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REGULAR ARTICLE

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Expression of the androgen receptor and 5α-reductase type 2 in the developing human fetal penis and urethra

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Abstract Normal penile development is dependent on testosterone, its conversion via steroid 5α-reductase type 2 to dihydrotestosterone, and a functional androgen receptor (AR). The goal of this study was to investigate the distribution of AR and 5α-reductase type 2 in the developing human fetal external genitalia with special emphasis on urethra formation. Twenty fetal genital specimens from normal human males (12–20 weeks gestation) were sectioned serially and stained by avidin-biotinylated peroxidase complex method with antigen retrieval. Stained sections throughout male genital development documented the expression of AR and 5α-reductase type 2 in the phallus. Between 12 and 14 weeks of gestation, AR was localized to epithelial cells of the urethral plate in the glans, the tubular urethra of the penile shaft, and stromal tissue surrounding the urethral epithelium. In the fetal penis between 16 and 20 weeks gestation, the density of AR expression was greatest in urethral epithelial cells versus the surrounding stromal tissues. There was a characteristic pattern of AR expression in the glandular urethral epithelium between 16 and 20 weeks gestation. AR expression was greater along the ventral aspect of the glandular urethra than along the dorsal aspect of the urethral epithelium. The expression of 5α-reductase type 2 was localized to the stroma surrounding the urethra, especially along the urethral seam area in the ventral portion of the remodeling urethra. These anatomical studies support the hypothesis that androgens are essential for the formation of the ventral portion of the urethra and that abnormalities in either the AR or 5α-reductase type 2 can explain the occurrence of hypospadias.

Keywords Urethra · Penis · Fetal development · Androgen receptor · Hypospadias · 5α-Reductase type 2 · Human

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Introduction

Androgens are crucial for the induction, growth and differentiation of the genital tubercle into the external male genitalia (Rey and Picard 1998). They act through binding and activation of the androgen receptor (AR), a ligand-dependent transcription factor that belongs to the superfamily of the steroid nuclear receptor (Brinkmann et al. 1999). Dihydrotestosterone synthesized by 5α-reductase type 2, an enzyme encoded by gene SRD5A2 on chromosome 2, is more potent than testosterone and is required for normal development of human and rat male external genitalia.

Abnormalities in the synthesis and metabolism of androgens and in the AR can result in abnormal phenotypic sexual genital development. For example, many studies document genetic alterations in the AR leading to the clinical disease, androgen insensitivity syndrome (Wiener et al. 1997). Furthermore, mutations that disrupt androgen synthesis, including those in 5α-reductase type 2, result in genital malformations such as hypospadias (Griffin 1992). Among the latter are a subset of patients with severe hypospadias (Albers et al. 1997; Silver and Russell 1999). For example, specific defects in the AR gene are associated with isolated hypospadias, but the frequency of these genetic defects accounts for only a small subset of cases (Allera et al. 1995). To improve our understanding of the role of androgens in human male fetal urethral development, it is necessary to know the distribution of the AR and 5α-reductase type 2 in the developing external genitalia. Several studies have been

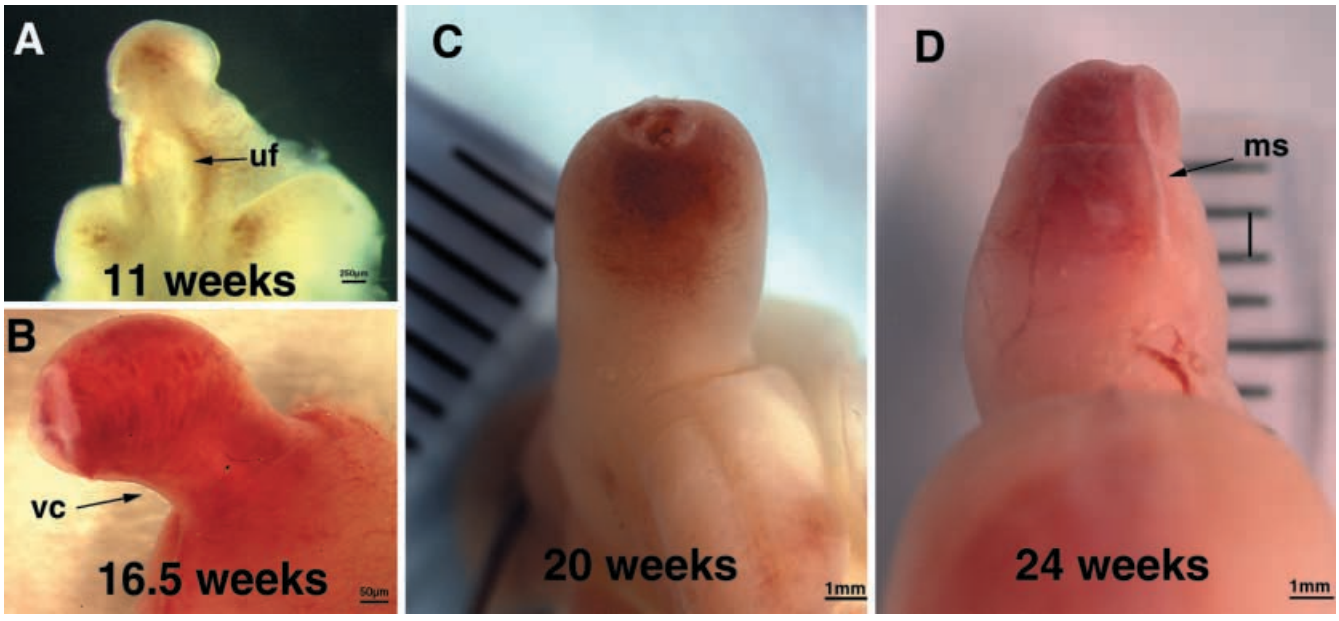

Fig. 1A–D Male human fetal external genitalia during gestation. **A** At 11 weeks, the urethra is open, and the urethral fold (*uf*) and groove are prominent in this transillumination view of the phallus. **B** At 16.5 weeks, the normal ventral curvature (*vc*) and foreskin are almost completely formed. **C** At 20 weeks, penile and urethral development are complete with the prepuce covering the glans, and the penile curvature is resolving. **D** At 24 weeks, the prepuce covers the entire glans. Note the midline seam (*ms*) and the progression of natural curvature to a straight phallus during development

