Abstract

The important role of genetic abnormalities is the causation of human infertility increasingly recognized. In this fast moving field much remains to be learned as considerable progress has been achieved over the past years both in clinical delineation of genetic forms of infertility and in the characterization of the responsible genes and their mutation. In reproductive medicine the application of molecular analysis (modern DNA technology) has already yielded a rich harvest. A considerable number of genes are known that have an essential function in human reproduction system with an eye on clinical relevance we review here the mutation analysis of certain genes SRY and WT1 which plays important role in sex determination pathway. Various genetic causes of infertility are also reviewed. In the present study conducted for the muational analysis of SRY and WT1 gene in infertile patients and correlating the mutation with the clinicopathological conditions of infertile patients. Nevertheless, specific genotypes and karyptypes have been associated with infertility phenotypes and studies of specific genes in humans shed light to the nature of the polygenic and multifactorial basis of infertility.

Here we described four muatations in SRY and WT1 gene in three infertile patients. Patient 1 with pure gonadal dysgenesis showed mutation in both genes which are required for the sex determination i.e., SRY and WT1 gene. This is the first time that we are reporting both gene muatation in one gonadal dysgenesis (46,XY) female patient (Case no 26,Table 9). The presence of SRY mutations observed in the present study reinforces previous literature data which suggests that SRY mutations in pure gonadal dysgenesis more frequent. Different WT1 muatation result in different phenotypes namely wilms tumor or DDS or pseudohermaphroditism. The majority of these mautations described are recessive nonsense or frameshift mutation. This patient showed frame shift mutation in WT1 gene in 46,XY female. We detected frameshift muatation at codon 389 glutamine altered to histidine by the insertion of ‘T’ nucleotide, the polarity of amino acid is changed due to insertion of ‘T’ as Glutamine neutral polar amino acid is changed to basic polar amino acid histidine(CAG(CAT). The significance of this gene mutation is it produces the truncated protein at ‘C’ terminus at codon 407 lacking 47 amino residues and it affects the third zinc finger domain (amino acids 384-405) and alternative splice site of exon 9 encoding 3 amino acids(KTS). Same patient showed SRY

gene point mutation at C terminal region at codon 149 by the substitution of C(G resulting in the amino acid proline (CCC(CCG ,Fig 23). This is a silent point mutation so it may not alter the SRY protein and does not have any impact in the phenotype. This mutation signifies the importance of muatiion in the open reading frame of SRY gene. Till date only 12 mutations are reported in the open reading frame of SRY gene. Gonadoblastoma is also observed which may be due to the presence of Y chromosome material in the genotype. It should be favourable to analyse for the gonadoblastoma in gonadal dysgenesis patients. No WT1 gene mutation were detected in other patients included in this study. The SRY gene mutation detected in two patients in one 45,X/46,XX female(Case no 05,Table 9) frame shift mutation at codon 128 lysine altered to aspergine with in the HMG box of SRY gene. The insertion 'C' nucleotide results in a truncated protein at 'C' terminus (final 25 amino acids) lacking the last 23 residues (AAG(AAC, Fig 24). This truncated protein cannot be verified invivo as their embryonic expression may be time and tissue specific. However this mutation affects the DNA bending and binding property and therefore may be responsible for the phenotype. The another missense mutation identified in the present study were in 46,XX male(Case no 02,Table 12). This missense mutation is due to the substitution of C(G at codon 109 phenylalanine (neutral non polar) amino acid altered to leucine (neutral non polar) amino acid,(TTC(TTG, Fig 25) with in the HMG box. Thus the two mutation of SRY gene further strengthen functional significance of HMG box. Thus the mutation observed in the present study reveals the importance of different point mutation (silent, frame shift, missense) in the SRY gene in gonadal dysgenesis patients. It also signifies the functional importance of HMG box of SRY gene and this also described that SRY act as a determining factor. The another observation is that WT1 activates the SRY gene in sex determination pathway and hence SRY is the direct target gene of WT1 gene in sex determination pathway and mutations in SRY and WT1 gene may be responsible for the pure gonadal dysgenesis.