Is hypospadias a genetic, endocrine or environmental disease, or still an unexplained malformation?

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Introduction

Hypospadias is the most frequent genital malformation in the male newborn and results from an abnormal penile and urethral development. This process requires a correct genetic programme, time- and space-adapted cellular differentiation, complex tissue interactions, and hormonal mediation through enzymatic activities and hormonal transduction signals. Any disturbance in these regulations may induce a defect in the virilization of the external genitalia and hypospadias. This malformation thus appears to be at the crossroads of various mechanisms implicating genetic and environmental factors. The genes of penile development (HOX, FGF, Shh) and testicular determination (WT1, SRY) and those regulating the synthesis [luteinizing hormone (LH) receptor] and action of androgen (5a reductase, androgen receptor) can cause hypospadias if altered. Several chromosomal abnormalities and malformative syndromes include hypospadias, from anterior to penoscrotal forms. More recently, CXorf6 and ATF3 have been reported to be involved. Besides these genomic and hormonal factors, multiple substances found in the environment can also potentially interfere with male genital development because of their similarity to hormones. The proportion of hypospadias cases for which an aetiology is detected varies with the authors but it nevertheless remains low, especially for less severe cases. An interaction between genetic background and environment is likely.

Summary

Hypospadias is one of the most frequent genital malformations in the male newborn and results from an abnormal penile and urethral development. This process requires a correct genetic programme, time- and space-adapted cellular differentiation, complex tissue interactions, and hormonal mediation through enzymatic activities and hormonal transduction signals. Any disturbance in these regulations may induce a defect in the virilization of the external genitalia and hypospadias. This malformation thus appears to be at the crossroads of various mechanisms implicating genetic and environmental factors. The genes of penile development (HOX, FGF, Shh) and testicular determination (WT1, SRY) and those regulating the synthesis [luteinizing hormone (LH) receptor] and action of androgen (5a reductase, androgen receptor) can cause hypospadias if altered. Several chromosomal abnormalities and malformative syndromes include hypospadias, from anterior to penoscrotal forms. More recently, CXorf6 and ATF3 have been reported to be involved. Besides these genomic and hormonal factors, multiple substances found in the environment can also potentially interfere with male genital development because of their similarity to hormones. The proportion of hypospadias cases for which an aetiology is detected varies with the authors but it nevertheless remains low, especially for less severe cases. An interaction between genetic background and environment is likely.

Keywords:
aetiology, androgen, child, environment, genetics, hypospadias, receptors, review, sex determination, sex differentiation disorders

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androgens is crucial, especially during the first trimester of pregnancy, but any environmental factor with anticholesterol activity can alter the complex regulation of male sex differentiation during foetal life.

Hypospadias thus appears at the crossroads of genetic, endocrine and environmental mechanisms. We here propose to review these mechanisms separately, as they may interact or remain independent (Table 1).

Genetics of hypospadias

Genetic factors play a crucial role in the occurrence of this early developmental defect, in both the isolated (non-syndromic) and syndromic forms. Mutations in the genes affecting penile development and those implicated in the determination of male gonad and the biosynthesis or cell action of androgens have been identified in various forms of hypospadias.

Arguments for a genetic aetiology of hypospadias

Familial clustering, defined as patients with one or more first-, second- or third-degree relatives also affected with hypospadias, is seen in about 10% of cases (Chen & Woolley, 1971; Czeizel et al., 1979; Kallen et al., 1986; Fredell et al., 2002). The recurrence risk in the male siblings of an affected patient is about 15% and, conversely, the incidence in fathers of a child with hypospadias is 7% (Bauer et al., 1979; Stoll et al., 1990; Asklund et al., 2007). The risk of recurrence depends on the severity of the hypospadias and the more proximal the malformation, the higher the risk is for the next male sibling (Bauer et al., 1979). Segregation analyses have suggested that hypospadias might be due to monogenic effects in a small proportion of families, whereas a multifactorial mode of inheritance is assumed to be more likely in the majority of families (Harris & Beaty, 1993; Fredell et al., 2002).