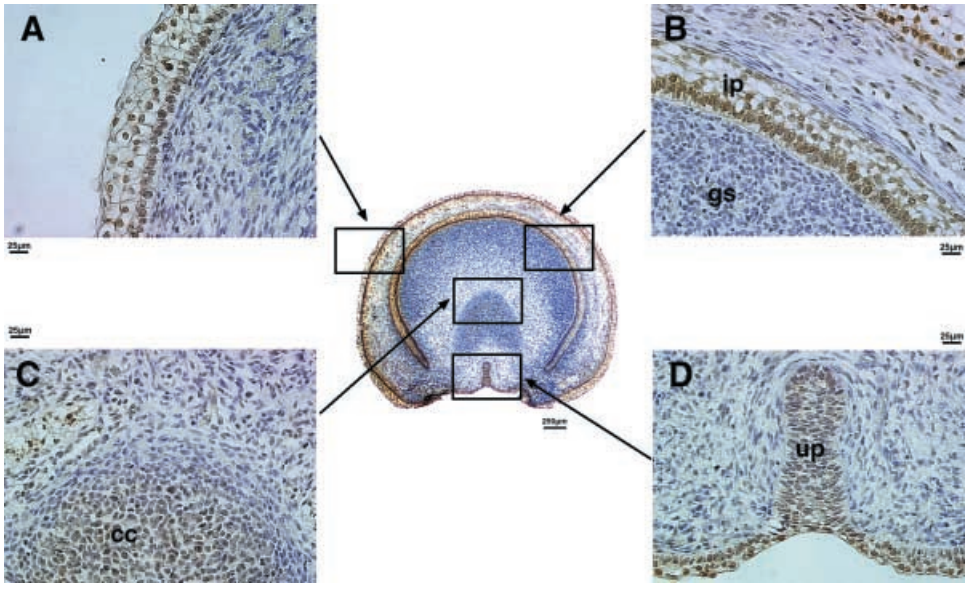

Fig. 2A–D Immunohistochemical detection of AR in human fetal genitalia at 13 weeks gestation. **A–C** The density of AR expression (*brown staining*) is strong in the skin, inner prepuce (*ip*), and corpus cavernosal tissue (*cc*), but weak in the stroma of the glans (*gs*). **D** The urethral plate (*up*) in this section of the proximal glans also shows a strong density of AR expression, as does the skin. The stromal tissue surrounding the urethral epithelium shows a relatively weak density of AR expression

performed in animals (Veyssiere et al. 1985; Cooke et al. 1991; Tsuji et al. 1994; Bentvelsen et al. 1995; Tian and Russell 1997); however, complete data are lacking in human tissues, and prior studies have not focused on urethral development in the human fetus (Kalloo et al. 1993; Levine et al. 1996).

We have shown previously that the urethra forms by fusion of the urethral folds of the urethral groove (Baskin 2000; Baskin et al. 2001). The epithelial fusion of the urethral folds forms the urethral seam, which is subsequently remodeled into the tubular urethra. Here, we investigate the distribution of the AR and 5α-reductase type 2 in the cells of the developing human fetal external genitalia with emphasis on their temporal expression as it relates to the formation of the urethra.

Materials and methods

Preparation of the human tissues

This investigation was approved by the committee on human research at the University of California, San Francisco. Twenty fetal

