***JB Minireview*—Reproductive / Urogenital Organ Development and Molecular Genetic Cascades** *J. Biochem.* **137**, 665–669 (2005)
DOI: 10.1093/jb/mvi085

Reproductive/Urogenital Organ Development and Molecular Genetic Cascades: Glamorous Developmental Processes of Bodies

Gen Yamada*

Center for Animal Resources and Development (CARD), Graduate School of Medical and Pharmaceutical Sciences, Kumamoto University, Honjo 2-2-1, Kumamoto 860-0811

Received March 28, 2005; accepted April 21, 2005

At the beginning of the 21st century, developmental biologists together with medical researchers in a wide range of fields are witnessing rapid progress in molecular developmental biology. For example, conditional gene knockout systems are being designed to tackle questions about organogenesis and body plan formation in experimental mouse models and experimental designs include several compound mutant analyses and genome modification strategies. On the other hand, several fields remain relatively unexplored. Molecular mechanisms of sex differentiation are one of the unexplored huge area. Unanswered questions include the molecular genetic cascade of gonad formation, reproductive organ formation, uterus, external genitalia and mammary gland formation, and also the molecular mechanisms of signal transduction, and gene regulation by nuclear hormone receptors. This special thematic review series entitled, "Reproductive/urogenital organ development and molecular genetic cascades: glamorous developmental processes of bodies," covers such a wide range of topics. For this special issue, I have asked active researchers to contribute reviews of these topics which I believe will be useful not only for molecular developmental biologists, but also for researchers in biochemistry and cell biology. It will be my great pleasure if this special thematic issue encourages scientists to study this exciting research field.

Key words: androgen, genitalia, gonad, growth factors, hormone, mammary gland, reproduction, sex differentiation, urogenital organ.

Molecular cloning of many of the genes controlling development, including growth factors developmental control genes and homeobox genes, has identified the basic plans of organogenesis (*1–6*). During fetal and neonatal development of mammals, reproductive/urogenital systems basically develop as late-forming structures compared with other organs.

Figure 1 represents schematically the male and female reproductive/urogenital tract organs of the adult human body. These organs show a tremendous degree of structural and functional diversity between the sexes. Various growth factors and transcription factors constitute molecular genetic cascades for the development of these structures. Nuclear hormone receptors have been also implicated in the regulation and modification of the developmental processes. Teratogens can potentially influence these processes. This fact has attracted researchers in environmental sciences to this interdisciplinary field. Concerns about the possible increase of reproductive organ cancers and reproductive problems such as infertility , endometriosis in the human population have also been growing.

Topics addressed in this review series are highlighted in Fig. 1. The blue organs shown at the bottom represent the ovary (left) and testis (right). The green organs represent the external genitalia, while the red organs with black hatching represent the uterus and vagina. This review series also covers nuclear hormone receptors, especially AR (androgen receptor) and the mammary gland.

To understand the several levels of reproductive biology related with fertilization, implantation, lactation, ejaculation, erection, copulation and ovulation, it is necessary to obtain integrated knowledge linking reproductive biology with cell biology and biochemistry. These processes include proper regulation of cell growth and differentiation. Thus, I hope that the reviews collected here will stimulate readers who have interests in cell biology, biochemistry and molecular developmental biology.

It is intriguing and important to note the potential similarities and also divergences of some "shared" developmental plans between "general" organogenesis and reproductive/urogenital organ formation. Figure 2 shows an example of the initial process of reproductive organ development in comparison with that of limb appendages as an example of somatic organ development (Fig. 2A).

Epithelial-mesenchymal interactions play an essential role in regulating a wide variety of developmental processes (*3*, *5*, *7–9*). Signaling between the epithelium and the mesenchyme governs many aspects of organogenesis, from the initiation of organ development to differentiation (*10*, *11*).

