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Androgen Insensitivity Syndrome: Somatic Mosaicism of the Androgen Receptor in Seven Families and Consequences for Sex Assignment and Genetic Counseling

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Androgen insensitivity syndrome (AIS) is caused by numerous mutations of the androgen receptor (AR) gene. The phenotype may range from partial AIS (PAIS) with ambiguous genitalia to complete AIS (CAIS) with female genitalia. In 70% of the cases, AR mutations are transmitted in an X-linked recessive manner through the carrier mothers, but in 30%, the mutations arise *de novo*. When *de novo* mutations occur after the zygotic stage, they result in somatic mosaicisms, which are an important consideration for both virilization in later life—because both mutant and wild-type receptors are expressed—and genetic counseling. We report here six patients with AIS due to somatic mutations of the AR and one mother with somatic mosaicism who transmitted the mutation twice. Of the four patients with PAIS, three presented spontaneous or induced virilization at birth or puberty. These cases underline the crucial role of the remnant wild-type AR for virilization because the same mutations, when they are inherited, lead to CAIS. We also report two novel mutations of the AR, with somatic mosaicism, detected in patients with CAIS. Thus, the remnant wild-type receptor does not always lead to virilization. In one of these patients, a high ratio of wild-type to mutant AR expression was found in the gonads and genital skin fibroblasts. Although no prenatal virilization occurred, the possibility of virilization at puberty could not be excluded, and early gonadectomy was performed. A seventh patient had a CAIS with a novel germline AR mutation. The mutation was inherited from the mother, in whom mosaicism was detected in blood and who transmitted the mutation to a second, XX, offspring. The detection of somatic AR mutations is particularly important for the clinical management and genetic counseling of patients with AIS. Before definite sex assignment, a testosterone treatment trial should be performed in all patients with PAIS, but it becomes crucial when an AR mosaicism has been detected. In patients with CAIS or severe PAIS raised as female, there is no consensus about when (early childhood or puberty) gonadectomy should be performed. When somatic AR mutations are detected, however, gonadectomy should be performed earlier because of the risk of virilization during puberty. When a germline *de novo* mutation is identified in the index case, the risk of transmission to a second child due to a possible germ cell mosaicism in the mother cannot be excluded. However, given the high number of AR *de novo* mutations and the rarity of such reports, this risk appears to be very low. (*J Clin Endocrinol Metab* 90: 106–111, 2005)

ANDROGEN INSENSITIVITY SYNDROME (AIS) is an X-linked disorder caused by mutations of the androgen receptor (AR) gene (1, 2). So far, over 300 mutations of the AR gene have been identified worldwide in patients with AIS (AR database at http://www.mcgill.ca/androgendb/) (3). In 70% of the cases, the mutations are germline mutations and are transmitted in an X-linked manner through the carrier mothers. In about 30% of the cases, the mutation appears *de novo* in the patient. *De novo* mutations may originate in the mother either in a single germ cell or as a germ cell mosaicism and then present as hemizygous germline mutations in the 46,XY offspring. If they arise in the index case after the zygotic stage, *de novo* mutations present as a somatic mosaicism (4). In somatic mosaicism, different proportions of cells containing mutant or wild-type protein are present in various tissues of the same individual. The presence of somatic mosaicism of the AR has an important impact for patients with AIS because further virilization is possible after birth.

Patients with AR mutations may present a genital phenotype ranging from ambiguous genitalia in partial AIS (PAIS) to female genitalia in complete AIS (CAIS) (1). In a proportion of these patients, mostly with PAIS, wide phenotypic variability has been found. The different phenotypes in pa-

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Abbreviations: AIS, Androgen insensitivity syndrome; AR, androgen receptor; Bmax, maximal binding capacity; CAIS, complete AIS; GSF, genital skin fibroblast; K_d, equilibrium dissociation constant; PAIS, partial AIS.

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tients with the same mutation might develop through factors that modify AR action (1). Individual differences in androgen levels and the timing of its production during the critical period of genital organogenesis are among the factors likely to be involved. In line with this is the report of different phenotypic expressions in two siblings with the same AR mutation but different expression of the 5α-reductase 2 gene in genital skin fibroblasts (GSFs) (5). Besides the role of the ligands themselves, somatic mosaicism of an AR mutation has been reported to cause genotype-phenotype discrepancies in AIS (6, 7).