Genes coding for non-endocrine-related morphogenetic factors

These genes are in fact implicated in the development of the phallus:

1. **Homeobox genes (HOX).** HOXA and HOXD genes are expressed in the foetal urogenital structures. Knock-out of these genes in mice induces a malformation in the external genitalia: loss of function in both HOXA13 genes induces an agenesis of the genital tubercle, and heterozygosity is associated with a defect in penile development and patterning (Morgan et al., 2003). Similarly, mutations of HomeoboxA3 (HOXA13) have been reported in humans with hand-foot-genital syndrome (HFGS), in which small hands, malformed thumbs with flat thenar eminence, small big toe and short first metacarpal and phalanx are associated with genital abnormalities, including hypospadias in males (Mortlock & Innis, 1997; Frisen et al., 2003). HOXA13 is essential for the normal expression of fibroblast growth factor (FGF) 8 and bone morphogenetic protein 7 in the developing urethral epithelium in mice. It also acts in androgen receptor expression and mediates glans vascularization (Mouriquand & Mure, 2001).

2. **FGF genes** also participate in the development of genital structures in mice (Petiot et al., 2005) and knock-out of FGF10 is associated with hypospadias (Yucel et al., 2004). In humans, the FGF family, especially FGF8,
FGF10 and FGFR2, is suspected to increase the risk of hypospadias (Beleza-Meireles et al., 2007).

3 Other genes are implicated in the interactions between mesenchyme and urothelium. Sonic Hedgehog (Shh) in mice is expressed in the endodermally derived urethral plate epithelium situated along the ventral side of the genital tubercle and is required for outgrowth and patterning of the genital tubercle (Digilio et al., 2003; Yucel et al., 2004). Mice with a targeted deletion of Shh have penile and clitoral agenesis, consistent with the crucial role of Shh in genital development (Haraguchi et al., 2001; Perriton et al., 2002). No mutations have yet been reported in children with hypospadias.

Genes or chromosomal aberrations leading to testicular dysgenesis

Severe abnormalities in testis development classically cause complete (pure) gonadal dysgenesis (Swyer syndrome) with marked underandrogenization and persistent Mullerian structures. However, gonadal dysgenesis can be viewed as a spectrum of disorders, with partial forms associated with normal Mullerian regression and varying degrees of testicular descent and external malformation, such as hypospadias. Thus, milder loss of function mutations in established testis determining/promoting factors can all present with hypospadias.

Heterozygous mutations of WT1 (Wilms Tumour 1 gene) are associated with severe hypospadias and other genital abnormalities. In humans and mice, WT1 is implicated in male gonadal determination and its knock-out in mice induces bilateral renal agenesis, anorchia and defective genital tubercle development (van Heyningen et al., 1990; Pritchard-Jones et al., 1990; Pelletier et al., 1991a,b; Shimamura et al., 1997; Gao et al., 2006; Kohler et al., 2007). In humans, its mutations are associated with the syndromes described below (Kaltenis et al., 2004).

Mutations in steroidogenic factor 1 (SF1) have yet to be identified as causes of isolated hypospadias.

SOX9, DMRT1 and GATA4 encode transcription factors acting immediately before the differentiation of the gonad into testis. Mutations of these genes may be associated with male disorders of sex differentiation (DSD), including severe hypospadias, often associated with testicular dysgenesis (Huang et al., 1999; Wang et al., 2004; Leipoldt et al., 2007; Maciel-Guerra et al., 2008). SOX9 may also be duplicated on a rearranged chromosome 17, which could explain the occurrence of penoscrotal hypospadias in patients with mosaicism 46,XX and 46,XX d17 (Huang et al., 1999). Last, the observation of 46,XX male hypospadiac patients with no detectable SRY or SOX9 suggests the existence of other virilizing genes.

Gonosomal abnormalities are also detected in about 7% of patients with hypospadias (Moreno-García & Miranda, 2002). They include Klinefelter’s syndrome, 47,XXY (Moriiyama et al., 1988), 48,XXYY (Neugebauer et al., 1991) and various mosaicisms, e.g. 45,X/46,XY, which is a relatively common chromosomal abnormality known as mixed gonadal dysgenesis (Telfi et al., 1999), 45,X/46,XYq-. (Mailhes et al., 1979), 45,X/46,X, idic(Yp) (Raff et al., 2000), 45,X/69,XXY (Quigley et al., 2005). Abnormal genital development in these patients may be related to a dosage effect of the SRY gene (Sinisi et al., 2003).

