LDL concentration and increase plasma HDL concentration .The decrease of LDL cholesterol is as a result of increased hepatic LDL receptor expression which increases clearance of plasma LDL and secretion of cholesterol to bile,this could also augment bile stone formation in females.(15)

In the liver ,growth hormone(GH) regulates the expression of a variety of genes.

Secretion of GH from the pituitary is subject to testosterone exposure which causes pulsatile secretion of GH in males from neonatal life to adulthood; but pituitary secretion is nearly continous in females. PPAR α promotes fatty acid oxidation and its activity is more during fasting.In liver PPAR α gene is more expressed in males than in females.(16) Steatotic liver is characterized by an abnormal retention of lipids in the hepatocytes. Lipid metabolism is gender-dimorphic and this is expected to be reflected in the prevalence of steatosis. Non alcoholic fatty liver disease appears to be more prevalent in males .The prevalence of hepatocellular carcinoma(HCC) is higher in men than women. .(17)

The roles of hormones on brown adipose tissue is in research stage. However, the female brown adipose tissue(BAT) shows larger mitochondria and higher cristie density compared to BATs present in males. During pregnancy and lactation , the modified hormonal milieu is accompanied by BAT atrophy.

This may be required to reduce thermogenesis in order to save energy for foetus. It has been proposed that oestrogen may control BAT activity that has the ability to modulate the leptinergic-melatonergic system,which is a major brown adipocyte thermogenesis. It has also been proposed that women oxidize proportionately more lipid and less carbohydrate during endurance exercises than men.The oxidation of amino acids is also lower in women.,these revelations could be due to higher 17 β oestradiol concentration in women.(18)

Testosterone is irreversibly reduced to Dihydrotestosterone(DHT) by 5-Reductase.There are three forms of 5-Reductase.Type I 5-Reductase is responsible for nearly $1/3^{rd}$ of circulating DHT while Type II is responsible for nearly $2/3^{rd}$. of the circulating DHT.Type III form is detected in cancer prostate.DHT plays a prenatal role like testicular descent, development of external genitalia,maturation of spermatozoa in epidedymis.DHT could also be responsible for visceral type fat deposition in males. It has also been stated that DHT inhibits lecithin-like oxidized LDL receptor 1 and prevents formation of foam cells,thus reducing atherosclerosis.(19)

Androgens increase the expression of the transcription factors PGC 1α in skeletal muscles stimulating mitochondrial biogenesis,substrate oxidation and muscle insulin sensitivity.Lower levels of PGC 1α are found in insulin resistant type of Diabetes mellitus patients.Further, androgen deficiency in men is associated with insulin

resistance and obesity;treatment of hypogonadal men with testosterone improves insulin sensistivity and reduces fat content. Aromatisation of Testosterone to 17 β oestradiol is important for energy homeostasis and an high androgen to oestrogen ratio promotes visceral adiposity in men.Men with genetic androgen resistance due to decreased AR expression also develop visceral obesity.(10)

In normal conditions circulating levels of leptin are positively correlated with adiposity.In humans , absence of endogenous leptin is associated with hypogonadism and absence of pubertal development.It has been shown that leptin enters the testes by passive ,nonsaturable process.Leptin modulates the paracrine network that controls gonadotropin stimulated testicular steroidogenesis.But leptin excess has adverse effect.In obese men who exhibit high leptin levels ,hypogonadism is observed which could be through a direct inhibition of leydig cell steroidogenesis.Obese men also exhibit increased levels of plasma estrogen and decreased levels of bioavailable androgens.

This is due to an increase in the aromatase activity which is responsible for conversion of androgen to estrogen. It has been stated that circulating values of testosterone should not be below 8nmol/L(230ngm/dl).Levels below this cut off value are associated with severe impairment of body composition and glucose metabolism.It could present with obesity,hypertension ,dyslipidemia,insulin resistance ,erectile dysfunction ,decreased bone mineral density ,decreased muscle mass and strength and depressed mood.Men affected by androgen resistance due to gene inactivation of the Androgen receptor(AR) show high visceral fat.furthermore, it has been proposed that in adipocytes, AR plays an inhibitory role in leptin production.(19).