Because AIS is the major genetic cause of male pseudohermaphroditism, an understanding of its transmission and outcome is indispensable for clinical decision making, particularly because it has an important impact on gender identity and the patient's later sex life (8). A thorough family history is important for genetic counseling. In general, sex of rearing is assigned on the basis of genital phenotype, hormonal data, clinical response to a testosterone treatment trial, the feasibility of reconstructive surgery, and molecular studies of the AR gene. Sex assignment at birth can be difficult in patients with PAIS. In these patients, special attention should be paid to somatic mutations of the AR because a certain quantity of the wild-type receptor is present and likely to be functionally active. Subsequently, with increasing androgen levels during puberty, virilization becomes theoretically possible. So far, only five patients with somatic mutations of the AR have been described (6, 9, 10). We report the phenotype at birth, clinical follow-up, genotype, and genetic counseling of seven families with somatic AR mutations (two new mutations) from a European screening center for the AR gene. Furthermore, we present data on significant virilization during puberty in two patients with PAIS due to AR mosaicism.

Patients and Methods

Patients

We reviewed the phenotypes of six patients with AIS due to somatic mutations of the AR, as well as those of their available family members. The records of all patients were analyzed for developmental abnormalities of the external and internal genitalia, hormonal data, and sex assignment. Informed consent for the genetic studies was obtained from all parents or patients. A summary of the patients' phenotypes, hormonal data at birth and puberty, and genotypes are presented in Table 1.

Patient 1 was born in the south of Italy. He presented ambiguous genitalia with a 1-cm phallus, severe hypospadias, and palpable gonads. Male sex assignment was made at birth, but the sex was changed to female at 18 months. At 17 yr, the patient was referred to the endocrine clinic in Naples, Italy, because of an absence of menarche. At that time, normal breast development was noted, as was a 6-cm phallus and a P4 pubic hair stage. Patient 2 was born in Russia and presented ambiguous genitalia and severe hypospadias at birth. Male sex assignment was made. At 14 yr, the patient was seen for the first time in the Russian Endocrine Center, Moscow. A 4.5-cm micropenis, scarce pubic hair, and severe gynecomastia were observed. Testosterone treatment improved virilization. Testicular volumes were normal with 15 ml. Patient 3 presented ambiguous genitalia at birth, with a 1.8-cm phallus, severe hypospadias, and palpable gonads. A good clinical response to a testosterone treatment trial was seen, with penile growth to 4.5 cm, so male sex assignment could be made. A somatic mutation, R840H, was detected. Patient 4 presented ambiguous genitalia at birth, with a 1.5-cm phallus, severe hypospadias, and palpable gonads. After a human chorionic gonadotropin stimulation test, a normal rise in testosterone (4.75

TABLE 1. Main clinical and hormonal data and genotype of the patients

Patient no.	Diagnosis	Sex assignment	Phenotype	Testosterone (T) [ng/ml (nmol/liter)]	AR mutation
1	PAIS	Male, then changed to female at 18 months	At 18 months, micropenis 1 cm, penoscrotal hypospadias, palpable gonads; at 17 yr, phallus 6 cm, penoscrotal hypospadias, breast B4, pubic hair P4	At 18 months, HCG test: T = 0.1 (0.37) to 5 (17.35); at 17 yr, T = 8.70 (30.19)	W751stop
2	PAIS	Male	At birth, micropenis, penoscrotal hypospadias, palpable gonads; at 14 yr, phallus 4.5 cm, breast B3, pubic hair P3	At 14 yr, T = 1.53 (5.30)	M895T
3	PAIS	Male	At birth, micropenis 1.8 cm, penoscrotal hypospadias, palpable gonads; after 2 × 50 mg testosterone: phallus growth from 1.8 to 4.5 cm	At birth, HCG test: T = 0.25 (0.87) to 3.5 (12.15)	R840H
4	PAIS	Female	At birth, micropenis 1.5 cm, perineal hypospadias, bifid scrotum, palpable gonad	At birth, HCG test: T = 0.05 (0.17) to 4.75 (16.50)	P766S
5	CAIS	Female	Normal female (at birth), palpable gonads	At birth, HCG test: T = 0.2 (0.69) to 5.1 (17.70)	F770X[a] (2-bp mutation, TC/AA at positions 2671–2672)
6	CAIS	Female	Normal female (at birth), palpable gonads	At birth, basal T = 1.25 (4.34)	Splice mutation +1 donor site intron 7 (see Fig. 1)
7	CAIS	Female	At 15 yr, normal female, no palpable gonads, pubic hair P2, breast B4	At birth, basal T = 5.7 (19.78)	2-bp (GT) deletion at position 2349–2354 (exon 6) leading to a frameshift from residue 785 and a premature stop codon at 827[a]

Patients 1–6 all presented somatic mutation. Patient 7 had a germline mutation. Her mother had somatic mosaicism and transmitted the mutation twice (see text). HCG, Human chorionic gonadotropin.