Genes driving to isolated androgen synthesis or action defects

Genes driving to androgen synthesis defects

Whereas early genital development is controlled by a genetic program that operates prior to the production of steroid hormones, the second phase of penile development requires exposure to an androgen, either testosterone or DHT (Abney, 1999). Androgenic steroids, synthesized by the Leydig cells of the testes, are first seen just prior to the onset of androgen-induced genital differentiation. 5α-reductase type 2, an enzyme that converts testosterone to 5α-DHT, is highly expressed in the mesenchymal stroma surrounding the urethra (Kim et al., 2002). Mutations of 5α-reductase have been identified in severe variants of hypospadias in combination with other genital abnormalities (Ocal et al., 2002; Wang et al., 2004; Nicoletti et al., 2005). Conversely, the V89 allele in the SRD5A2 gene reduces the risk of hypospadias (Thai et al., 2005).

Other defects in the androgen synthesis pathway are secondary to an abnormality in Leydig cell development or an enzymatic defect in testosterone synthesis. These defects are characterized by low concentrations of plasma testosterone in the neonatal period.

- Mutations of the LH receptor (Leydig cells hypoplasia) are associated with hypospadias and micropenis. Testosterone secretion is dramatically low and contrasts with higher values of LH in early life (Huhtaniemi & Alevizaki, 2006).

- A deficit in 3β-hydroxysteroid-deshydrogenase induces a testicular and adrenal block which is autosomal and recessive. Diagnosis is based on the association of hypospadias and adrenal insufficiency and an increase in dehydroepiandrosterone (DHEA) and 17-hydroxyprogrenolone (Perrone et al., 1985; Codner et al., 2004).

- A defect in 17-hydroxysteroid-reductase induces a testicular block (autosomal and recessive) by altering the final step in testosterone synthesis. A marked increase in Δ4 androstenedione with low testosterone despite an HCG test allows the diagnosis. If the diagnosis is missed in the neonatal period, the patient presents with viriliza-
tion at the time of puberty (Mendonca et al., 2000; Lee et al., 2007).

- Rare defects are also described in steroidogenic acute regulatory protein (STAR) and CYP11A1 (P450scc), which usually cause a salt-losing adrenal phenotype and more severe underandrogenization, although in rare cases hypospadias may theoretically be the presenting feature of these conditions. Combined 17a-hydroxylase/17,20-lyase deficiency (or isolated 17,20-lyase deficiency) or P450 oxidoreductase deficiency can present with varying degrees of hypospadias or micropenis.

Overall, endocrine investigation confirms the aetiology of hypospadias as a defect in androgen synthesis in 20% of cases (Rey et al., 2005).

Genes driving to androgen action defects

Mutations in the androgen receptor gene (AR) have also been found in patients with severe forms of hypospadias (Sultan et al., 2001), e.g. perineo-scrotal hypospadias (Kaspar et al., 1993; Holterhus et al., 2005), hypospadias associated with cryptorchidism (Hiort et al., 1994), and micropenis (Sultan et al., 1993; Li et al., 2004). The phenotype is variable in partial androgen insensitivity syndrome (Sultan et al., 1993; Deeb et al., 2005), and a mutation in one of the eight exons is found in less than 10% of cases. Similarly, AR is expressed in the epithelium of the urethra (Kim et al., 2002), as is the FGF receptor 2 gene (FGF2), a transcriptional target of AR (Petiot et al., 2005).

New genes of hypospadias

The ATF3 gene is a suspected aetiology of hypospadias for several reasons. First, microarray analysis of tissues from normal and hypospadiac patients revealed upregulation of this gene in hypospadias (Wang et al., 2007). Second, using a mouse model of steroid hormone-dependent genital tubercle development, ATF3 messenger RNA levels were found to be elevated in all oestrogen-exposed foetal genital tubercles compared with controls (Liu et al., 2006). Third, immunohistochemical analysis on human foreskin showed 86% of the hypospadias samples to be positive for expression of ATF3 whereas only 13% of those from normal penises were positive (Liu et al., 2005). In addition, ATF3 expression and promoter activity in human foreskin fibroblasts were responsive to in vitro exposure to ethinyl oestradiol (Liu et al., 2005). Finally, ATF3 is implicated in cell cycle suppression and its upregulation may interfere with urethra formation (Willingham & Baskin, 2007).