As an example of organogenesis based on such interactions, the external genital anlage, the genital tubercle (GT), differentiates into a penis in males and a clitoris in females. Pioneering studies have suggested that GT development may have some similarities to limb appendage development, with both structures exhibiting organ outgrowth (*12*, *13*). Vertebrate limb development depends

*For correspondence Tel: +81-96-373-6569, Fax: +81-96-373-6560, E-mail: gen@kaiju.medic.kumamoto-u.ac.jp

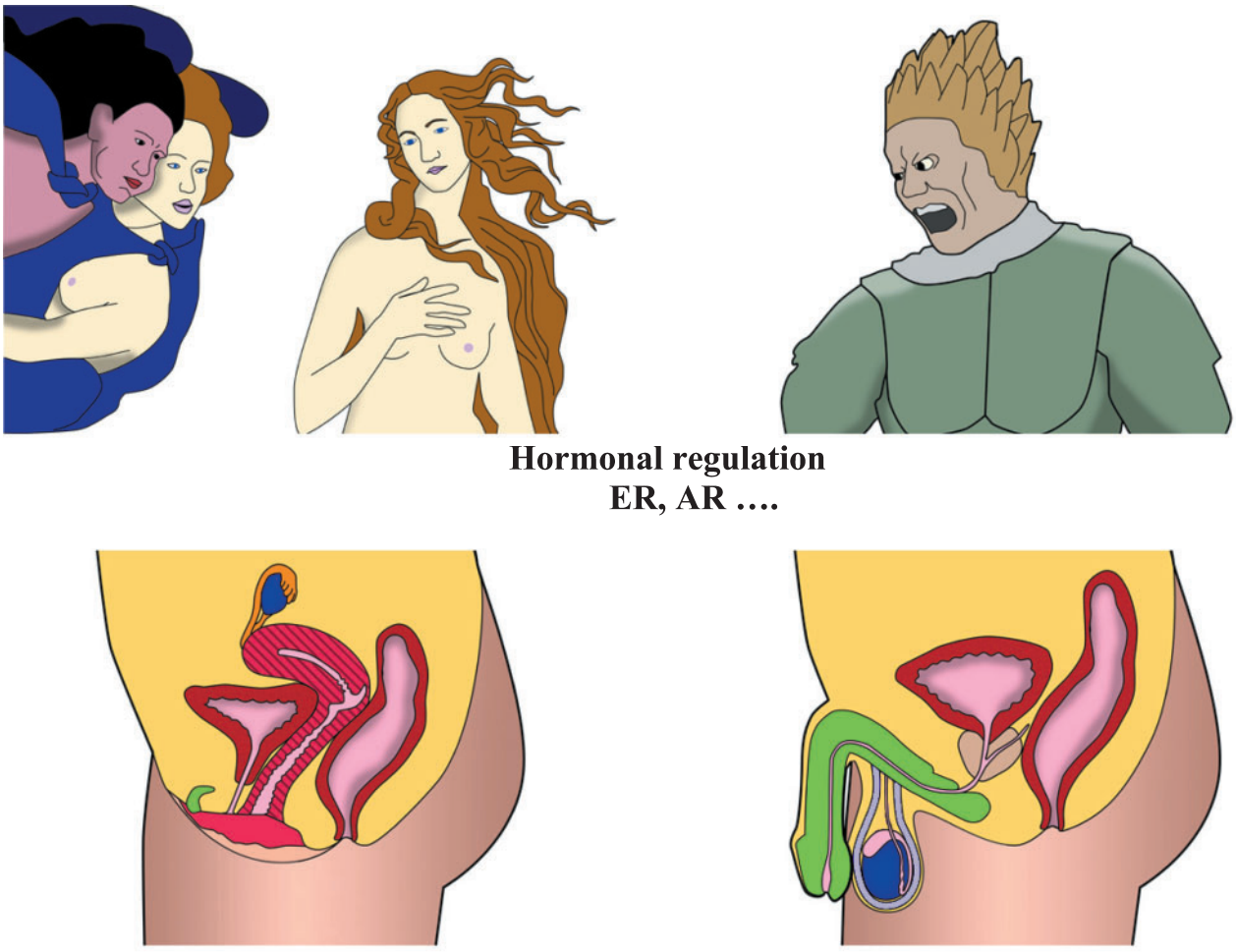

Fig. 1. **Schematic illustration of female and male reproductive/urogenital organ development.** The upper part shows cartoons of the female upper body; a simplified sketch of *The Birth of Venus* by Sandro Botticelli (1445–1510). The upper right part of male body is a simplified sketch of *Juni Sinsho* (Basara) of Shin yakushiji Temple (Nara) one of the masterpieces of Nara-period Buddhist art. The lower part of the figure shows the female reproductive/urogenital organs at left and the male reproductive/urogenital organs at right. Various growth factors/developmental regulatory genes are involved the regulation of developmental processes. Nuclear hormone receptors modify and regulate these processes, leading to dimorphic of development of these structures as shown in the middle. AR, for example, is vital for the development of bones, reproductive organs and behaviors.

on the establishment and maintenance of the apical ectodermal ridge (AER), a specialized ectoderm region at the distal tip of the limb bud (*3*, *9*, *14*). It has been speculated that the GT epithelium and mesenchyme develop through epithelial-mesenchymal interactions. In this review series, Dr. Stadler group will review these developmental similarities and divergence among limbs and external genitalia, focusing also on distal signaling epithelia (termed DUE or UPE; *15–19*).

