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Review of genetic and environmental factors leading to hypospadias

Erin M. Shih [a,*], John M. Graham Jr. [b]

[a] Center for Endocrinology, Diabetes, and Metabolism, Children's Hospital Los Angeles, 4650 Sunset Blvd, #61, Los Angeles, CA 90027, USA
[b] Medical Genetics Institute, Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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ABSTRACT

Hypospadias is one of the most common congenital malformations, affecting about 4–6 males per 1000 male births, and ranging in severity from a urethral meatus that is slightly off-center to a meatus in the perineal area. Over the past three decades its prevalence may have increased due to changes in reporting of mild cases and/or increased survival of low birth weight infants due to improved neonatal care. However, despite the increasing numbers of males with hypospadias, the overall etiology remains unclear and likely multifactorial in nature. The purpose of this review article is to provide a comprehensive overview of the various factors implicated in hypospadias etiology, including genetic and environmental factors. In addition, we list syndromes in which hypospadias is a relatively common association and delineate the areas that require further investigation in an effort to understand this condition.

1. Introduction

Hypospadias is defined by the *Elements of Morphology* as a ventrally-placed urethral opening [Hennekam et al., 2013] and is one of the most common congenital malformations, affecting 1 in 200–300 male newborns (if mild forms are included) [Paulozzi et al., 1997]. Some data suggest that the incidence of hypospadias may have increased over the past three decades, which may be related to increased genetic susceptibility, environmental exposure, increased survival of low birth weight infants, and changes in reporting [Aho et al., 2000; Paulozzi et al., 1997]. Hypospadias involves the incomplete development of the penis between 8 and 14 weeks gestational age, resulting in an abnormally placed urethral opening on the ventral side of the penis [Holmes, 2012; Manson and Carr, 2003]. Various terminologies exist in the literature for hypospadias classification [Brouwers et al., 2010; Hennekam et al., 2013; Holmes, 2012; van der Zanden et al., 2012] (Fig. 1). Anterior hypospadias, which is also known as distal or 1st-degree hypospadias, can be divided into hypospadias *sine* (ventral curvature of the penis with a normally-placed urethral meatus, often omitted from research or not considered to be a true form of hypospadias), glandular (mildest form involving extension of the urethral meatus down to the ventral part of the glans), and sub-coronal (urethral meatus next to the coronal sulcus). Middle hypospadias, which is also known as 2nd-degree hypospadias, can be divided into distal penile, mid-shaft, and proximal penile types, all of which involve the midline placement of the urethral meatus in various positions on the ventral surface of the penile shaft. Posterior hypospadias, also known as proximal or 3rd-degree hypospadias, can be divided into penoscrotal (urethral meatus located where the base of the penis and the scrotum meet), scrotal (urethral meatus located in the scrotum), and perineal (urethral meatus positioned below the scrotum and on the perineum) [Holmes, 2012]. Approximately 70% of cases are considered 1st degree (distal), and the remaining 30% are considered 2nd or 3rd degree with the urethral meatus located in the penoscrotal or perineal area. Hypospadias can occur in isolation or can be accompanied by additional abnormalities, most commonly other genitourinary abnormalities including cryptorchidism, bifid scrotum, vesicoureteral reflux, and inguinal hernia [Holmes, 2012]. In addition, hypospadias can be associated with various syndromes as described below.

Some cases of hypospadias can be attributed to underlying genetic causes or syndromes (<10%), but most are idiopathic [Carmichael et al., 2012]. In addition, many of these cases are associated with intrauterine growth restriction (IUGR) and being small for gestational age (SGA). The purpose of this article is to provide a comprehensive review of the multifactorial etiologies of hypospadias, with a focus on various genetic and environmental contributors that may be interacting to cause this disorder.

* Corresponding author. Tel.: +1 323 361 8705; fax: +1 323 361 1350.
E-mail addresses: eshih@chla.usc.edu, erinshih7@gmail.com (E.M. Shih).

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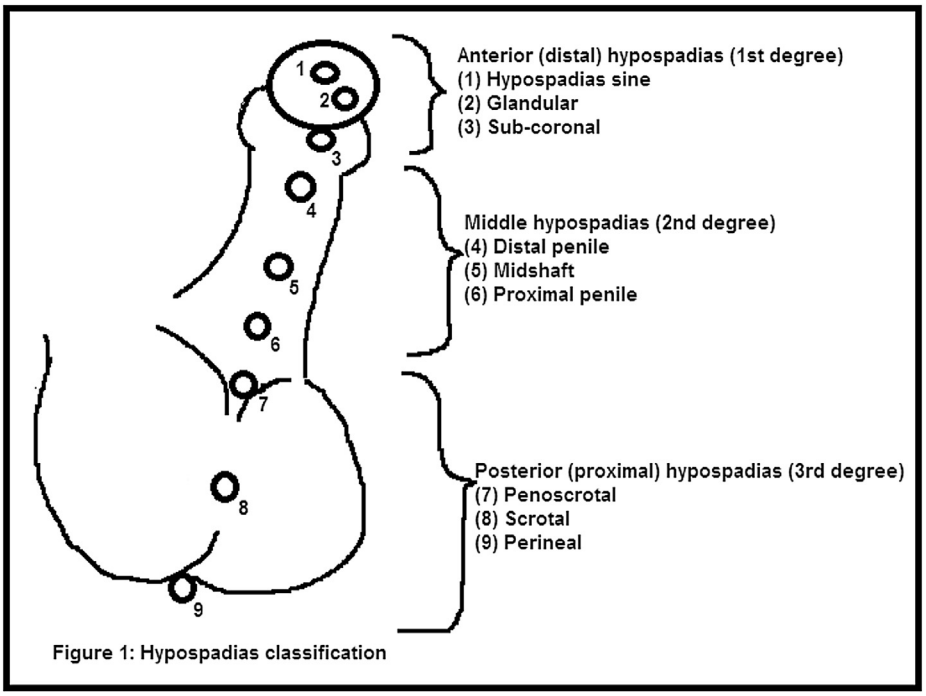

