

Exploring novel causes contributing to Differences of Sex Development

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In human sex development, two main processes can be distinguished, sex determination and sex differentiation. Sex determination refers to the developmental processes by which the bipotential gonads develop as either testes or ovaries. The second process known as sex differentiation occurs once the sex determination choice has been made through factors of gonadal origin that decide the development of the phenotypic sex. As will be reflected in this thesis, the majority of knowledge we have about the factors involved in sexual development are derived from studies in animal models and studies of cases in whom the genetic or the gonadal sex does not correspond to the phenotypical sex, that is, patients affected by differences of sex development (DSD; also known as disorders of sex development). DSD are defined as a heterogeneous group of rare conditions that encompass a wide range of phenotypic manifestations and account for 7.5 % of all congenital disorders. The most common of these defects, hypospadias, represent an average of 1 in every 250-350 male births. While ambiguous genitalia occur in approximately 1 out of every 4500 babies worldwide.

Rare diseases as a whole imply an enormous economic impact to society. The reason for this is that affected persons present unique challenges for primary care, as they often do not find adequate diagnosis and managed care, thereby inducing big negative impact on them. Besides, DSD constitutes a very special group of rare conditions, because on the one hand, they are mostly not life threatening, nor should they constitute an obvious physical inhibition in most daily activities. However, the sensitive nature of the condition and affected organs, the decision-making of sex/gender assignment, as well as the discussion on multiple surgical interventions and the lack of individualized hormonal therapy are great challenges to health care providers and have a major impact on the quality of life of those affected and their families. In addition, the social context of raising a child and living with DSD has all too often been misunderstood and ignored.

Generally speaking, sex determination seems to be governed by major genetic factors such as transcriptional regulators, whereas factors controlling sex differentiation include secreted hormones and their receptors. This doctoral dissertation discusses both the molecular genetic mechanisms triggering disease and the endocrine factors orchestrating masculinization of the human fetus with the view to a better understanding of the nature of the sexual development biological process in humans.

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