Another of the most recently identified candidate genes in the development of the male genitalia is CXorf6 (formerly F18). This gene, discovered in the course of identifying the gene responsible for X-linked myotubular myopathy, MTM1, maps to proximal Xq28 (Laporte et al., 1997a,b). CXorf6 is expressed ubiquitously, but its expression is especially high in skeletal muscle, brain and heart. It is also hypothesized to be implicated in male genital development. Indeed, myopathic individuals with intragenic mutations of MTM1 have normal sexual development whereas those with microdeletions of MTM1 extending to the CXorf6 locus have abnormal genitalia (Hu et al., 1996; Bartsch et al., 1999; Biancalana et al., 2003). Subsequent studies have demonstrated that CXorf6 is mutated in 46,XY disorders of sexual development (46,XY DSD): Fukami et al. (2006) recently identified three nonsense mutations in four individuals with 46,XY DSD including micropenis, bifid scrotum and penoscrotal hypospadias. The exact mechanism by which CXorf6 induces hypospadias remains to be established but CXorf6 augments testosterone production and contains the SF1 target sequence (Fukami et al., 2008).

Overall, a genetic basis of hypospadias is likely when the defect is associated with an inactivating mutation of the genes involved in penile development or the hypothalamo–pituitary–testicular axis, including testicular dysgenesis, defect in the synthesis or the molecular action of testosterone (5αR, AR), and a chromosomal abnormality.

Environmental factors affecting gene expression or endocrine pathways

A ‘web of arguments’ for an environmental contribution

1. Hypospadias, whether associated or not with micropenis, has been reported in numerous wildlife species when the habitat is particularly contaminated by pesticides (Hayes et al., 2002).

2. Male rat pups exposed to DES during gestation (at concentrations similar to those measured in first-trimester human foetal tissues) developed hypospadias. Hypospadias in male rodents was found after maternal treatment with vinclozolin (dose–response effect) (Gray et al., 2001), and similar findings were recorded for prenatal exposure to polychlorinated biphenyls (PCB), phthalates and dioxin (Baskin et al., 2001; Gray et al., 2001; Fisher et al., 2003).

3. Over the last 30 years, male reproductive health has been marked by a deterioration in sperm count and an increasing number of undescended testes, testicular cancers and hypospadias (Czeizel et al., 1986; Paolozzi et al., 1997; Canning, 1999). This phenomenon has raised some concerns regarding environmental chemicals, such as industrial and agricultural by-products.

4. In a recent epidemiologic study, we observed a 4% incidence of hypospadias in neonates whose mothers were treated with DES during pregnancy. This incidence was
8.4% in the neonates of the second generation and suggests a transgenerational effect [Sultan C., personal data; (Klip et al., 2002)].

**Endocrine environmental disruptors**

Multiple substances found in the environment can potentially interfere with male genital development because of their similarity to hormones. Humans are in constant contact with these substances (Brock et al., 1998; Gray et al., 2001) as they are found in water, soil, food and air (Restrepo et al., 1990a,b). Although there is a long list of suspicious substances contained in herbicides, fungicides, insecticides, and industrial by-products and end-products (plasticizers, cosmetics, paints, etc), none of them has been clearly identified as causing the hypospadiac penis (Restrepo et al., 1990a,b; Brock et al., 1998; Zumbado et al., 2005). These pollutants enter the body by ingestion, inhalation, or absorption or they may be conveyed through the placenta. Individual exposure varies with diet, lifestyle and workplace. As most of these chemicals use the same pathways as natural hormones, they have been named xenooestrogens and/or environmental disrupting chemicals (EDC). The molecular actions of xenooestrogens are listed in Table 2. Xenooestrogens have both oestrogenic and anti-androgenic actions and compete with natural androgens for the ligand-binding domain (LBD) of the AR (Paris et al., 2002). The conformation of the LBD is therefore changed and the nuclear transfer of AR is altered, as are the transcriptional co-activators and the expression of the androgen-specific gene.

To date, three epidemiologic studies have reported the possible relationship between exposure to pesticides and hypospadias. Kristensen found a moderate increase in the odds ratio (OR) for hypospadias in individuals exposed to farm chemicals (OR = 1.5%). Weidner observed that maternal farming or gardening led to a low risk of hypospadias (OR = 1.27), and Longnecker found no significant risk of hypospadias (OR = 1.2) when mothers were exposed to DTT. The critical level of exposure to EDCs was not assessed in any of these epidemiologic studies (Kristensen et al., 1997; Weidner et al., 1999; Longnecker et al., 2002). Residence in the vicinity of hazardous waste-disposal sites has been associated with a high incidence of hypospadias (Dolk et al., 1998). Similarly, an increased rate of hypospadias was reported in boys from parents exposed to dioxin after the Seveso industrial accident (Mastroiacovo et al., 1988). A vegetarian diet in pregnant women is reported to carry a significant risk of hypospadias (Fig. 1, OR = 4.99) (North & Golding, 2000).