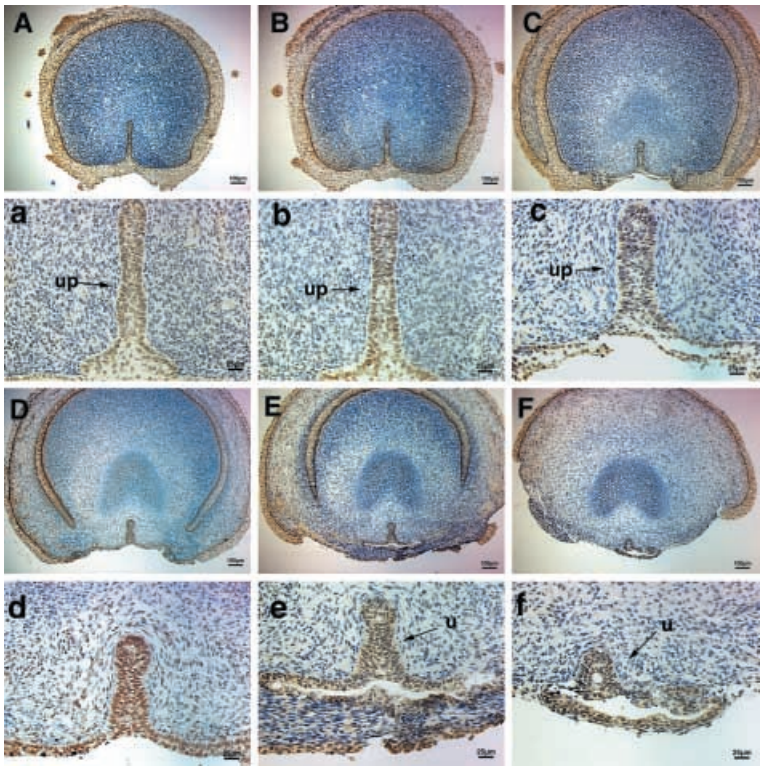

Fig. 3A–F Immunohistochemical detection of AR in serially sectioned human penis at 13 weeks gestation. Sections include distal glans (**A**), mid glans (**B**), proximal glans (**C**), distal penile shaft (**D**), and proximal penile shaft (**E, F**). Note the increased density of AR expression (*brown staining*) in the skin, inner prepuce, and corpus cavernosal tissue compared with the lower density in the stroma of the glans. In the magnified figures (**a–f**), note the AR-positive epithelial cells of the urethral plate (*up*) in the glans (**a–c**) and also the strong positive epithelial cells of the formed urethra (*u*) in the penile shaft (**e, f**). The stromal tissues surrounding the urethral epithelium show AR-positive localization but at a much decreased density than the urethral epithelial cells

genital specimens from normal human males of gestational ages 12–20 weeks were utilized. Based on past experience, the age of the fetal specimens, and previous experience with fetal and postnatal hypospadias, we made the assumption that the specimens analyzed represented normal development (Baskin et al. 1997, 1998, 2001; Baskin 2000). The specimens were subdivided into two gestational age groups, 12–14 weeks and 16–20 weeks. Sex was assigned by visual examination (dissecting microscope) of the specimen, the presence of testes, and fluorescence in situ hybridization with probes to the Y chromosome gene SRY. Gestational age was determined by foot length and clinical history (Hern 1984). All tissues were fixed in formalin and embedded in paraffin.

Immunohistochemical staining of AR

Serial 6-µm-thick sections were deparaffinized and hydrated. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Antigen retrieval was performed by microwave processing at full power for 30 min in 0.01 M citrate buffer, pH 5.6–6.0 (Taylor et al. 1994). Rabbit polyclonal antibody (Affinity Biogenetics, Colo., USA) was used to detect the human AR. After an overnight incubation at 4°C with the primary antibody, a biotinylated donkey anti-rabbit secondary antibody was applied. Slides were treated with avidin-biotinylated peroxidase complex and developed in a solution containing diaminobenzidine tetrahydrochloride (DAB). All sections were counterstained with hematoxylin. The specificity of AR immunohistochemical staining was confirmed by the use of positive (prostate) and negative controls (uterus; data not shown; Takeda and Chang 1991). AR-positive staining was defined as nuclear staining with relatively stronger staining density characterized as ++ and weaker staining density as +. Histologic sections representative of glans, distal shaft, and proximal shaft of the phallus were selected for imaging.

Immunohistochemical staining of 5α reductase type 2

Representative tissue sections were deparaffinized in xylene (3×5 min changes) and were hydrated gradually through graded alcohols. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol for 10 min, and antigen retrieval was achieved by treatment with 0.5% trypsin at 37°C for 15 min. Rabbit polyclonal antibody against a 25-amino-acid segment of the human 5α-reductase type 2 protein was used (Tian and Russell 1997). The specificity of the AR immunohistochemical staining was confirmed by the use of positive (prostate) and negative controls (uterus; data not shown). Tissue sections were incubated with primary antibody (10 µg/ml) at 4°C overnight, followed by a corresponding secondary antibody (goat anti-rabbit) conjugated with horseradish peroxidase. Slides were developed in a solution containing DAB and hydrogen peroxide. Stained sections representative of glans, distal shaft, and proximal shaft of the phallus were imaged.

Three-dimensional reconstruction

Three-dimensional reconstruction of AR expression was performed by using serial histologic sections, image capture by Abode Photoshop, and rendering by means of the Surf Driver computer program as previously described (Akman et al. 2001; Baskin et al. 2001).

Results

The gross morphology of the human fetal penis at various ages of gestation is shown serially in Fig. 1A–D. There is a natural progression of penile curvature as a function of time. There is also progression of urethral development from an open urethra and incompletely formed prepuce to a straight phallus with a completely formed urethra and prepuce.

Fetal genital specimens were grouped based on developmental age. The specimens at 12–14 weeks had com-

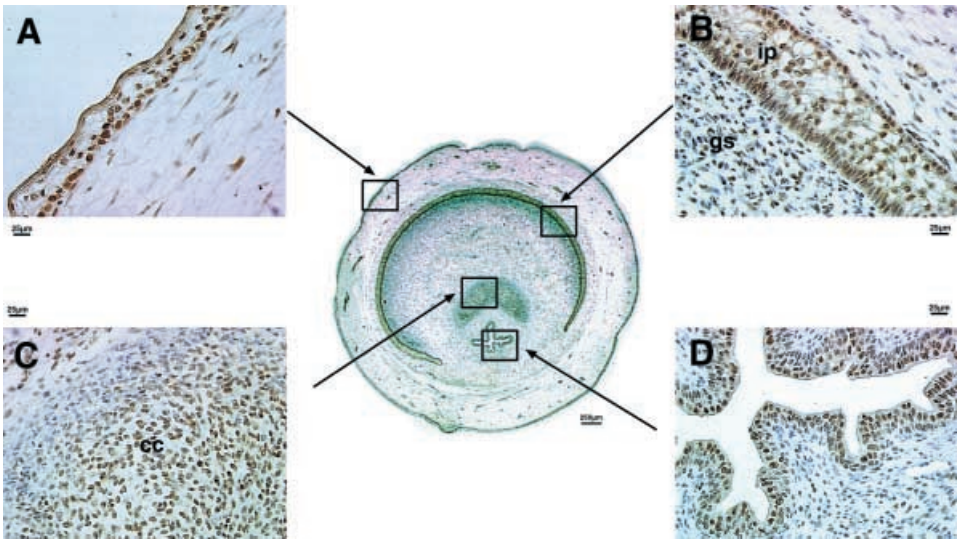

Fig. 4A–D Immunohistochemical localization of AR in the fetal penis at 16.5 weeks gestation. **A–C** The intensity of AR expression (*brown staining*) is strong in the epithelial cells of the skin, inner prepuce (*ip*), and corpus cavernosal tissue (*cc*), and moderate in the stroma of the glans (*gs*). **D** The urethral epithelial cells in the proximal glans show strong AR staining compared with the stromal tissue surrounding the urethral epithelium