[a] Novel AR mutations.

ng/ml) without growth of the micropenis was noted. Genitography revealed a short blind vagina. Subsequently, female sex assignment was made. Patient 5 showed normal female external genitalia with bilateral inguinal gonads at birth along with normal testosterone level. Patient 6 showed clinical and hormonal features similar to those of patient 5. Patient 7 presented female genitalia at birth. When she was 15 yr old, CAIS was assumed because of an absence of menarche along with normal breast development (B4), very scarce pubic hair, absence of uterus, and a 46,XY karyotype.

Molecular analysis of the AR gene

DNA analysis was performed as previously described (11). Briefly, genomic DNA was isolated from peripheral blood leukocytes using kits from Qiagen (Courtaboeuf, France). Exons 2–8 of the AR gene and flanking intron sequences were amplified using the Taq PCR Master Mix Kit (Qiagen). Sequencing of the PCR products was performed using the ABI Prism Dye terminator sequencing kit and the ABI sequencer (Applied Biosystems, Courtaboeuf, France). Sequencing was repeated twice on new PCR products with antisense primers. In family 7, sequencing of peripheral blood leukocyte DNA in the mother was repeated on a second blood sample.

In patient 6, we also studied RNA extracted from GSFs. Sequencing was performed on cDNA and allowed us to characterize the consequence of the splice mutation identified on genomic DNA. Western immunoblot and AR binding experiments were performed on cultured fibroblasts from patient 6 as previously described (12).

Results

Molecular data of the patients

In patient 1, sequencing of the AR gene revealed a somatic nonsense mutation, W751X. In patient 2, a somatic mutation in exon 8 leading to a missense mutation, M895T, was detected.

In patient 3, the somatic mutation, R840H, was found. In patient 4, the P766S mutation was detected in a somatic pattern.

In patient 5, somatic mutations of two contiguous nucleotides in exon 5 were identified, which led to a previously unreported nonsense mutation, F770X. In patient 6, a G to A mutation at position +1 of the donor splice site in intron 7 was detected. The associated presence of the wild-type allele suggested a somatic mutation. RT-PCR of the patient's RNA extracted from GSFs showed two bands, confirming somatic mosaicism. Sequencing of the lower band (mutant) revealed that the mutation led to exon 7 skipping (Fig. 1). Interestingly, in RT-PCR, the intensity of the mutant band was weaker than the wild-type band, indicating a rather low quantity of the mutant RNA (data not shown). Immunoblot analysis performed on fibroblasts cultured from gonadal tissue showed the same low proportion of mutant in comparison with the wild-type protein (Fig. 1). Unfortunately, stored GSFs were lost, and analysis of protein expression in GSFs was not possible. However, the normal androgen binding capacities found by androgen binding assay, and Scatchard analysis on GSFs confirmed the preponderance of wild-type AR [maximal binding capacity (Bmax), 504 fmol/mg protein; equilibrium dissociation constant (K_d), 0.49 nM; normal range, Bmax, 450-1100 fmol/mg; K_d, 0.1–0.5 nM].

In patient 7, sequencing of the AR gene revealed a novel hemizygous germline mutation (2-bp deletion in exon 6 leading to a frameshift and premature stop codon at position 827). The healthy XX sister was found to be heterozygous for the mutation. Most interestingly, the mother presented a sequence pattern compatible with somatic mosaicism of the mutation.

