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RESEARCH

Changes in the clinical management of 5α -reductase type 2 and 17β -hydroxysteroid dehydrogenase type 3 deficiencies in France

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Abstract

Objectives: To examine the changes in diagnostic practices and clinical management of patients with 5 α -reductase type 2 (SRD5A2) or 17 β -hydroxysteroid dehydrogenase type 3 (HSD17B3) deficiency since molecular diagnoses became available.

Methods: Clinical, laboratory, and therapeutic data were retrieved from the medical records of 52 patients with a molecular diagnosis of SRD5A2 ($n = 31$) or HSD17B3 ($n = 21$) deficiency. Temporal trends regarding age at assessment and initial sex assignment over 1994–2020 were qualitatively analyzed. Age at molecular diagnosis was compared between two subgroups of patients according to their year of birth.

Results: Fifty-eight percent ($n = 30$) patients were diagnosed during the perinatal period, 33% ($n = 17$) during infancy, and 9% ($n = 5$) during adolescence or adulthood. Over the studied period, the patients' age at initial assessment and diagnosis frankly decreased. The median (range) age at diagnostic confirmation was 10.5 (0–53.2) years for patients born before 2007 and 0.4 (0–9.3) years for those born in 2007 or later ($P = 0.029$).

Genetic testing identified 27 different variants for the SRD5A2 gene (30% novel, $n = 8$) and 18 for the HSD17B3 gene (44% novel, $n = 8$). Before 2002, most patients were initially assigned as females (95%, $n = 19$), but this proportion dropped for those born later (44%, $n = 14$; $P < 0.001$). The influence of initial genital appearance on these decisions seemingly decreased in the most recent years. Therapeutic interventions differed according to the sex of rearing. Ten percent ($n = 2$) patients requested female-to-male reassignment during adulthood.

Conclusion: This study showed, over the past two decades, a clear trend toward earlier diagnosis and assignment of affected newborns as males.

Key Words

- ▶ 5 α -reductase type 2 deficiency
- ▶ 17 β -hydroxysteroid dehydrogenase type 3 deficiency
- ▶ 46,XY disorders of sex development
- ▶ sex assignment
- ▶ change in practices

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Introduction

Disorders/differences of sex development (DSD) in patients with a 46,XY karyotype may result from disorders of androgen synthesis such as 5 α -reductase type 2 deficiency (SRD5A2) and 17 β -hydroxysteroid dehydrogenase type 3 deficiency (HSD17B3). These two rare autosomal recessive conditions display a great heterogeneity at both the genotypic and phenotypic levels (1, 2, 3, 4, 5, 6). Clinical presentations of external genitalia at birth range from a female appearance with or without clitoromegaly to hypospadias and micropenis. Both conditions are characterized by a marked virilization at puberty, as other enzymatic mechanisms allow complete steroidogenesis up to dihydrotestosterone (DHT) (1, 7, 8). Hence, they are associated with the highest, although highly variable, rates of gender change in patients with a 46,XY DSD who have been birth assigned as females (9, 10, 11). When suspected at birth, these conditions may raise ethical dilemmas regarding patients' sex of rearing (12, 13), while a diagnosis made during infancy may lead to early change of sex of rearing (14).

Diagnostic practices have significantly progressed over the past two decades. Laboratory diagnosis used to

be guided by the determination of the testosterone/DHT ratio (elevated at baseline and/or after human chorionic gonadotrophin (hCG) stimulation test in SRD5A2 deficiency) and of the testosterone/androstenedione ratio (low at baseline and after hCG stimulation test in HSD17B3 deficiency). However, since the publication of several studies in the 1990s (15, 16), molecular analysis has proved to be the most effective method for diagnostic confirmation (17, 18, 19) and has allowed the identification of a growing number of genetic variants underpinning the two conditions (1, 2, 3, 4, 5, 6, 7, 8, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32).

Over the same period of time, clinical practices have evolved in the wake of the 2006 Chicago Consensus and other recent professional guidelines (1, 33, 34, 35, 36). In particular, a clear trend has been observed in favor of rearing newborns and infants diagnosed with SRD5A2 or HSD17B3 deficiencies as boys, contrary to what was previously done (1, 24, 37). This trend has concerned a growing proportion of patients with 46,XY DSD since the late 1990s and is likely related to a shift in medical practices and attitudes (35). However, its relationships with wider changes in the medical management of these patients,

such as changes in diagnostic practices, have not been specifically studied.