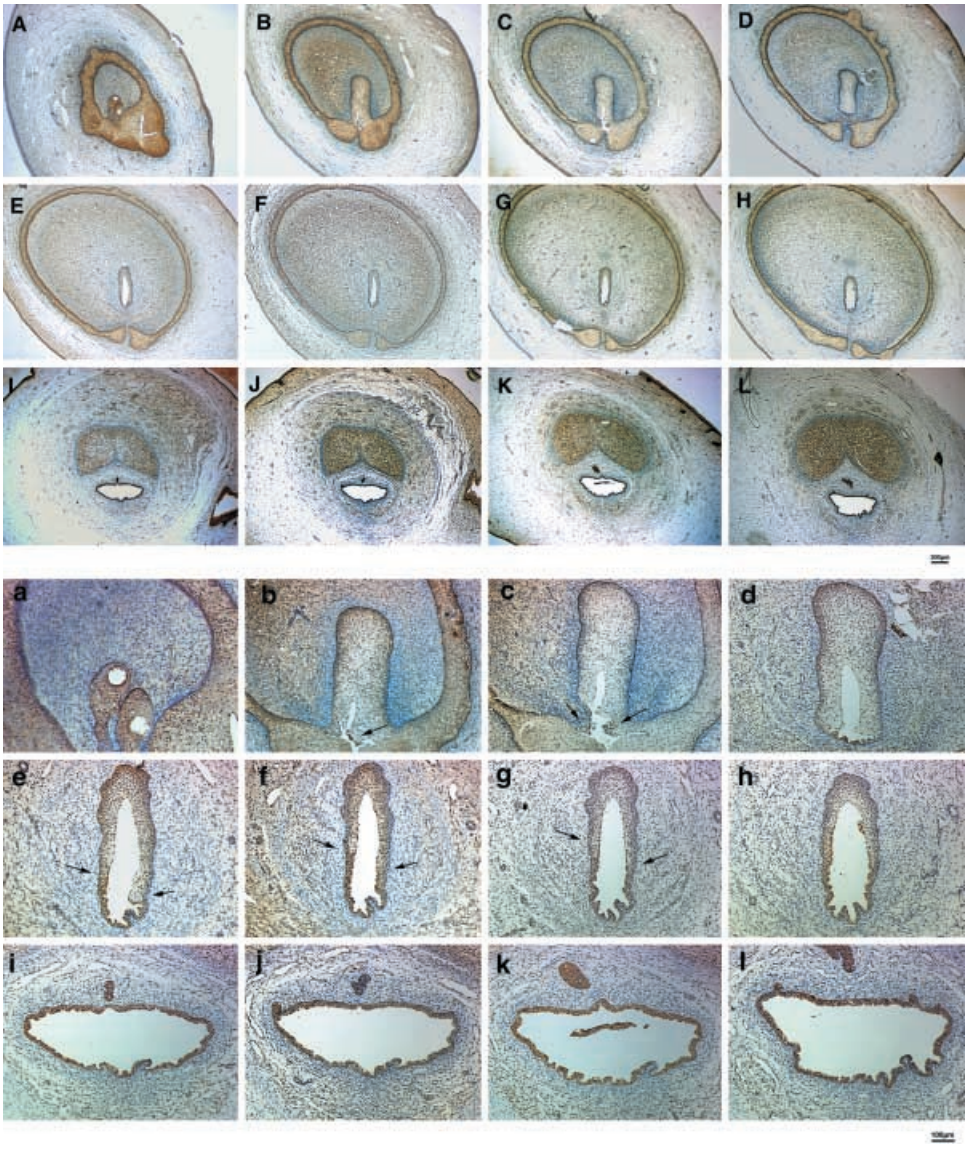

Fig. 5A–L Immunohistochemical detection of AR in serially sectioned penis at 19.5 weeks gestation. Sections include distal glans (**A–D**), mid to proximal glans (**E–H**), and distal to proximal shaft (**I–L**). Magnified views of the urethral portion of each are shown in panels *below* labeled with *small letters* (**a–l**). Note the increased density of AR expression in the corpora cavernosa, skin, and urethra. The urethral epithelial cells that show the strongest density of AR expression (*black arrows* upper margin of the strongly AR-positive cells in **a–h**) are localized to the ventral aspect of the glandular urethra and the entire urethra in the penile shaft

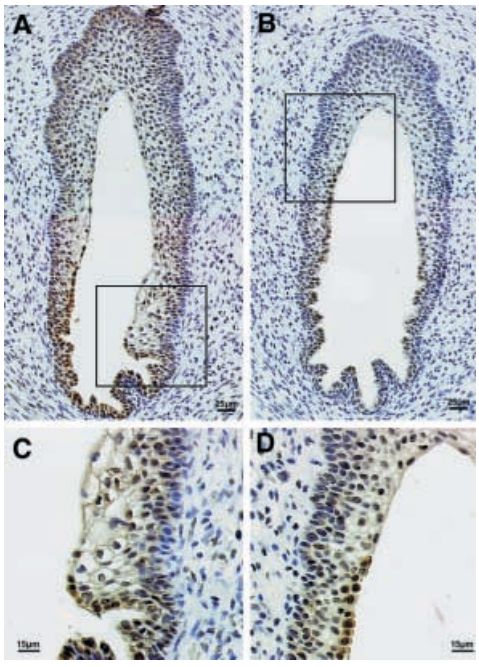

Fig. 6A–D The expression of AR is different between the ventral and dorsal portions of the urethral epithelium in the mid to proximal glans. A greater density of AR-positive cells is seen in the ventral portion of the urethra. *Arrows* indicate upper margins of increased AR expression (**A, B**). Note the luminal cuboidal epithelial cells in rows showing strong AR expression (**C, D**)

plete penile shaft urethral formation and incomplete glandular urethral formation. The group at 16–20 weeks had complete formation of the penile and glandular urethra.