Apart from the mother of patient 7, all investigated moth-

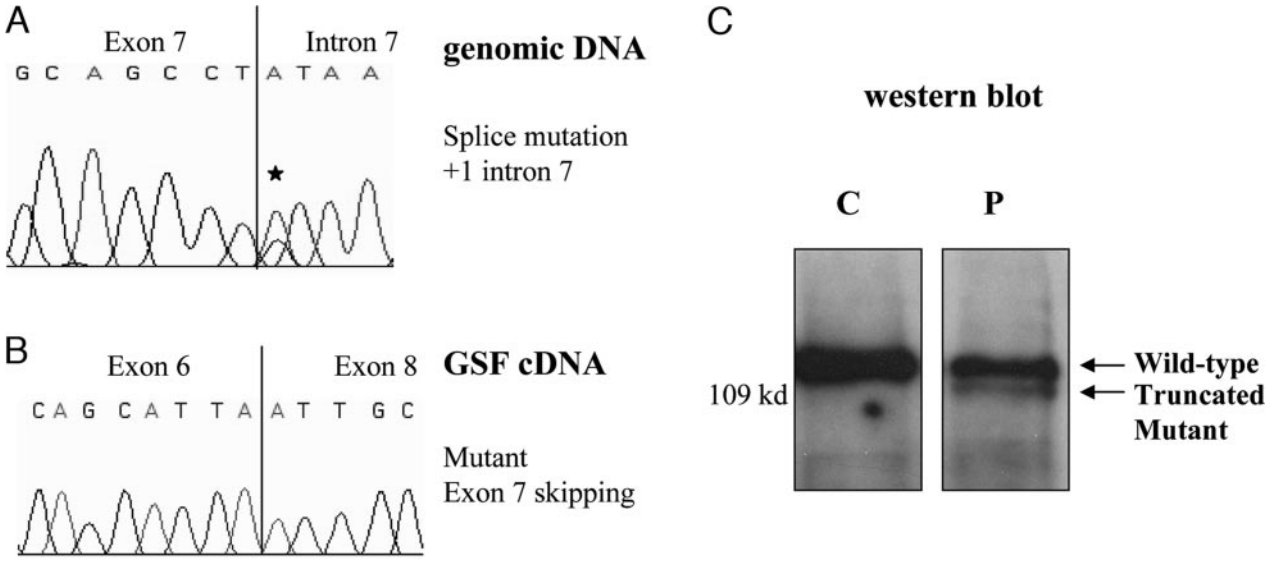

FIG. 1. Characterization of patient 6's mutation by sequencing of genomic DNA (A), sequencing of cDNA obtained from genital skin (B), and Western blot analysis of gonadal tissue (C). A, Mosaic pattern of a G to A change was found at the exon 7/intron 7 boundary in the patient's genomic DNA in blood. A similar pattern was observed in GSFs and gonads (data not shown). B, Sequencing of cDNA showed that the splice mutation was responsible for exon 7 deletion. Agarose gel electrophoresis of an exon 6 to 8 RT-PCR fragment revealed two bands corresponding to wild type (*upper band*) and mutant (*lower band*) (data not shown). Both bands were excised from gel, and DNA was purified for sequencing. Sequence of the lower, mutated fragment showed exclusion of exon 7. C, Wild-type and mutant AR proteins were detected by Western blot in the patient's gonadal tissue. It confirmed that the mutant protein was truncated (*lower band*). In addition, it showed that the amount of mutant protein was much lower than wild-type protein (C, control; P, patient). Furthermore, determination of androgen receptor binding capacity was performed in the patient's GSF and gonadal tissues (data not shown). Androgen binding properties were normal for both Bmax and K_d (see text).

ers (families 2–4 and 6) showed normal AR gene sequences, confirming that the mutation occurred *de novo* in the patients.

A summary of the patients' phenotypes, hormonal data at birth and puberty, and genotypes are presented in Table 1.

Discussion

Molecular analysis of the AR gene has been possible for the past 15 yr, but somatic mutations of the gene have only recently been reported (4, 6, 7, 9, 13). Identification of these mutations in AIS has important consequences for sex assignment because a certain amount of the functionally active wild-type AR is present and could induce virilization at puberty. Identifying the mutation as somatic can be difficult, however, because the wild-type receptor might be present only in a small number of cells. Thus, excellent sequencing techniques and wide experience in sequence interpretation are essential to detect somatic mutations. Because a somatic mosaicism will have a strong impact on management choices and genetic counseling, the confirmation of the mutation must be definitive. Thus, it is often necessary to repeat the PCR and sequencing with different primers and to analyze a second blood sample.