Dimorphism in brain function:

In several species of song birds,males sing more than females,a functional difference that matches structural difference in their brains: the forebrain regions controlling song such as Higher Vocal Centre(HVC) and Nucleus Robustus

Archstriatum are much larger in males and contain more neurons than females.(20) The regions of CNS closely associated with sexual behavior are hypothalamus,the amygdala, and the bulbocavernosus nucleus of the spinal cord. Preoptic area and anteroventral nucleus exhibit high amount of estrogen receptors. Spinal bulbocavernosus nucleus exhibits only androgen receptors. Granulin is an androgen induced modulator of epithelial growth is highly expressed in the ventromedial and arcuate nucleus of hypothalamus.(20)

Although intelligence in general is similar both men and women,cognitive skills differ in both sexes.During mental rotation tasks,men preferentially use the right hemisphere and are more lateralized while women use both the hemispheres and present lower lateralization.In general men are better in logical reasoning and abstract mathematics. Females on average outperform males in cognitive empathy, verbal communication and emotional intelligence. Testosterone involved in brain organization is believed to be involved in these differences.(21) It has also been proposed that testosterone therapy in aging individuals may provide positive effects on cognition and that neural regions that are linked to cognition such as the hippocampus and/or etorhinal cortex may be involved in such process.Testosterone is also discussed as a cognitive enhancer.(20) Several studies confirm the effect of testosterone on formation and loss of synaptic connections,cell growth,migration ,apoptosis or neurotransmitter metabolism modulating neuronal activity.Sex steroid affect myelination through their direct impact on glial cells,increase synapse number and dendritic branching.(22).

Amygdala processes fear, triggers aggression and stimulates competitiveness and can be influenced by hormones. It is larger in males compared to females .Male amygdala has testosterone receptors that heightens responses and provides a reason asto why males are more aggressive than females.(23)

The prefrontal cortex is the decision making executive centre of the brain.It oversees emotional information and puts a check on amygdala.The prefrontal cortex is bigger in women and matures faster in women.Women have less testosterone and more estrogen which flows through this part of the brain. It is proposed that this could be the reason why women look for solutions to conflict while males prefer confrontation. The anterior cingulated cortex is another part of the rational decision making centre of the brain which evaluates options ;this part is also larger in women.It has been labeled as the "worrywart" centre for women-anxiety is four times more common in women than men. Hippocampus is the centre for learning,memory and emotion. It is larger in females. It is also sensitive to estrogen and is a relay centre for processing memories into words. Women have 11% more neurons than men in the brain centres for language and hearing. Further ,since the connections between the two sides of the brain is better in women, they use language to talk about feelings and develop consensus more efficiently than men do.(23)

It has also been reported that posteromedial amygdala(MePD) is strongly associated with emotion,decision making,male sexual arousal and is strongly dependant on adult testosterone .Further,MePD volume is 1.5 times larger in males compared to females in experimental animal models.(24) During development the peak in human testosterone production occurs between 10^{th} and 18^{th} week of gestation.

During this period not only the brain ,but bone lengths are affected as evidenced by growth of phalanges and metaphyseal growth.In the metaphyseal tissues,steroids act via estrogen receptor α and β,as

testosterone is locally aromatized.the length of 4rth.digit (4D-ring finger) is thought to be an index of prenatal testosterone exposure relative to the length of 2nd. Digit (2D-index finger),which is thought to represent an index of prenatal estrogen exposure. In males 2D/4D is lower with a mean of 0.98 while that in females is 1.0(equal length of ring and index finger).This parameter is believed to be fixed in utero. It can be reliably measured at 2nd. Year of life and stable throughout life. Further, for men,there is a negative association between low 2D/4D and higher no. of children and sperm. Women display positive relation between higher 2D/4D and fertility.(20).

Dimorphism in immune response :

There is a difference in incidence of allergic episodes between males and females.The risk of allergy is greater among boys in childhood but from adolescence onwards it is the females who suffer more.an association of asthma and oral contraceptives and a risk for asthma exacerbations during pregnancy has been observed.Even persons on HRT present higher incidence of wheeze and hay fever.This could be due to estradiol-receptor dependant mast cell activation.(25).Estrogens have been shown to act as immunomodulators by suppressing T-lymphocyte effector function and enhancing Th2 function and consequent antibody production and delayed hypersensitive type reaction. Estrogens are natural enhancers of humoral immunity and support autoimmunity ,whereas androgens and progesterone(and glucocorticoids) physiologically function as immunosuppressants.(26) It has also been stated that estrogens support allergic reactivity in females by acting via the α receptor on mast cells which might explain peaking allergic reactions in females around menstruation and pregnancy.Women may also become hypersensitive to their own sex hormones as evidenced by reactivity to intradermal injection of estrogen and progesterone;this specific hypersensitivity is associated with recurrent miscarriages. (25) It has been stated that hepatic epithelial growth factor receptor which is over expressed in HCC is enhanced by Androgen Receptor(AR) activation.Estrogen receptor activation reduces inflammation in females and AR activity sustains infection and steatosis in men.(16).It has also been shown that human and female mice were more resistant than males to amoebic liver abscess due to increased early interferon γ production in response to infection.Androgen steroids have positive effect on growth and viability of E.Histolytica.(27)

II. Conclusion

Scientists dealing with evolutionary psychology state that humans descend from a mating system where males compete hard to become fathers while females work hard to raise and support the young. Testosterone drive makes males aggressive ,competitive and dominating in nature. Estrogens modulate the neuronal activity in such a way that female brains are programmed more for keeping social harmony. The identification of several transcription factors during sex differentiation in foetal life opens up the complexity of development of a normal phenotype. The interest in sexual dimorphism and its effects on metabolism is relatively recent .This research opens up to reveal disease susceptibility among the two sexes including allergic responses,information on this front could have great impact the planning of therapeutic aspects.