Reproductive/urogenital organ development includes hormone-independent bipotential developmental processes to hormone-dependent dimorphic processes, as shown in Fig. 2. Many of the reviews included in this series will give readers concise summaries of recent ideas of such genetic cascades (Fig. 2).

This special thematic review series includes contributions on a wide range of topics by active researchers in their respective fields. These include intriguing reviews about uterus formation and external genitalia formation for female and male organ formation, respectively. Molecular developmental research on these organs has just begun. Their formation implies some shared functions of developmental plans including various growth factors and developmental control genes. These reviews have been contributed by the laboratories of Dr. Liang Ma and Dr. Scott Stadler, respectively. The two reviews cover some conserved functions of regulatory genes such as Hox genes, which are required for both sex organs. This will give ideas and propose interesting questions about the conserved and diversified functions of genetic networks for both sex organs. The Stadler lab also identified intruiguing link between Bmps-Hox a13.

Two topics related to gonad formation have been contributed by Dr. Yoshiakira Kanai, Dr. Humphrey H-C Yao and Dr. Blanche Capel. Bipotentioal gonad formation has been regarded as one of the central issues of developmen-

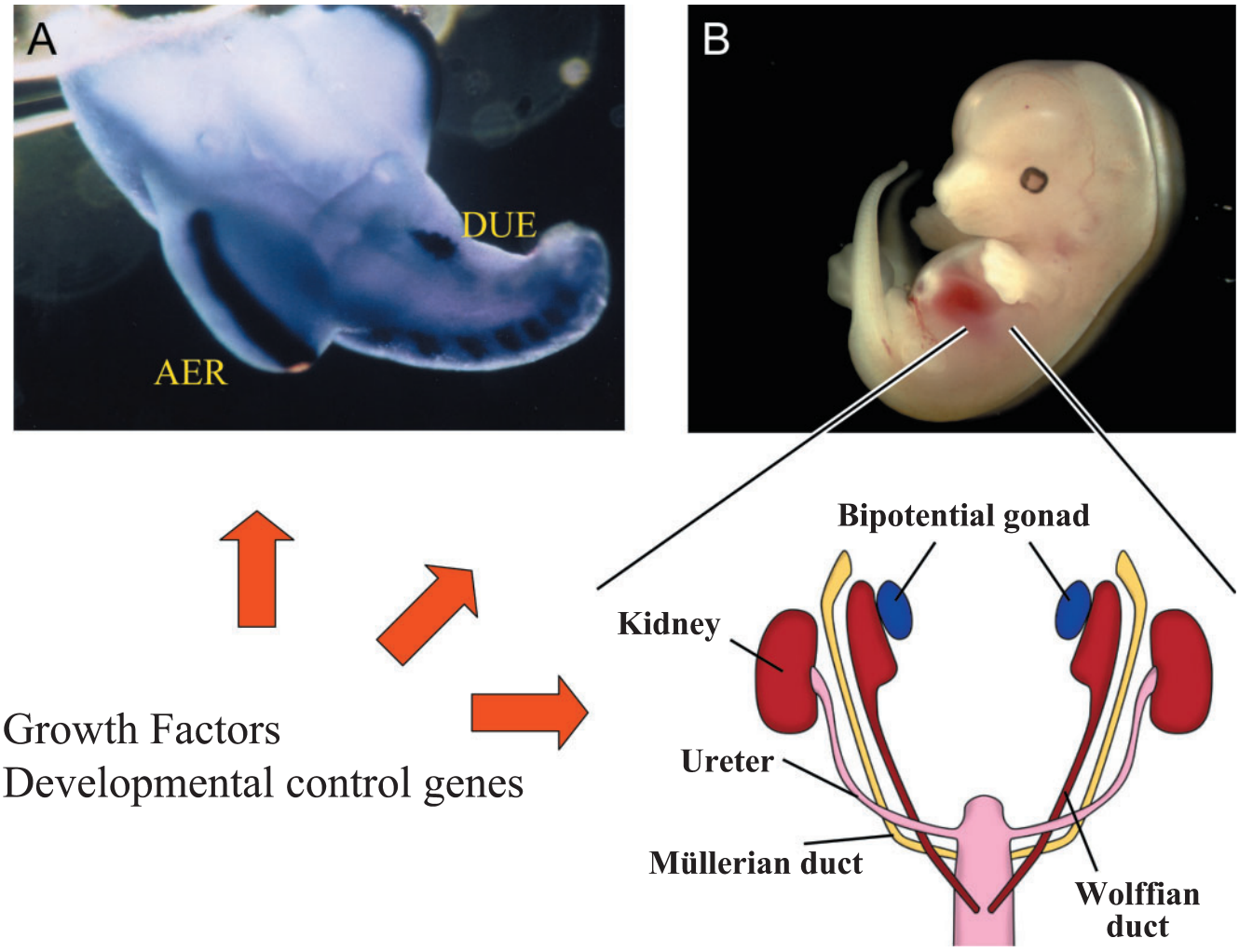

Fig. 2. **Embryonic development of appendages (external genitalia and hind limbs) and internal reproductive organs (bipotential gonad).** (A) External genital organ development is regulated by DUE (distal urethral epithelia). Likewise, transient signaling epithelia AER (apical ectodermal ridge) is formed at the tip of a developing limb. (B) Bipotential reproductive organs show dimorphic developmental diversities. The above processes are regulated by developmental regulators under hormonal influence at a late stage.

