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Extended Abstract

The Genetics and Disorders of Sexual Development

Kulvinder Kaur

Dr. Kulvinder kaur centre for human reproduction, India

Email: kulvinder.dr@gmail.com

Abstract

Sex determination in mammals is different, as a single bipotential gonad can develop either into a testes or an ovary. If this genetic process which is largely complex gets disrupted during development of a human being it can lead to disorders of sex development. There are two separate processes by which sex development takes place namely i) sex determination whereby the bipotential gonad forms either a testes or ovaries and sex differentiation of internal and external genitalia along with extragonadal tissues like the brain. DSD's may occur due to different genetic lesion pathways. In this review we have concentrated in details of various genetic pathways causing DSD's and signal transduction pathways by which various manifestations of gonadal forms like gonadal dysgenesis to ovotestis and genital forms from mild hypospadias or clitoromegaly to ambiguous genitalia phenotype may result. Here we do not touch on sex differentiation of internal genitalia and external genitalia. Keywords: DSD's; Genetics; Signal Transduction System; Ambiguous Genitalia; Gonadal Dysgenesis; Ovotestis; SRY related high mobility group box (Sox) transcription factors have emerged in the animal kingdom to help cells maintain stemness, commit to a specific lineage, proliferate or die. Encoded by 20 genes in humans and mice they show a highly conserved high-mobility group boxdomain, which was originally identified in SRY, the sex determining region on the Y chromosome. This has derived from a high mobility group domain characterized of chromatin associated proteins. HMG (high mobility group) non histone chromosomal proteins include the AT hook, HMGN, and HMG domain families [1]. Members of the Sox SRY (Sex determining region on the Y chromosome) related HMG box family of chromatin remodelling factors play important development roles. SRY plays a key role in mammalian sex determination as determined by the fact that 15% of all XY sex reversal individuals carry mutations in SRY [2-5]. It is located on the end of short arm of Y chromosome and encodes a protein of 204 amino acids. It is not a typical eukaryotic transcript unit but a single exon-containing gene without any intron. It is not a conservative gene as well in mammals SRY is expressed 7 weeks post fertilization in humans with a specific role in the nucleus, activating/coordinating the expression of genes such as related proteins Sox9 which also results in differentiation of presertoli cells to produce a testis and suppress genes favouring formation of female gonads. In the case of XY sex reversal due to impaired action of SRY (Swyers syndrome), patients present with complete gonadal dysgenesis (CGD) or partial gonadal dysgenesis. The majority of sex reversal mutations in SRY results in impaired DNA binding/bending, but a number of which do not affect DNA binding map to one of SRY's two independently functioning nuclear localization signals [NLS], which flank the HMGbox domain of these C terminal β-NLS mediates nuclear import conventionally through the molecule importin β (Imp-β) courtesy by Wilhelm D. This facilitates transport through the nuclear pore complex(NPC) found embedded in nuclear envelope and release the nucleus on interaction with G protein monomeric binding proteins Ran activated G protein bound form. The 2nd N terminal NLS, Calmodulin (CaM)-NLSbinds the Ca2+ binding protein CaM Kaur, et al., showed a dual nuclear import and calmodulin dependent nuclear import importance in role of SRY in sex reversal after examining missense mutations in SRY CaM NLS from human XY sex reversal females. Patients with pure or Complete Gonadal Dysgenesis (CGD) also known as Swyer's Syndrome have a normal female phenotype, including uterus and fallopian tubes but they have streak gonads, mullerian structures due to insufficient AMH/MIS secretion and a complex absence of androgenisations. AMH/MIS is low and testosterone (T) response to human chorionic gonadotropin (HCG) stimulation is impaired. These patients are free of turners like malformations and attain normal height. Patients with partial gonadal dysgenesis (PGDordysgenetic gonads) may provide enough MIS to regress the uterus and sometimes sufficient for partial androgenisation. GD can result from mutations or deletions of testis promoting genes WT1 (wilms tumor-related gene), SF1 (steroidogenic factor 1), SR1, SOX9 (SRY related HMG box gene 9), DHH (desert hedgehog), ATRX (α-thallasemia, mental retardation on the X), ARX (Aristaless related homeobox, X linked), DMRT (double sex and mab3 related transcription factor 1). Also duplication of chromosomal loci containing antitestis genes e.g. WNT4 (wingless type mouse mammalian tumor virus integration site 4), RSPO1(R- spondin 1), DAX 1 also called NROB1 account for ~1% of the resolved cases (dosage sensitive sex reversal adrenal hypoplasia acute regulatory protein) as reviewed by Wilhelm D and Mendonca BB. Among these deletions or mutations of SF1 (NR5A1) appear

to be the most common but still collectively account for ~1% of the resolved case (dosage sensitive sex reversal adrenal hypoplasia acute regulatory protein) as reviewed by Wilhelm D and Mendonca BB. Among these deletions or mutations of SF1 (NR5A1) appear to be the most common but still collectively account for cartilage abnormalities (Campomelic dysplasia-a familial dwarf) are the predominant clinical feautures of SOX 9 mutations. Similarly recently 46XY DSD with CGD and chondrodysplasia has been found with a homozygous mutation (G287V) within coding sequence of O-acetyl transferase HHAT gene. HHAT gene codes for attachment of palmitolyl residues that are critical for multimerization and long term signaling of hedgehog secreted proteins. Similarly recently 46XY DSD with CGD and chondrodysplasia has been found with a homozygous mutation (G287V) within coding sequenceof O-acetyl transferase HHAT gene. HHAT gene codes for attachment of palmitolyl residues that are critical for multimerization and long term signaling of hedgehog secreted proteins. A family history of DSD or premature ovarianin sufficiency is important. Intra-abdominal dysgenetic testis should be removed or prevent malignancy and oestrogens can be used to induce secondary sex reversal in 46XY individuals raised as females with absent (vanishing testes syndrome-(bilateral anorchia)- reflect regression of the test is during development. The etiology is unknown but the absence of mullerian structures indicates adequate secretion of AMH in utero and in most case and rogenisation of the external genitalia is either normal or slightly impaired e.g. small penis, hypospadias). These individuals can be of feredprosthesis and should receive androgen replacement in adolescence. Role of noncoding RNA'S in male differentiation In mammalians SRY is expressed for a short period in presertoli cells, which in this small time organizes for all other cell types where key roles for SRY in up regulation of Sox 9 which encodes a transcription factor belonging to the same SRY like HMG domain family.