Conflict of interest-Nil

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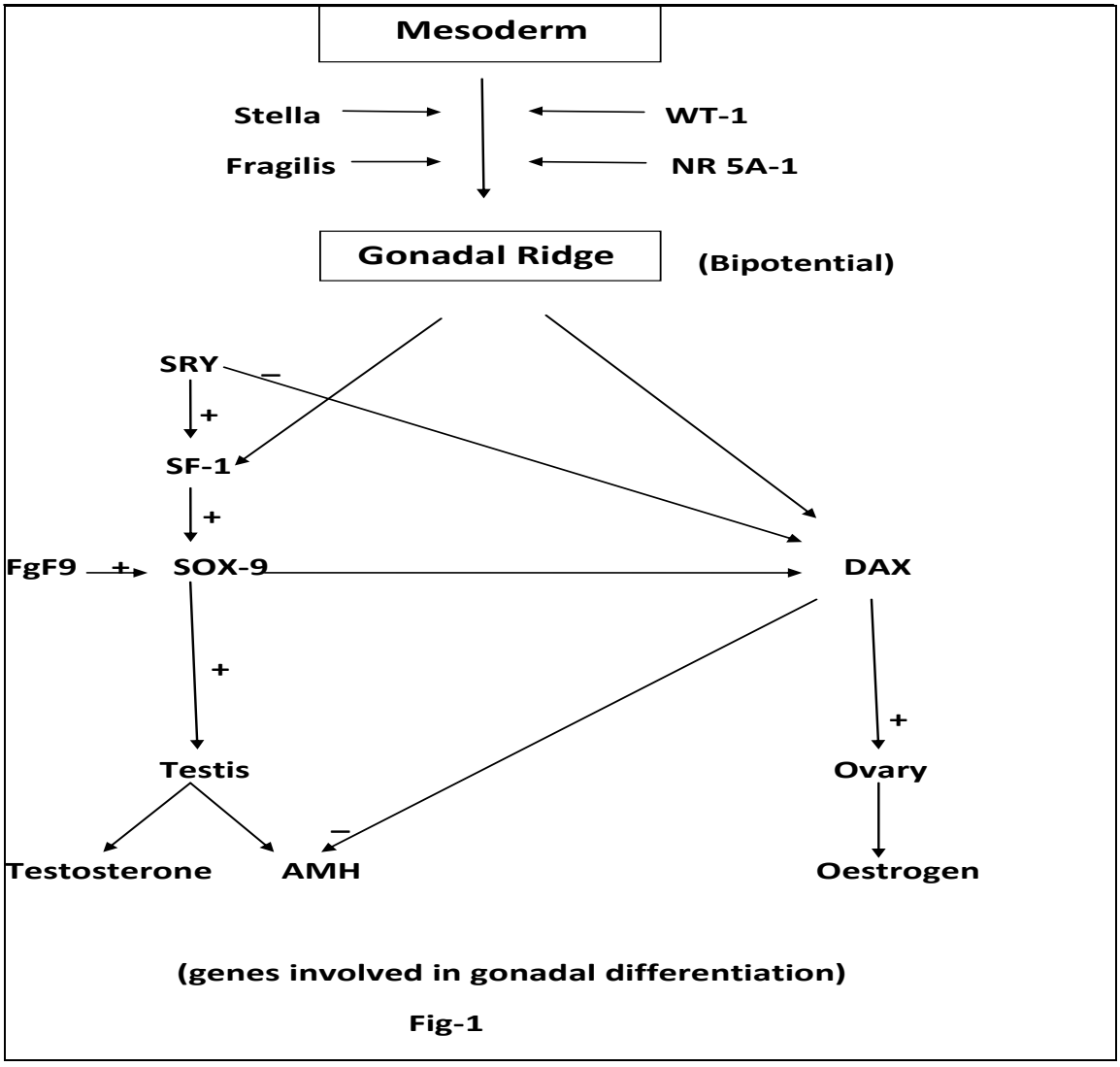

(genes involved in gonadal differentiation)

Fig-1