In France, these changes were fostered by the development, in the early 2000s, of a national DSD reference network, which aimed at centralizing and homogenizing the medical management of all patients with disorders of sex development. In 2006, it was structured as part of the first national plan for rare diseases ('Plan National Maladies Rares'), which widened its field of action. This network allowed a more systematic referral of children with DSD to specialized teams and laboratories and contributed to the local dissemination of international guidelines on the management of DSD (33, 35, 36).

Thus, the present study aimed to examine the various facets of the changes in the medical management of disorders of androgen synthesis, through a retrospective examination of the clinical, laboratory, and treatment characteristics of a cohort of patients with SRD5A2 or HSD17B3 deficiencies who have been followed and treated in France since the first molecular diagnoses of the conditions were made in the mid-1990s.

Methods

Patients' identification strategy

Two national rare disease databases (CEMARA, created in 2005, and BAMARA, created in 2018) were initially searched to identify patients with code ORPHA 752 and 753 (corresponding to SRD5A2 deficiency and HSD17B3 deficiency, respectively), referred to all the hospitals working within the DSD National Reference Network (Centre de référence du développement génital – DEVGEN – and Centre de référence des maladies endocriniennes de la croissance et du développement – CRMERCD). This initial research was completed by direct solicitation of every leading physician of the teams of the Network in order to get access to the most exhaustive list of patients with these conditions and to their medical records.

Ethical aspects

Collaboration conventions were signed with each concerned hospital. An information note was sent to all the referring physicians, who forwarded it to their patients in order to obtain their agreement to have their medical data collected for the purpose of the study. The ethics committee of the Hospices Civils de Lyon

(HCL) approved this study on October 1, 2021 (number 21_269). The processing of personal data carried out for this study falls within the frame of the 'Reference Methodology number 4' (MR-004) of the Commission nationale de l'informatique et des libertés (CNIL, French commission for data protection) for which the HCL has signed a compliance commitment and respects the General Data Protection Regulation (CNIL registration number 21_5269).

Inclusion criteria

All patients with a genetically confirmed diagnosis of SRD5A2 deficiency or HSD17B3 deficiency were included, except those who expressed their refusal.

Data collection and analyses

Data were collected between October 2021 and September 2022. The paper and/or computerized files of 52 patients from 12 different hospitals were examined in order to extract the relevant data concerning clinical presentation, laboratory data, therapeutic management, and follow-up. The oldest included file dated back to 1994 and the most recent one to 2020.

All data were transcribed as they appeared in the medical records, except for the external masculinization score (EMS) that was calculated retrospectively on the basis of the initial description of patients' external genitalia (38, 39), in order to homogenize and compare the phenotypic descriptions of the neonatal period.

Endocrinological investigations were performed at diagnosis. DHT, testosterone, and androstenedione levels were determined using either an immunological assay or liquid chromatography-tandem mass spectrometry.

Molecular analyses were performed at diagnosis. The first molecular diagnoses dated back to 1999 for SRD5A2 deficiency and to 1995 for HSD17B3 deficiency. These diagnoses were mostly made by two laboratories (in Montpellier and in Lyon) who were historically the first to perform these analyses, but three other laboratories developed these techniques later on. Genomic DNA was extracted from peripheral leukocytes using standard procedures. Exons and exon/intron boundaries of the SRD5A2 or HSD17B3 genes were initially analyzed by Sanger sequencing ($n=39$) and since 2013 by targeted next-generation sequencing ($n=12$). The limited number of patients did not allow a detailed analysis of the correlation between genotype and phenotype to be performed.

Temporal changes regarding the timing of diagnosis and decisions on initial sex of rearing were qualitatively described. The whole cohort was represented on a graph indicating each patient’s initial sex of rearing and age at molecular diagnosis according to the year of birth. Due to an insufficient number of patients, no statistical trend analysis was performed. However, regarding the timing of molecular diagnosis, a statistical comparison was made between two subgroups of patients according to their year of birth (before 2007, and beyond). This year was chosen for two reasons: it corresponded to the median year of birth of the cohort and it corresponded to the year immediately following the creation of the national DSD reference network in 2006, which supposedly fostered the changes of practices at a national level.

Statistical analyses

Categorical variables were expressed as count (percentage). Continuous variables were expressed as mean ± s.d. or median (range), according to their distribution. A graphical assessment and a Shapiro–Wilk test were used for the assessment of normality. Continuous variables were compared using the Mann–Whitney test due to the small sample sizes considered.

