Genetic Mechanisms of Sex Development and New Approaches

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Sexual development is an extremely complex process. The disruptions in this process can evince as disorders of sex development (DSDs). DSDs are defined as "congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical and contain a wide phenotypic spectrum such as mild hypospadias, ambiguous genitalia, gonadal dysgenesis and sex reversal. Male or female development is genetically determined. Sex determination occurs as the bipotential gonad becomes either a testis or an ovary. Sexual differentiation together with the development of the gonad is maintained. Both internal and external genital organs are formed. These processes are influenced by the action of genes that were found by studies of DSDs patients. The molecular mechanisms underlying sex development have been clarified with amazing advances in genetic technologies. However, a specific molecular diagnosis is made in only 20% of patients. Today, this situation is likely to change with the development of genomic technologies. Studies of multigenic diagnostic screening and genome wide approaches such as array-comparative genomic hybridization and next-generation sequencing can be applied in the diagnosis of patients with DSDs. Herewith, more patients with DSDs will receive a definitive genetic diagnosis and prognostic prediction and long-term management will improve. This presentation will cover genetic mechanisms of sex development and current approaches in detail.

Key words: Sexual development, sex determination, disorders of sex development, genetic diagnosis, genetic technologies

Difficulties in the Clinical Approach to Disorders of Sexual Development: Role of the Genes in the Approach

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Sexual differentiation is a complex process which is completed during the first trimester of intrauterine life. Three biological parameters are crucial to precisely delineate the sex of an individual: Chromosomal constitution (XX or XY), undifferentiated structures (reproductive organs and genital bridge) and gonadal histology. Sex determining genes organize this differentiation and each of these parameters can be disrupted in disorders of sexual development (DSD) defined as congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. DSD are complex and often a confusing medical problem. Lots of gene mutations are characterized by a range of heterogenic phenotypes in individuals (ex: *SF1* gene mutations). In most of the disorders, there is a wide range of presenting phenotypes. Not all genes are functional during sexual development. Additionally, the time of expression is different for genes and the same genes are not expressed in the same way in different cells. After differentiation, extracellular factors such as hormones or growth factors can modify gene expression. Interpretation of the gonadal function depends on the age of the patient and the methodology of the tests. It is obviously quite different when it comes to dealing with a neonate compared to an older child or an adolescent as the presenting symptoms are variable according to age. Furthermore, normal gonadal function could deteriorate gradually. Sometimes, genotype-phenotype differences can be observed. In some cases, the same mutation causes a clinically different phenotype in different individuals and diagnostic problems can arise. Because many patients are compound heterozygotes for two or more different mutant CYP21A2 alleles, a wide spectrum of phenotypes may be observed. It is well known that compound heterozygosis with a severe and a mild mutation is associated with mild clinic [ex: Val281 compound heterozygote; non-classic congenital adrenal hyperplasia (Non-CAH)]. Severe homozygous mutation can occur in rare cases where it causes mild clinic and this may lead to diagnostic difficulties (ex: intron2 homozygous non-CAH). In such cases, laboratory technical issues or mutant gene duplicated in a single allele should be considered. Advances in genetics have made their diagnosis easier and most importantly, quite rapid. Although progress in management strategies has been observed, they remained controversial. Easily accessible and inexpensive genetic analyses have become beneficial in solving the problems in this regard.

Key words: Sexual differentiation, disorders of sex development, sex, gonad, genetic analysis