tal and reproductive biology. It also clearly includes issues of cellular differentiation of somatic cells and germ cells inside the developing gonad (Fig. 2). Sex differentiation from immature gonad to mature testis or ovary also requires a precise set of transcription networks including factors such as Ad4BP/SF1, Sry, Sox, Wt1, Fgf, Dmrt1 *etc.*

Mammary gland formation also implies hormone-dependent and hormone-independent (early) organogenesis, which have been well studied recently by using gene knockout mouse models. Dr. Lothar Hennighausen's group reviews these processes, understanding of which will not only be helpful for developmental mammary gland biology, but will also be essential for studying cancer biology and breast cancer theraputic studies. It will give ideas about signaling cascades composed by key genes such as those of the Stat pathways.

Lastly, in all the processes, nuclear hormone receptors are involved in important regulatory gene cascades. A review by Dr. Shigeaki Kato lab summarizes these nuclear hormone receptors, primarily focusing on AR gene functions using gene knockout mouse models and other species models. They explain the underlying mechanisms about the sex organ formation and offer ideas about the transcription mechanisms of these phenomena and also explain the AR gene functions for nervous system development, behavior controls and other organogenesis such as bone formation.

Figure 3 shows the remarkable features of body-shape diversity that exists among species. Inside each of these bodies, various reproductive/urogenital organs are formed which reflect species diversity. Various species perform reproduction depending on their biological lifestyles and based on their various physiological functions and anatomical structures. This review series also describes some aspects of species divergences and Evo. Dev. biology. In fact, examining the diversities and similarities of such development will help to identify a putative mode of basic processes among species. Granted that studies utilizing gene knockout mice models or conditional gene knockout mice models possess some merits for functional analysis, experimental species such as turtles, Drosophila, chicks and fish models will also draw