**Multifactorial aetiology involving the interaction of environmental factors and genetic polymorphisms**

Three risk factors of hypospadias illustrate the multifactorial aspect of this malformation.

Low birth weight, small head circumference and birth length are also associated with increased risk of hypospadias. Studies that controlled for length of gestation found that the association remained, indicating that at least in part it may be related to growth retardation [×10 according some authors (Hussain et al., 2002)]. This intra-uterine growth retardation may be related to a dysfunction of the placenta, which is at the crossroads of maternal and foetal genetics and environmental influences (Brouwers et al., 2007).

A number of studies have shown an association between hypospadias and a prolonged time to pregnancy (mother older than 35 years: 50% increase in the risk of hypospadias) or subfertility (Sweet et al., 1974; Czeizel, 1985) (Czeizel & Toth, 1990). Several authors have even hypothesized a central role of subfertility in the aetiology of this defect (Wennerholm et al., 2000). Low sperm motility was noted in fathers of boys with hypospadias in one study (Fritz & Czeizel, 1996) but not in two others (Sweet et al., 1974). However, an association with assisted reproductive technology has been found, particularly with intracytoplasmic sperm injection (ICSI) (Wennerholm et al., 2000; Lie et al., 2005). The subfertility of parents and an alteration in the spermogram, both of which are associated with hypospadias, may themselves be dependent on genetic, endocrine and environmental factors (Wennerholm et al., 2000; Ericson & Kallen, 2001).

**Interactions between genetics and environment**

Beleza-Meireles et al. (2006) reported that polymorphisms of ERβ2 may increase susceptibility to xenooestrogens and increase the risk of hypospadias (10%). Similarly, Baskin (Liu et al., 2005, 2007; Wang et al., 2007) demonstrated that the expression of ATF3 (a CREB family

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**Table 2** Molecular actions of xenooestrogens

| Binding of ERα/ERβ nuclear receptor and transcription of activation (or repression) of specific gene expression |
| Non-genomic actions mediated by a plasma membrane oestrogen receptor |
| Induction of more potent oestrogenic metabolites |
| Reduced binding of endogenous oestrogens to sex hormone-binding globulin |
| Inhibition of transcription of androgen-dependent genes |
| Potential additive effects |
| Oncogenic effects |

transcription factor) was oestrogen-dependent in human and animal models. Thus, susceptibility to environmental factors might depend not only on the endocrine disruptor itself, but also on individual sensitivity, which is modulated by genetic background, including polymorphisms.

Isolated hypospadias vs. syndromic hypospadias

Autosomal dominant forms of syndromic hypospadias are caused by mutations in genes involved in early genital development. Hypospadias may also be associated with various chromosomal abnormalities, including gonosomal mosaicism (exposed in previous sections) and autosomal deletions.

Almost 200 syndromes have been associated with hypospadias. For example, Smith-Lemli-Opitz (SLO) syndrome, which includes mental retardation, microcephaly, facial dysmorphism, 2–3 syndactyly of the toes and, in males, hypospadias and a hypoplastic scrotum, is caused by a defect in sterol biosynthesis. SLO syndrome is because of recessive mutations of the DHCR7 gene coding for 7-dehydrocholesterol reductase, localized on chromosome 11q13 (Ryan et al., 1998; Mnayer et al., 2006).

Wilms’ tumour, aniridia, genital abnormalities, and growth and mental retardation (WAGR) syndrome is considered to be a contiguous gene syndrome because of a deletion involving band 11p13 (Kaltenis et al., 2004). The WT1 gene, which maps within the deleted WAGR region and encodes a zinc-finger transcription factor involved in the development of the kidneys and gonads, may be responsible for the genital abnormalities observed in this syndrome (Bickmore et al., 1989; van Heyningen et al., 1990). WT1 point mutations may also result in urogenital abnormalities, depending on the nature and location of the mutation: Denys-Drash syndrome (mesangial sclerosis, gonadal dysgenesis and high risk of Wilms’ tumours) (Pelletier et al., 1991a,b; Ogawa et al., 1993), Frasier syndrome (focal glomerular sclerosis, gonadal dysgenesis (Klamt et al., 1998), or severe hypospadias and Wilms’ tumour (Kohler et al., 1999).