AR expression at 12–14 weeks gestation

Representative immunohistochemical staining of the AR in the gestation group at 12–14 weeks is shown in Figs. 2 and 3. AR expression is strongest in the skin, urethral plate, inner prepuce, and corpus cavernosal tissue, with weaker expression in the stroma of the glans (Fig. 2). The epithelial cells of the urethral plate and tubular urethra in the penile shaft also exhibit strong AR expression compared with that of the stromal tissue surrounding the urethral epithelium (Fig. 3).

AR expression at 16–20 weeks gestation

Representative immunohistochemical staining patterns of the AR between 16 and 20 weeks gestation are shown in Figs. 4, 5, 6, and 7. AR expression is strongest in the skin, inner prepuce, and corpus cavernosal tissue and weakest in the stroma of the glans. The urethral epithelial cells in the proximal glans show strong AR expression compared to the surrounding stroma (Figs. 4, 5).

Table 1 The immunohistochemical expression of AR in the developing penis. The number of + symbols reflects the relative AR staining intensity in the indicated tissues

Tissue	12–14 week gestation		16–20 week gestation	
	Glans	Penile shaft	Glans	Penile shaft
Urethral epithelium				
Ventral aspect	++	++	+++	+++
Dorsal aspect	++	++	+	+++
Urethral mesenchyme	+	+	+	+
Corporal body	++	+++	++	+++
Skin	+++	+++	+++	+++

The density of AR expression in the glandular urethra was dependent on either a dorsal or ventral location between 16 and 20 weeks of gestation (Fig. 5). In the urethral epithelium of the mid to proximal glans, AR density was stronger in the ventral portion than in the dorsal portion of the urethra. Figure 6 shows the intense staining in the luminal cells. The urethral epithelial cells that stained strongly for the AR were present in a small population in the distal glans, with about half of them lying in the mid to proximal glans, and the remainder in the urethra of the penile shaft (Figs. 5, 7). Table 1 summarizes the density of AR expression. The topographic expression of the AR in the urethra is shown schematically in Figs. 7 and 8 by three-dimentional reconstruction.

5α-Reductase type 2 expression at 16–20 weeks gestation

Between 16 and 20 weeks of gestation, there is expression of 5α-reductase type 2 in the skin, corpus cavernosa, and spongiosum. In the urethra, there is strong staining in the stroma but only faint staining in the urethral epithelium. There was strong expression of 5α-reductase type 2 along the remodeled urethral seam area in the ventral portion of the urethra (Fig. 9).

Figure 10 shows the expression of 5α-reductase type 2 and the AR in serial adjoining sections. In the mid glans, a high level expression of 5α-reductase type 2 is seen in the stroma of the urethral seam area. In the proximal shaft within the ventral stroma, this expression of 5α-reductase type 2 becomes progressively weaker (Fig. 10A–D). In the mid glans, there is strong AR expression in the urethral epithelium and corresponding strong expression of 5α-reductase type 2 in the stroma of the urethral seam area (Fig. 10B, F). The results of the 5α-reductase type 2 immunohistochemistry staining in 12-week to 14-week male fetuses were similar to those for the older (16–20 week) fetuses (data not shown).

Discussion

Our study describes the anatomical localization of the AR and the 5α-reductase type 2 enzyme within the de-