Fig. 1. Hypospadias classification. Hypospadias can be divided by location into Anterior (aka distal or 1st degree), Middle (aka 2nd degree), and Posterior (aka proximal or 3rd degree) hypospadias. Anterior hypospadias is further subdivided into hypospadias sine, glandular, and sub-coronal subtypes. Middle hypospadias is further subdivided into distal penile, midshaft, and proximal penile subtypes. Posterior hypospadias is further subdivided into penoscrotal, scrotal, and perineal subtypes.

2. Genetic etiologies

2.1. Familial occurrence

Many studies have demonstrated that hypospadias is a highly heritable condition, with overall heritability estimated to be 57–77% [Schnack et al., 2008; Stoll et al., 1990]. Data have shown that hypospadias is equally transmitted through both the maternal and paternal sides [Schnack et al., 2008], with 7% of patients affected with hypospadias noted to have 1st-, 2nd-, or 3rd-degree relatives affected as well [Fredell et al., 2002]. Specifically, the brother of an affected male with hypospadias has a 9–17% risk of also having hypospadias [Schnack et al., 2008; Stoll et al., 1990]. Interestingly, some studies have shown anterior (or distal/1st-degree) and middle (or 2nd-degree) hypospadias to occur more frequently in familial cases in comparison to posterior (or proximal/3rd-degree) hypospadias [Brouwers et al., 2010; Fredell et al., 2002]. Brouwers et al. [2010] noted that less severe types of hypospadias were associated with familial occurrence (OR 10.4; CI 4.5–24.1), while low birth weight (a proxy for placental dysfunction) was more closely associated with proximal cases (OR 9.1; CI 3.4–24.4) [Brouwers et al., 2010].

2.2. Gene mutations

The androgen receptor (*AR*) gene plays an important role in penile and urethral development and rarely *AR* gene mutations have been found to be associated with hypospadias [Allera et al., 1995; Hiort et al., 1994; Nordenskjold et al., 1999; Sutherland et al., 1996; Thai et al., 2005; Wang et al., 2004]. Partial androgen insensitivity syndrome, which is due to various *AR* gene mutations, varies in presentation, but typically involves perineoscrotal hypospadias and micropenis with normally functioning testes [Deeb et al., 2005]. In addition, abnormal expansion of AR trinucleotide repeats, such as CAG [(CAG)nCAA and a glycine repeat] and GGN [(GGT)3(GGG)(GGT)2(GGC)n)] repeats, have also been found in cases with hypospadias, although the association between increased CAG repeats with hypospadias has not been replicated in three subsequent studies [Aschim et al., 2004; Chamberlain et al., 1994; Lim et al., 2000; Muroya et al., 2001; Radpour et al., 2007]. Other aspects of the AR, such as the dihydrotestosterone (DHT) binding capacity as well as various proteins integral in AR function, have also been investigated as a possible link to hypospadias development, but thus far studies have not consistently shown significant differences between hypospadias patients and controls [Allera et al., 1995; Beleza-Meireles et al., 2007a; Bentvelsen et al., 1995; Gearhart et al., 1988; Schweikert et al., 1989; Terakawa et al., 1990].

Steroid 5-α reductase type 2 (SRD 5A2) is an enzyme that converts testosterone to DHT and plays a role in the formation of male external genitalia [van der Zanden et al., 2012]. SRD 5A2 is specifically expressed around the ventral part of the remodeling urethra during male genitourinary development. Pseudovaginal perineoscrotal hypospadias, due to a *SRD 5A2* gene mutation, is an autosomal recessive condition that includes hypospadias, a bifid scrotum, and a blind vaginal pouch in a 46,XY individual, and during puberty results in the development of a male body habitus with phallic enlargement and semen production [Holmes, 2012].

The sex-determining region Y (*SRY*) gene is located on the Y chromosome and initiates male sexual differentiation by activating male-specific transcription factors, thus ultimately leading to testicular differentiation [van der Zanden et al., 2012]. However, research in this area has failed to show an association between hypospadias and *SRY* gene mutations [Wang et al., 2004] or Y-chromosomal microdeletions [Castro et al., 2004; Tateno et al., 2000].

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