Other autosomal abnormalities have also been reported with syndromic hypospadias. For example, deletion syndromes with hypospadias have been observed on chromosomes 3q29 (Willatt et al., 2005), 4p (Balci et al., 2006), 9p23 (Ogata et al., 1997), 9q34.3 (Iwakoshi et al., 2004), 10q26 (Ogata et al., 2000) and 13q32-q34 (Bartsch et al., 1996).

Hypospadias of unknown origin

The proportion of hypospadias cases for which aetiology is detected varies according to the authors but it remains low, especially for less severe cases. For example, McPhaul (Allera et al., 1995) identified an AR mutation in only one case of nine isolated hypospadias, and Marcelli in one of 40 cases (Sutherland et al., 1996). In a series of 90 patients, Wang et al. (2004) described a mutation of AR in no more than two cases, a mutation of 5αR2 in two cases and three mutations of WT1. The proportion of hypospadias with an identified endocrine disorder, even if significant, remains low: Cassorla (Rey et al., 2005) identified hormonal abnormalities in 13 cases of 61 isolated hypospadias (20% of patients). The occurrence of hypospadias thus remains unexplained in most cases. A multifactorial explanation and the implication of unknown genes or unidentified environmental factors remain possible.

Conclusion

Is hypospadias a genetic disease?

Yes, especially in familial and syndromic forms, and hypospadias due to abnormal genital development (phallic or testicular dysgenesis) or associated with a defect of the androgens pathway (20% of the cases).

Is hypospadias an environmental disease?
Probably yes, especially when the hormonal work-up is normal or the parents are known to live or work in an at-risk environment. But a definitive demonstration remains to be made!

Is hypospadias still an unexplained malformation?
Yes, in most cases, especially the less severe ones...

References


Recent trends in the aetiology of hypospadias

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ratio of WT1 +/− Kts splice isoforms. Human Molecular Genetics 7, 709–714.


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Sutherland, R. W., Wiener, J. S., Hicks, J. P., Marcelli, M.,
Gonzales, E. T., Jr, Roth, D. R. & Lamb, D. J. (1996) Andro-
gen receptor gene mutations are rarely associated with iso-
Study of the incidence of hypospadias in Rochester, Minne-
sota, 1940–1970, and a case–control comparison of possible
Telvi, L., Lebbar, A., Del Pino, O., Barbet, J. P. & Chaussain, J.
L. (1999) 45,X/46,XY mosaicism: report of 27 cases. Pedi-
atics 104, 304–308.
Thai, H. T., Kalbasi, M., Lagerstedt, K., Frisen, L., Kockum, I.
polymorphism in the 5-alpha-reductase gene confers a
reduced risk for hypospadias. Journal of Clinical Endocrinol-
ogy and Metabolism 90, 6695–6698.
Wang, Y., Li, Q., Xu, J., Liu, Q., Wang, W., Lin, Y., Ma, F.,
candidate genes in Chinese patients with hypospadias. Euro-
Wang, Z., Liu, B. C., Lin, G. T., Lin, C. S., Lue, T. F., Willing-
responsive genes in hypospadias: microarray analysis. Journal
of Urology 177, 1939–1946.
Weidner, I. S., Moller, H., Jensen, T. K. & Skakkebaek, N. E.
Wennerholm, U. B., Bergh, C., Hamberger, L., Lundin, K.,
congenital malformations in children born after icsi. Human
Reproduction 15, 944–948.
Willatt, L., Cox, J., Barber, J., Cabanas, E. D., Collins, A.,
Donnai, D. et al. (2005) 3q29 microdeletion syndrome:
Clinical and molecular characterization of a new syndrome.
American Journal of Human Genetics 77, 154–160.
Willingham, E. & Baskin, L. S. (2007) Candidate genes and
their response to environmental agents in the etiology of
Yucel, S., Liu, W., Cordero, D., Donjacour, A., Cunha, G. &
growth factor-10 mutant, sonic hedge hog mutant and
androgen receptor mutant mouse genital tubercle. Advances
in Experimental Medicine and Biology 545, 123–148.
Zumbado, M., Goethals, M., Alvarez-Leon, E. E., Luzardo, O.
(2005) Inadvertent exposure to organochlorine pesticides
DDT and derivatives in people from the Canary Islands