In this study, we report seven families with somatic mutations of the AR gene. Four patients presented at birth with ambiguous genitalia (PAIS) and three with normal female genitalia (CAIS). In the four patients with PAIS, the phenotype was in line with somatic mosaicism of the AR. In fact, the mutations in three of these patients were previously reported as germline mutations and, in this case, they led to CAIS (see the AR database at http://www.mcgill.ca/androgendb/). Thus, the degree of virilization of the external genitalia during embryonic development in our patients was likely due to the action of wild-type AR. The R840H mutation identified in patient 3, who presented with micropenis and hypospadias and was reared as male, has been described several times in PAIS patients with female sex of rearing, although phenotypic variability has been noted (1). In our patient, a testosterone treatment trial was performed after birth to evaluate the possibility of virilization under high testosterone levels. The patient showed a good penile growth response, which is consistent with the presence of a sufficient amount of wild-type receptor. In this case, male sex assignment was made because spontaneous penile growth during the pubertal testosterone rise could be expected. So far, no data have been presented from the clinical follow-up of patients with somatic AR mutations and PAIS who have reached pubertal age. We report two patients (patients 1 and 2) who showed significant virilization. In patient 2, exogenous testosterone administration was necessary to achieve sufficient virilization. These observations show that, in the presence of AR mosaicism, sufficient virilization in PAIS is possible at puberty. Holterhus *et al.* (6) have previously reported an AR somatic mutation in an adult XY woman referred at puberty and presenting with clitoral hypertrophy and pubic hair growth.

The presentation of CAIS in patients with somatic AR gene mutations showing normal female external genitalia is difficult to explain because the presence of active wild-type receptor in these patients should have led to visible prenatal virilization. However, genomic analysis is generally done in blood cells, and the cellular distribution of the mosaicism in target tissues, particularly GSFs, might be different. In this study, we performed RT-PCR and Western blot analysis of GSFs and gonadal tissue in one patient with CAIS (patient 6). Surprisingly, these tissues showed a very low proportion of the mutant receptor compared with wild type, with normal AR binding capacities in the GSFs, as well (Fig. 1). Yet the patient's CAIS phenotype was contradictory to these findings. An important point to bear in mind is that postnatal findings are not representative of the prenatal situation during organogenesis. Possibly, the number of embryonic cells with mutant AR was higher than those with wild-type AR during the crucial phase of sex differentiation. As the AR is known to be involved in cell differentiation and growth, the presence of the mutant AR could have led to a selective disadvantage of these cells, thereby causing a change in the mutant to wild-type ratio after birth (14, 15). Another explanation of the inverse mutant to wild-type ratio after birth could be the occurrence of a back mutation during organogenesis because back mutations have also been found to lead to different phenotypes in autosomal-recessive diseases, such as Fanconi anemia and Lesh-Nyhan syndrome (7, 16) (17, 18). Because the preponderance of wild-type AR raised the risk of virilization during puberty, gonadectomy was performed before puberty in this patient raised as a girl as a precautionary measure.

In family 7, a novel germline AR gene mutation was found (Table 1). Sequence analysis of the mother's DNA extracted from peripheral blood leukocytes revealed the presence of a somatic mutation (data not shown). The patient's XX sister showed a heterozygous pattern. Because the mother transmitted the mutation twice, a germ cell mosaicism can be assumed. Because the germ cells of the mother obviously could not be studied, however, a precise transmission rate could not be determined (15). So far, only one similar family, with a hemizygous mutation in the index case and a somatic and germline mosaicism in the mother, has been reported (13). Although no general conclusions can be drawn from these two cases, the identification of a somatic mosaicism in the peripheral blood leukocytes of the mother makes likely the presence of a germline mosaicism, as well, and hence a high risk of transmission of the mutation to the offspring.

As far as genetic counseling is concerned, the majority of *de novo* mutations in AIS patients are germline mutations and thus arise either from a single germ cell or a germ cell mosaicism. Apart from the two very particular cases discussed above, there is no report of a transmission to a second child, and the risk seems to be very low. It cannot be excluded, however, and in genetic counseling for *de novo* germline mutations of the AR gene, one should be cautious. Conversely, mosaicism in the index case—as for patients 1–6 of this report—indicates that the mutation was not inherited but occurred after the zygotic stage. In this case, the risk for other offspring is similar to that for the normal population. We propose in Fig. 2 a general flow sheet for genetic counseling of a *de novo* mutation in the index case.

