Journal of Pediatric Urology (2015) 11, 12–19

Review article

# Environmental, parental and gestational factors that influence the occurrence of hypospadias in male patients

Giacinto Marrocco [a], Paola Grammatico [b], Santiago Vallasciani [c], Caterina Gulia [d], Andrea Zangari [a], Francesca Marrocco [e], Zhoobin Heidari Bateni [f], Alessandro Porrello [g], Roberto Piergentili [h]

[a]UOC Division of Pediatric Surgery and Urology, Hospital San Camillo - Forlanini, Rome

[b]UOC Laboratory of Medical Genetics, San Camillo - Forlanini, Rome, Italy

[c]UOSD of Pediatric Urology, IRCCS Ca' Granda Hospital, Milan, Italy

[d]Department of Gynecology - Obstetrics and Urological Sciences, Policlinico Umberto I, Sapienza - University of Rome, Italy

[e]University Biomedical Campus, Rome, Italy

[f]Division of Urology, Sick Kids Hospital, Toronto, Ontario, Canada

[g]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

[h]Institute of Molecular Biology and Pathology, CNR, Department of Biology and Biotechnology, Sapienza - University of Rome, Italy

Correspondence to: R. Piergentili, Tel.: +39 0649912873; fax: +39 064456866

roberto.piergentili@uniroma1.it (R. Piergentili)

**Keywords**
Disorders of sex development; Gene–environment interaction; Genetic polymorphisms

Received 27 April 2014
Accepted 29 October 2014
Available online 3 February 2015

## Summary

### Objective
Hypospadias is a congenital defect, which affects normal development of the male urogenital external tract. In this malformation, the urethral orifice of the penis is positioned ventrally, thus interfering with normal urination and creating, in some adults, problems during sexual intercourse. Heritability of hypospadias has been shown in some reports, and the abnormality has been associated with the presence of mutations in one of the genes involved in urogenital development. However, even for patients who were born in families with a higher incidence rate of this defect, no evident genetic alteration could be identified in known genes, indicating that the list of loci involved is still incomplete. To further complicate matters, recent reports also underline that epigenetic changes, without any identifiable gene sequence mutation, may be involved in gene function impairment. Therefore, the inheritance of most hypospadias cases is not evident, suggesting that the genetic background is not the only cause of this malformation; indeed, the majority of hypospadias cases are classified as sporadic and idiopathic.

### Materials and methods
Evidence has accumulated highlighting the role of the environment and of its relationships with the genome in the etiology of this abnormality. In particular, the interaction between some chemicals, which are able to mimic endogenous molecules such as sexual hormones — for this reason called endocrine disrupting compounds (EDC) — and specific receptors has been extensively investigated during the pregnancy. Additionally, several articles have shown that parental and gestational factors play a significant role too. Indeed, physiological alterations, such as body weight of the mother and/or of the newborn, mother's diabetes, impaired father fertility, and exposure of one parent to job-related pollutants, show in many cases a direct correlation with hypospadias incidence. The overall prevalence of this condition has been studied in many countries, suggesting that at least in some periods and/or in specific populations there are detectable fluctuations, probably mirroring the different natural environments. However, many articles present data that do not agree with these findings and, consequently, most causes of hypospadias are still highly debated.

### Results
In this review, we summarize the developmental steps involved in urogenital tract formation, with a particular emphasis on the genes that most frequently are associated with this condition, or that are subject to environmental stress, or that may be the targets of hormone-like, exogenous molecules. Then, we make an overview of the identified factors able to impair the function of important genes, even in the absence of their mutations, including those for which contradictory reports have been published. Finally, we propose an explanation of sporadic cases of hypospadias that reconciles these contradictions and suggest some steps for moving forward in the research focused on this condition.

### Conclusion
We hypothesize that most patients develop hypospadias because of gene–environment interactions acting on polymorphic genes that, in the absence of environmental stimuli, would otherwise cause no developmental anomaly during urogenital development.

http://dx.doi.org/10.1016/j.jpurol.2014.10.003

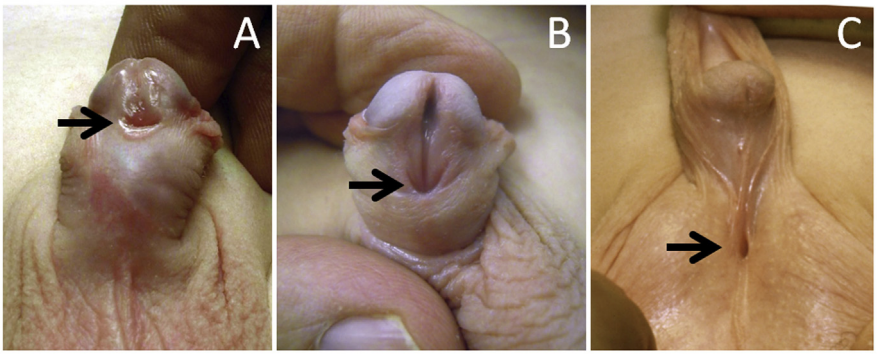


**Figure** Three cases of boys affected by hypospadias; the arrows indicate the position of the urethral meatus in the distal (A), midshaft (B) and proximal (C) positions.