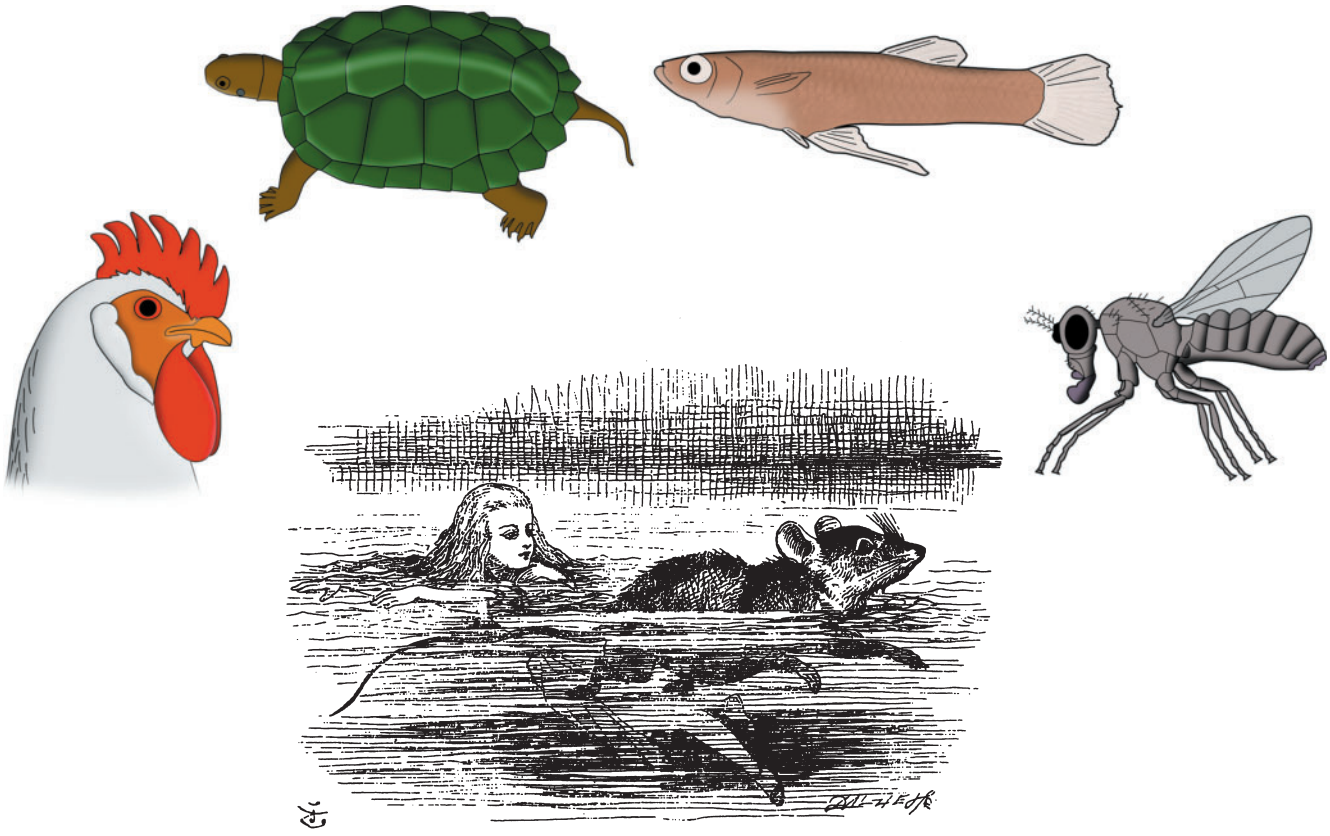

Fig. 3. **Diversities in species: tools for molecular developmental analyses of reproductive/urogenital organ formation in various experimental animal species.** Comparison of the possible similarity and divergence of the mechanisms of reproductive/urogenital organ development among animal species will provide information as described in this review series. In Alice's Adventures in Wonderland, Lewis Carroll might have asked to us whether mouse are among such research objects. Integrated knowledge based on various species will be very essential in reproductive biology. "'O Mouse, do you know the way out of this pool? I'm very tired of swimming about here.' The mouse looked at her rather inquisitively, and seemed to her to wink with one of its little eyes, but it said nothing. (The lower part of the illustration is from *Alice's Adventures in Wonderland* by Lewis Carroll, and illustrated by Sir John Tenniel.)" All parts have been reproduced by written permission of Macmillan Children's Books, Macmillan Publishers, London.

very much attention from researchers [an example of Gambusia is also listed showing a copulatory organ, gonopodium, which is derived from fins (*20*)].

I express my sincere gratitude to all the contributors to this special issue for spending important time out of their busy schedules. I hope this review series will give essential ideas and hints to readers not only who are already interested in this field, but also stimulate the curiosity of more scientists in this growing field.

I thank Drs. Atsushi Miyajima, Toru Nakano, Ken-Ichiro Morohashi, Yoshitaka Nagahama, Virginia E. Papaioannou, John Fallon, Gary C. Schoenwolf, Denis Duboule, Scott Stadler, Anne M. Moon and Shigeaki Kato for encouragement. I also thank Ms. Shiho Kitagawa and Mr. Eiichi Matsuda for help. This publication was supported by a Grant-in-Aid for Scientific Research on Priority Areas (*1*) General Promotion of Cancer Research in Japan, by a Grant-in-Aid for Scientific Research on Priority Areas (*2*) Mechanisms of Sex Differentiation, by the 21st Century COE Research Program; and by a Grant for Child Health and Development (14C-1) from the Ministry of Health, Labour and Welfare. I would like to also thank for Macmillan Children's Books, Macmillan Publishers, London. The illustration is reproduced by written permission of the Publisher.

