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REVIEW ARTICLE

Genetic pathway of external genitalia formation and molecular etiology of hypospadias

Yoshiyuki Kojima, Kenjiro Kohri, Yutaro Hayashi*

Department of Nephro-urology, Nagoya City University Graduate School of Medical Sciences, 1, Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

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Abstract Hypospadias is one of the most common congenital disorders in males. Impaired fetal androgen action interferes with masculinization, including external genitalia formation, and can result in this anomaly; however, the molecular etiology remains unknown. Recent molecular approaches, including gene-targeting approaches in mice and single nucleotide polymorphisms analyses in humans, might provide an opportunity to identify the causative and risk factors of this anomaly. Several genes, such as *sonic hedgehog*, *fibroblast growth factors*, *bone morphogenetic proteins*, *homeobox* genes, and the *Wnt family* regulate external genitalia formation. *Mastermind-like domain containing 1/chromosome X open reading frame 6* mutation and *activating transcription factor 3* variants have been shown to be associated with the incidence of isolated hypospadias. In addition, this anomaly may be associated with a specific haplotype of the gene for estrogen receptor alpha, which mediates the estrogenic effects of environmental endocrine disruptors, and the effects of these disruptors on external genitalia formation might depend on individual genetic susceptibility. These molecular studies will refine our knowledge of the genetic mechanism involved in external genitalia formation, and lead to new strategies for the clinical management of hypospadias.

Introduction

Hypospadias, which results from abnormal penile and urethral development, is the second most common congenital malformation in males, occurring in approximately one in 125 live male births [1]. Despite the spectacular surgical successes gained, we are no further along in understanding the etiology of hypospadias. Androgens from the testes are key hormones to complete external genitalia formation; therefore, impaired fetal androgen action can result in this anomaly; however, how impaired androgen action produces 'isolated' hypospadias lacks a convincing explanation.

* Corresponding author. Tel.: +81 52 853 8266; fax: +81 52 852 3179.
E-mail address: yutaro@med.nagoya-cu.ac.jp (Y. Hayashi).

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Recent remarkable advances in molecular approaches have provided new knowledge on the molecular genetics of external genitalia formation and have contributed to finding causative and risk factors for hypospadias. The purpose of this review is to summarize recent insight into the genetic pathway of external genitalia formation from animal models, including gene-targeting approaches, and to discuss the molecular etiology of patients with isolated hypospadias. Information for this review was obtained from searches of the PubMed database for the period January 1970 to May 2009, the ISI Web of Knowledge and the authors' files. Search terms included 'external genitalia', 'hypospadias', 'molecular etiology', 'knockout mouse' and 'polymorphism'. Additionally, reference lists from the retrieved articles were examined to identify and select appropriate articles according to a review of the original abstracts.

External genitalia formation and hypospadias

Anatomical anomalies in hypospadias are an abnormal ventral opening of the urethral meatus, abnormal ventral curvature of the penis and abnormal distribution of the foreskin around the glans with a ventrally deficient hooded foreskin [2]. Some cases are associated with chromosomal abnormalities and disorders of sex development (DSD) [3–5]. Additionally, *MID1* is a candidate gene in Opitz G/BBB syndrome, which is characterized by midline abnormalities such as hypertelorism, cleft palate, and hypospadias [6]. However, most hypospadias cases show spontaneous occurrence and have no obvious cause, because the genetic pathways governing external genitalia formation are poorly understood.

The development of external genitalia occurs in two phases, an early hormone-independent phase and a late hormone-dependent sexual differentiation phase. In the early hormone-independent phase (5–8 weeks), the external genitalia of the male and female fetus are indistinguishable. The embryonic anlage of external genitalia, the genital tubercle (GT), which consists of lateral plate mesoderm, surface ectoderm, and endodermal urethral epithelium derived from the urogenital sinus, is morphologically identical in both sexes. In the late hormone-dependent sexual differentiation phase (8–20 weeks), male external genitalia are becoming visible as a male structure as a result of testosterone secretion by the fetal testis. The GT elongates into a phallus and its tip rounds into the glans, and finally this phallus becomes the penis. In addition, the edges of the urethral folds begin to fuse progressively from posterior to anterior, forming the urethra. The variety of anatomic locations of the urethral meatus in boys with hypospadias may be due to the disturbance of several steps in external genitalia formation in the late hormone-dependent sexual differentiation phase (Fig. 1).

Molecular and genetic regulation of external genitalia formation and causative factors of hypospadias

The genetic variants of human isolated hypospadias are summarized in Table 1.

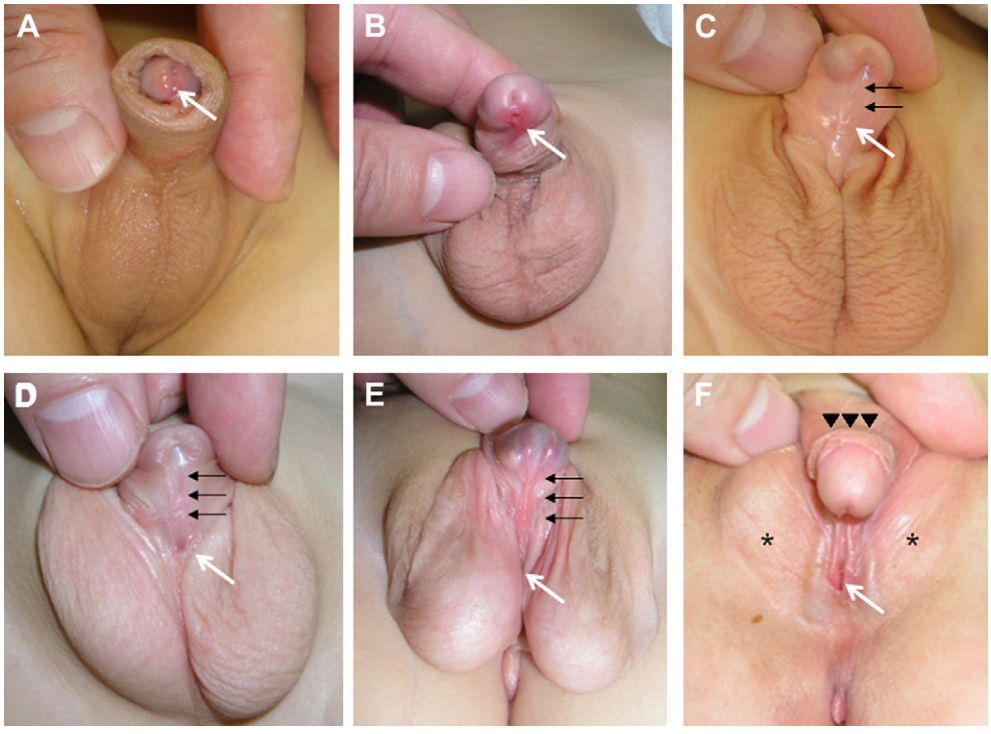

Figure 1 Normal external genitalia (A) and classification of hypospadias based on the location of the urethral meatus (B–F) in boys. (A) Normal male external genitalia. (B) Glanular type. (C) Penile type. (D) Penoscrotal type. (E) Scrotal type. (F) Perineal type with bifid scrotum (*). White arrow, urethral meatus; black arrow, urethral plate; arrowhead, hooded foreskin.