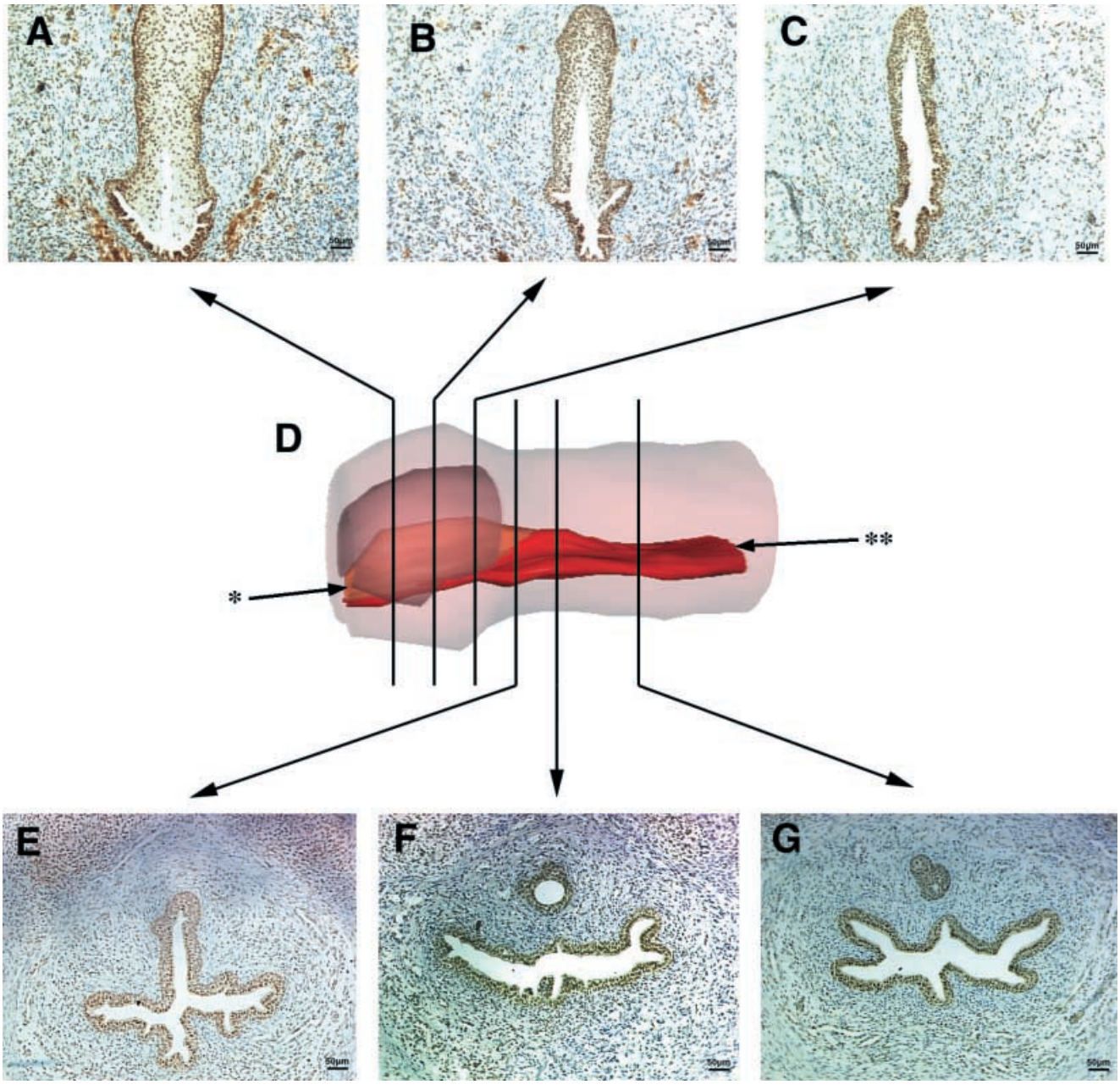

Fig. 7A–G Three-dimensional reconstruction of AR expression in the fetal penis at 16.5 weeks. A greater density of AR-positive cells is seen in the ventral portion of the urethral epithelium in the distal glans (**A**), mid glans (**B**), and proximal glans (**C**). *Arrows* indicate the upper margin of cells that are strongly AR-positive (**A–C, E**). In the distal (**E**), mid (**F**), and proximal (G) shaft of the penis, all portions of the urethral epithelium show the same density of expression. **D** Data from the serial sections of the AR staining experiments was used to create a three-dimensional reconstruction to demonstrate the urethral AR expression pattern. *Light brown color* (*asterisk*) indicates weaker density, whereas strong AR expression is indicated by *red* (*double asterisk*). The glans is represented in *dark gray* and the skin in *light gray*. Note that half of the urethral epithelium is strongly positive in the proximal glans transitional zone

veloping penis as a function of gestational age. We have found a characteristic cell-type-specific pattern of expression for these proteins in association with urethral formation and urethral seam remodeling.

The density of AR in the human fetal penis strongly localizes to the skin, inner prepuce, and urethra and to the stromal cells of the corpus cavernosa. In contrast, AR density is lower in stromal cells of the corpus spongiosum and glandular tissues. These findings are true for both gestational age groups examined (12–14 weeks and 16–20 weeks). Our results differ in some respects from previous observations in humans and other species. Kalloo et al. (1993) have reported AR immunohistochemical studies in human fetal tissues between 18 and 22 weeks gestation. Their study has reported that skin epithelial cells are negative, and the periurethral stroma

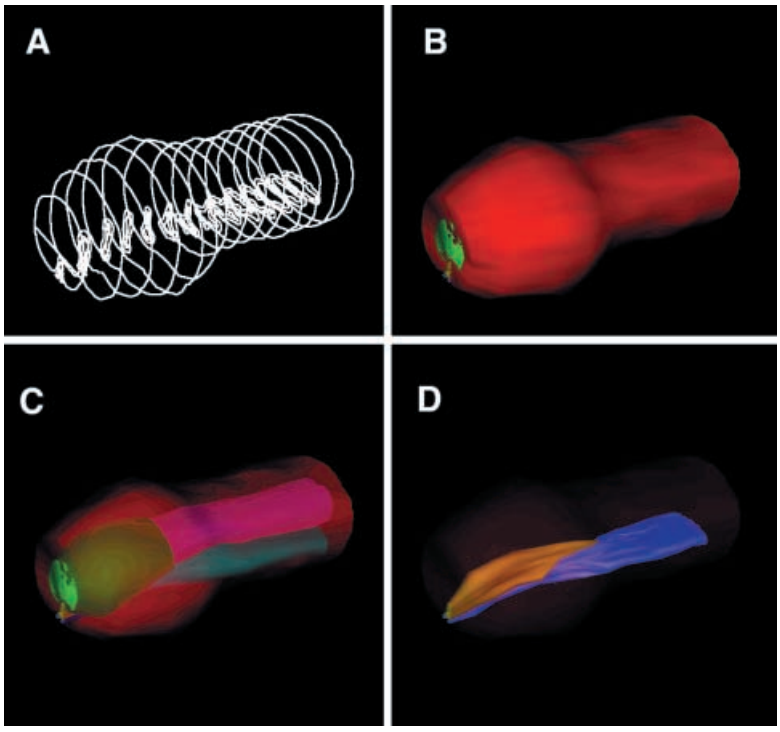

Fig. 8A–D Three-dimensional reconstruction of AR expression in the fetal penis at 16.5 weeks. **A** Depicts a wire frame image of the outer penile skin and urethra. **B** Depicts the outer skin in orange and glans in *green*. **C** Depicts the outer skin in *brown*, corpora cavernosa in *pink*, glans in *green* and *olive*, penile urethra in *blue*. **D** The glans has been artificially removed, and the whole urethra is visible with the greater density of AR depicted in *blue* and the weaker density in *yellow*. Note that the greater density is localized to the ventral aspect of the glandular urethra and the entire penile urethra