The detection of somatic mutations of the AR gene in AIS is of great clinical relevance. Knowledge of a somatic mosaicism is indispensable for correct sex assignment at birth

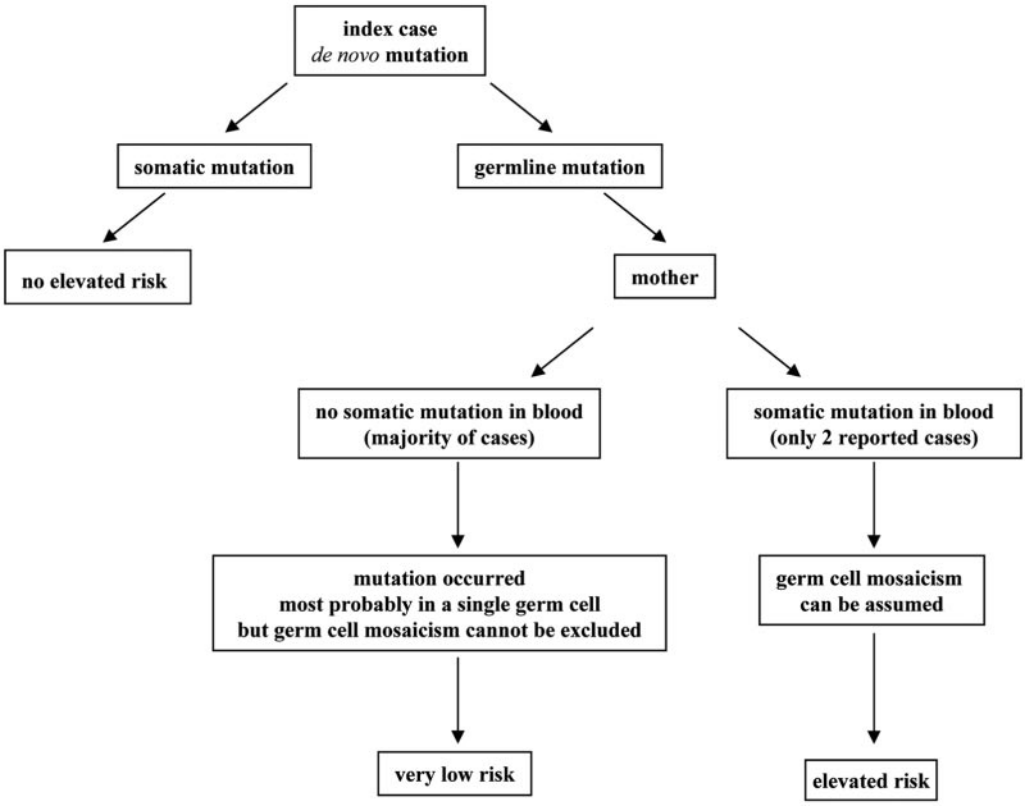

FIG. 2. Flow sheet for genetic counseling of a *de novo* mutation in the index case. The most frequent case (70%) of AR mutations inherited and transmitted in an X-linked fashion is not represented. In this situation, there is a theoretical risk of 50% for an XY offspring to be affected and for an XX offspring to be a healthy carrier. *De novo* mutations represent 30% of AR mutations, and the risk of transmission can be considered to be very low (see *Discussion*).

because the presence of a functional wild-type AR receptor can induce virilization during puberty. We suggest a testosterone treatment trial in all patients with PAIS, especially if an AR mosaicism is identified at birth. By doing so, the virilizing capacity of the newborn external genitalia under the influence of exogenous androgens can be evaluated before sex assignment. Androgen sensitivity after 3 months of treatment is evaluated by measuring the penile length increase and scrotal development. A positive response favors male orientation. Pediatric endocrinologists should be very careful with definitive sex assignment, however. They need to take into account all the diagnostic possibilities because we now know from patient support groups that several patients with PAIS are not satisfied with former doctors' decisions. The testosterone treatment trial in newborns is currently a controversial topic among pediatric endocrinologists because there is no evidence that a good response to exogenous testosterone in neonates will be followed by a similar response at puberty. However, in the particular case of AR somatic mosaicism, the presence of wild-type AR may predict satisfactory virilization (either spontaneous or induced) at puberty, as exemplified by patients 1 and 2. Another issue raised by the testosterone treatment trial in newborns is the possibility of postnatal brain imprinting by androgens. In our opinion, the administration of exogenous testosterone can be proposed in PAIS patients because they already spontaneously present high androgen levels during the pre- and postnatal periods.

Furthermore, when patients with germline AR mutations are raised as females (CAIS or severe PAIS), there is no consensus about when the gonadectomy should be done: early in life or later, after spontaneous pubertal development. In these cases, if a somatic mosaicism is present, the risk of virilization during puberty must be considered and gonadectomy before puberty is indicated.

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