## Introduction

Hypospadias is a relatively common malformation, typically affecting 1 in 300 live male births [1], of the male external urinary tract, which is characterized by defective development of the penile ventral surface. It is defined as a 'hypoplasia of the tissues forming the ventral aspect of the penis beyond the division of the corpus spongiosum' [1]. The morphological characteristics of this condition in hypospadiac children are: (i) a ventral opening of the urethral meatus, (ii) a ventral downward curvature of the penis (also called chordee) and (iii) a ventrally deficient, hooded foreskin [1]. Notably, these three features are not always present at the same time [1]. The urethral meatus may be located in several different positions between the glans and the perineum, thus allowing the classification of hypospadias as distal, medial and proximal. A further classification is derived by intermediate positions of the meatus, as illustrated (Fig. 1) [2].

The clinical significance of hypospadias is related to psychological, aesthetical and functional aspects: the abnormal position of the meatus interferes with the normal flux of urine, and the possible presence of a shaft curvature in adults may cause painful erections and difficult penetration during sexual intercourse, caused by chordee and penile hypoplasia, especially in proximal forms [3]. Distal hypospadias impacts patients' lives to a significantly lesser extent.

The etiology of hypospadias is currently an issue in most situations. In a few selected cases of families with a higher incidence rate it is possible to establish a genetic origin of this condition, and several reports are available that this is a multifactorial, non-Mendelian defect [2]. Some cases of hypospadias are associated with syndromes, such as the Smith—Lemli—Opitz syndrome (a defect in cholesterol synthesis that involves mutations of the *DHCR7* gene), Robinow syndrome (that depends on *ROR2*, a gene coding for a tyrosine-protein kinase transmembrane receptor), Klinefelter syndrome (involving the *SRY* gene and affecting males with an XXY karyotype, even in the form of mosaics), Denys-Drash and Frasier syndromes (both characterized by *WT1* mutations) or other complex conditions, such as disorders of sex development (DSD) [1,2]. In many of these cases it was possible to identify some of the genes involved, and consequently to link those genes also to the impairment of urogenital development and its molecular mechanisms. However, the causes of hypospadias remain mostly unknown, as it is estimated that more than 90% of cases are idiopathic [4]. Indeed, there is growing evidence to suggest that non-genetic factors might be evoked to explain at least some of the reported clinical cases.

In this review we focus on the factors that can alter the normal development of the external genitourinary tract even in the absence of specific DNA anomalies and highlight the target genes/proteins whose function is impaired.

## Development of the normal external genitourinary tract in male children

There are three main molecular pathways for male external genitalia formation: (i) androgen-independent, (ii) androgen-dependent and (iii) dependent on endocrine and environmental factors [4]. The last point may involve the first two, and it also has genetic and epigenetic ground.

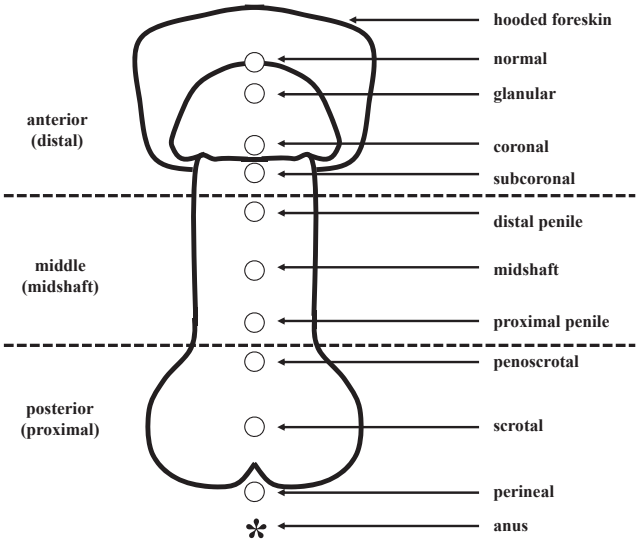


**Figure 1** Classification of hypospadias based on the approximate (left side) and precise (right side) localization of the urethral meatus.