and peripheral area of the glans are strongly positive for AR. In contrast, we have found that all skin epithelial cells are consistently positive from 12 to 20 weeks gestation, showing typical nuclear staining (Figs. 2, 3, 4, 5, 6, 7). The AR density of stromal cells within the urethral and glandular tissues is less than that in epithelial cells of the urethra. Recent advances in antigen retrieval methods, which provide sensitive and specific immunohistochemical assays for paraffin-embedded tissues may account for the difference in these studies (Taylor et al. 1994).

Previous studies have shown that epithelial cells of adult genital skin are AR-positive (Blauer et al. 1991). In animal studies, AR expression is initially present only in mesenchymal cells and appears later in the epithelium (Cooke et al. 1991; Bentvelsen et al. 1995). Similar findings have been observed in the epididymis, ductus deferens, seminal vesicles, and prostate, which are derived from Wolffian ducts and urogenital sinus. In the specimens between 12 and 14 weeks gestation, AR has been detected in the tubular urethra of the penile shaft and in the urethral plate of the glandular urethra. The presence of the AR during this developmental period suggests that the effects of androgen on the development and growth in the first trimester are mediated through AR.

The expression of AR in cells of the urethral epithelium between 16 and 20 weeks gestation is regionally distributed. The most distal part of the glandular urethra shows a low density of positive cells in the ventral urethral epithelium. In the mid glans, the density of AR is greatest in the ventral aspect of the urethra. Beyond the coronal sulcus, the urethra of the penile shaft exhibits an equivalent density of AR expression without a preferential dorsal or ventral distribution. This pattern of variable androgen expression is schematically shown in the three dimensional reconstructions in Figs. 7 and 8. Kalloo et al. (1993) have also observed similar findings in the area of the mid glans and described an abrupt transition from AR-negative glandular urethra to AR-positive epithelial cells in the distal shaft urethra.

The expression of 5α-reductase type 2 has been localized to the stroma of the corpora cavernosa, spongiosum, skin, and inner prepuce in the male fetus between 16 and 20 weeks gestation, whereas the epithelial cells of the urethra are negative. Especially intense staining for 5α-reductase type 2 has been noted on the ventral aspect of the urethra at the site of the remodeled urethral seam (Figs. 9, 10). These findings are consistent with the study of Levine et al. (1996) who have localized 5α-reductase type 2 to this area between 19 and 22 weeks of gestation. The expression of 5α-reductase type 2 is strongly localized to the stromal tissue in contrast to the expression of the AR, which is localized to the urethral epithelial cells. High levels of 5α-reductase type 2 activity in the ventral urethral seam may concentrate dihydrotestosterone in this area, thereby facilitating urethral seam remodeling. The location of the 5α-reductase type 2 enzyme in the ventral stroma of the remodeled urethral seam argue for its importance in the final fusion process of the urethral folds into the tubular urethra. This is consistent with the clinical syndrome of severe hypospadias and female phenotype of 5α-reductase type 2 deficiency. The immunohistochemical localization of the 5α-reductase type 2 enzyme is also consistent with a recent report from Silver and Russell (1999) that mutations