REFERENCES

1. Dubrulle, J. and Pourquie, O. (2004) Coupling segmentation to axis formation. *Development* **131**, 5783–5793
2. Koopman, P. (2001) The genetics and biology of vertebrate sex determination. *Cell* **105**, 843–847
3. Johnson, R.L. and Tabin, C.J. (1997). Molecular models for vertebrate limb development. *Cell* **90**, 979–990
4. Kobayashi, A. and Behringer, R.R. (2003) Developmental genetics of the female reproductive tract in mammals. *Nat. Rev. Genet.* **12**, 969–980
5. McMahon, A.P., Ingham, P.W., and Tabin, C.J. (2003) Developmental roles and clinical significance of hedgehog signaling. *Curr. Top. Dev. Biol.* **53**, 1–114
6. Lovell-Badge, R., Canning, C., and Sekido, R. (2002) Sex-determining genes in mice: building pathways. *Novartis Found. Symp.* **244**, 4–18; discussion 18–22, 35–42, 253–257
7. Oxburgh, L., Chu, G.C., Michael, S.K., and Robertson, E.J. (2004) TGFbeta superfamily signals are required for morphogenesis of the kidney mesenchyme progenitor population. *Development* **131**, 4593–4605
8. Naiche, L.A. and Papaioannou, V.E. (2003) Loss of Tbx4 blocks hindlimb development and affects vascularization and fusion of the allantois. *Development* **130**, 2681–2693
9. Tickle, C. and Eichele, G. (1994). Vertebrate limb development. *Annu. Rev. Cell. Biol.* **10**, 121–152

10. Dassule, H.R. and McMahon, A.P. (1998). Analysis of epithelial-mesenchymal interactions in the initial morphogenesis of the mammalian tooth. *Dev. Biol.* **202**, 215–227
11. Tucker, A.S., Yamada, G., Grigoriou, M., Pachnis, V., and Sharpe, P.T. (1999). Fgf-8 determines rostral-caudal polarity in the first branchial arch. *Development* **126**, 51–61
12. Dolle, P., Izpisua-Belmonte, J.C., Brown, J.M., Tickle, C., and Duboule, D. (1991). HOX-4 genes and the morphogenesis of mammalian genitalia. *Genes Dev.* **5**, 1767–1767
13. Yamaguchi, T.P., Bradley, A., McMahon, A.P., and Jones, S. (1999). A wnt5a pathway underlies outgrowth of multiple structures in the vertebrate embryo. *Development* **126**, 1211–1223
14. Duboule, D. (1993). The function of Hox genes in the morphogenesis of the vertebrate limb. *Ann. Genet.* **36**, 24–29
15. Haraguchi, R., Suzuki, K., Murakami, R., Sakai, M., Kamikawa, M., Kengaku, M., Sekine, K., Kawano, H., Kato, S., Ueno, N. *et al.* (2000). Molecular analysis of external genitalia formation: the role of fibroblast growth factor (Fgf) genes during genital tubercle formation. *Development* **127**, 2471–2479
16. Haraguchi, R., Mo, R., Hui, C., Motoyama, J., Makino, S., Shiroishi, T., Gaffield, W., and Yamada, G. (2001). Unique functions of Sonic hedgehog signaling during external genitalia development. *Development* **128**, 4241–4250
17. Suzuki, K., Bachiller, D., Chen, Y.P., Kamikawa, M., Ogi, H., Haraguchi, R., Ogino, Y., Mishina, Y., Ahn, K., Crenshaw, III E.B., and Yamada, G. (2003). Regulation of outgrowth and apoptosis for the terminal appendage, external genitalia, development by concerted functions of Bmp signaling. *Development* **131**, 6209–6220
18. Morgan, E.A., Nguyen, S.B., Scott, V., and Stadler, H.S. (2003). Loss of Bmp7 and Fgf8 signaling in Hoxa13-mutant mice causes hypospadia. *Development* **130**, 3095–3109
19. Perriton, C.L., Powles, N., Chiang, C., Maconochie, M.K., and Cohn, M.J. (2002). Sonic hedgehog signaling from the urethral epithelium controls external genital development. *Dev. Biol.* **247**, 26–46
20. Ogino, Y., Katoh, H., and Yamada, G. (2004). Androgen dependent development of a modified anal fin, gonopodium, as a model to understand the mechanism of secondary sexual character expression in vertebrates. *FEBS Lett.* **575**, 119–126