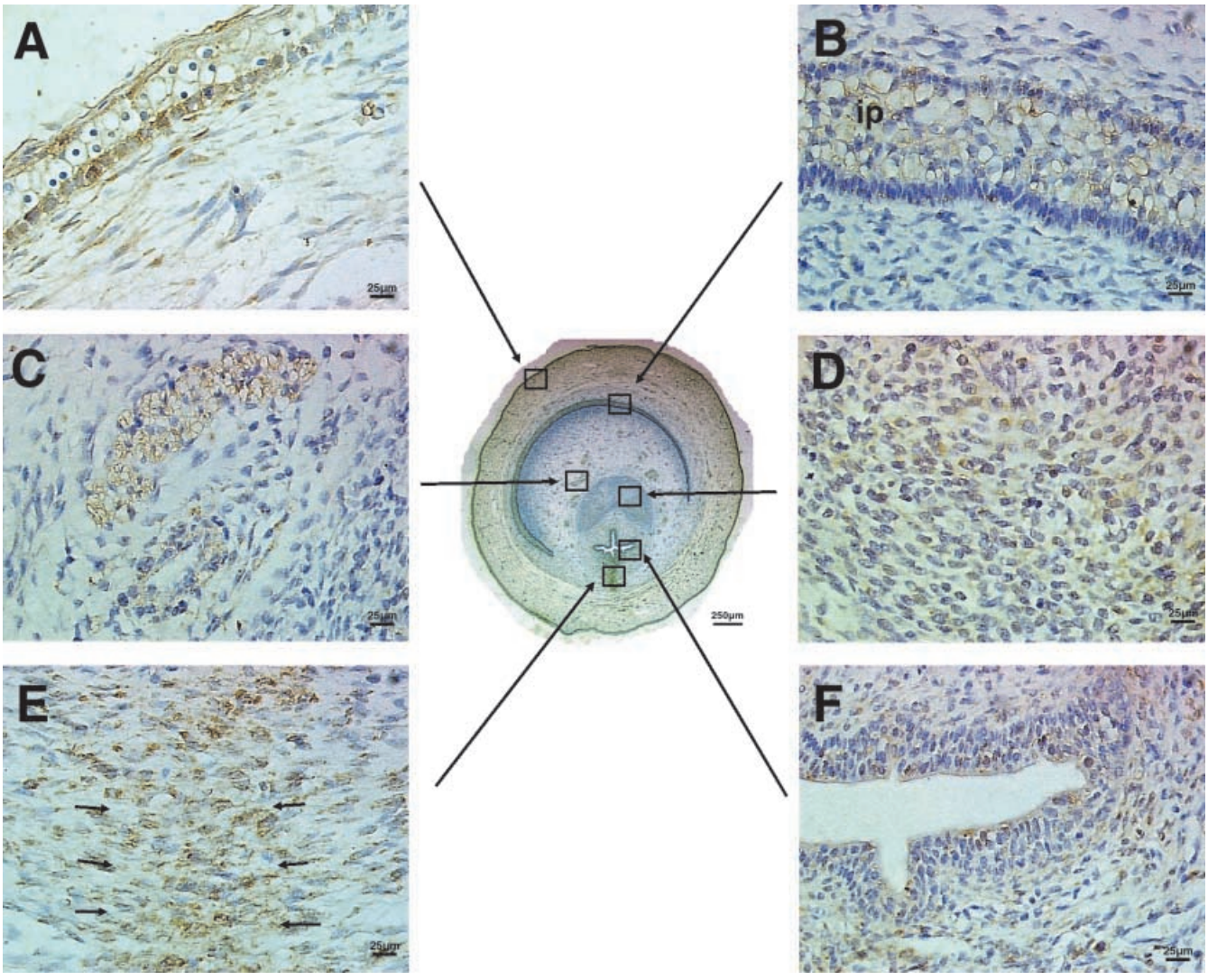

Fig. 9A–F Immunohistochemical detection of 5α-reductase type 2 in the fetal external genitalia at 16.5 weeks of gestation. Note the expression (*brown stain*) in the skin (**A**), inner prepuce (**B**), glans (**C**), and corpus cavernosum (**D**). In the urethra, note the strongly positive stain in the stroma, the faint positive stain in the luminal epithelial cells, and the lack of staining in the basal cells (**F**). The stroma of the urethral seam area (*arrows*) is strongly positive (**E**)

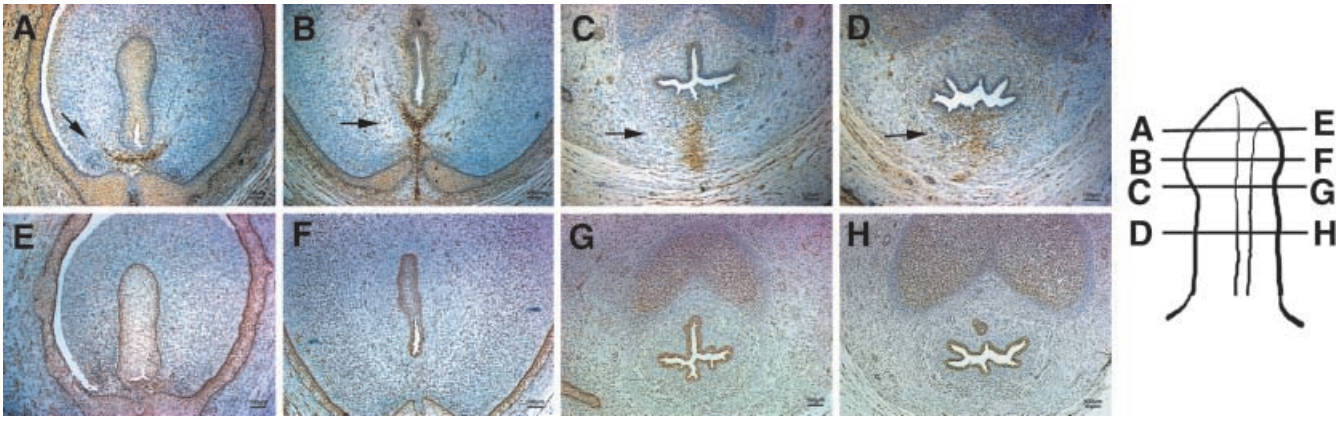

Fig. 10 Immunohistochemical localization of 5α-reductase type 2 (**A–D**) and AR (**E–H**) in the same fetal penis at 16.5 weeks of gestation. Note the strong expression of 5α-reductase type 2 along the urethral seam area (*arrows*). Staining for 5α-reductase type 2 in the urethral epithelium is faint. The expression of AR is strong in the urethral epithelium but is not increased in the stroma of the seam area. **A, E** Distal glans. **B, F** Mid glans. **C, G** Proximal glans. **D, H** Penile shaft

in one or both of the 5α-reductase type 2 alleles can cause isolated hypospadias. Silver and Russell (1999) suggest that a partial deficiency of 5α-reductase type 2 enzyme activity may explain isolated hypospadias (no family history of the disease).

Conclusions

The presence of AR expression in the urethral plate between 12 and 14 weeks gestation suggests that androgens play an important role during urethral formation of the penile shaft. Regional differences in the expression of AR in the developing urethra show that the fused ventral seam exhibits strong expression of AR in contrast to the weaker expression of the dorsal urethral plate. Simultaneously, there is regional localization of the 5α-reductase type 2 enzyme in the ventral midline portion of the stroma where the urethral seam has remodeled. These anatomical studies support the hypothesis that androgens have an important role in formation of the ventral portion of the urethra and that expression abnormalities in either the AR or 5α-reductase type 2 can explain the occurrence of hypospadias.

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