Results

Clinical presentation, age at diagnosis, and sex assignment

A total of 69 patients from 12 hospitals were assessed for eligibility; among them, 17 were excluded due to the absence of genetic confirmation of the diagnosis ($n = 10$) or due to refusal to participate ($n = 7$). Eventually, 52 patients (31 with *SRD5A2* deficiency and 21 with *HSD17B3* deficiency) were included in the present study (Fig. 1). Patients were born between 1966 and 2020, and their median (range) age was 15 (1–55) years. There were nine patients who were not born in France and who were sometimes first treated (even if not formally diagnosed) in their native country. Consanguinity was reported in 37% ($n = 19$) of cases. A familial history of DSD was reported in 37% ($n = 19$) of cases and concerned 13 different families; five of these cases also presented consanguinity (Tables 1 and 2).

For both conditions, patients’ external phenotypic characteristics highly varied. For 58% ($n = 30$) of patients, the diagnostic process began during the perinatal period, as they exhibited atypical genitalia. Among them, seven had an antenatal diagnosis due to a discordance between external genitalia and the karyotype: two had

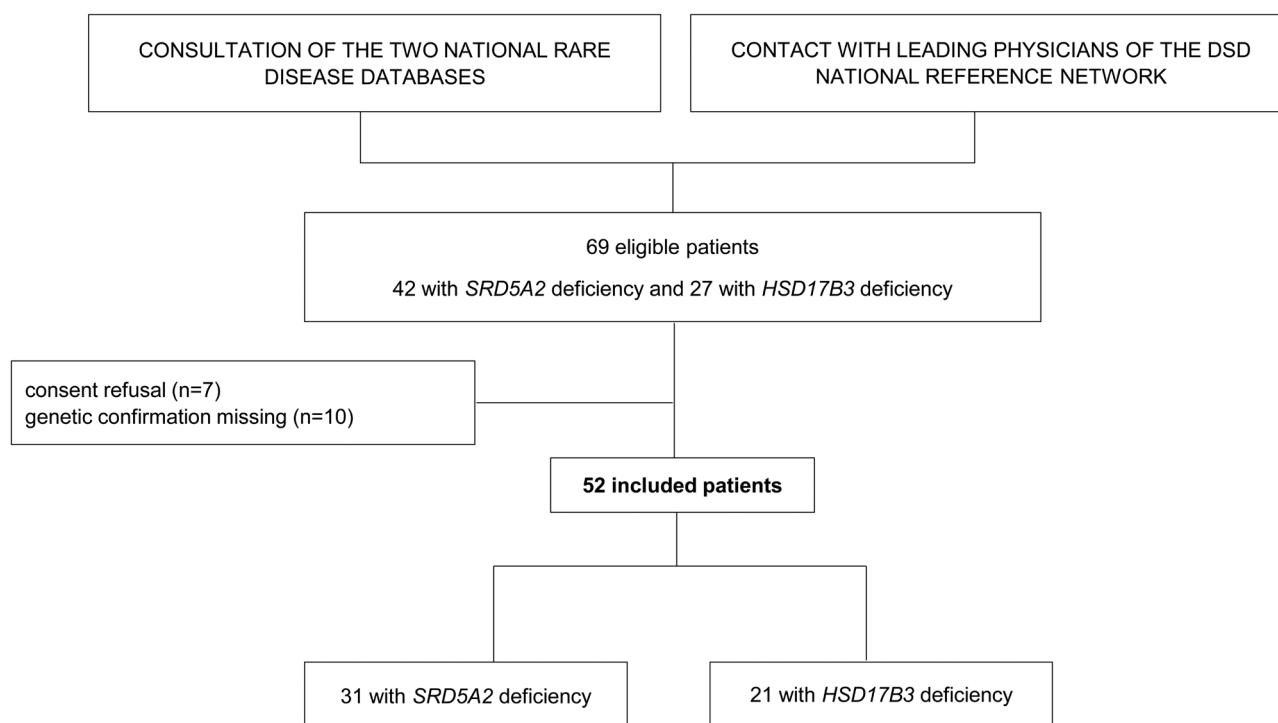


Figure 1
Participant flowchart.

Table 1 Characteristics at diagnosis of patients with SRD5A2 deficiency.

Case number	Year of birth	Sex of rearing	Phenotype at diagnosis	Ethnic group	Consanguinity	DSD in family	EMS	Clitoromegaly	Age at hormonal evaluation / molecular diagnosis	Basal testosterone/ DHT ratio	estosterone/ DHT ratio post-hCG test	Mutation	DNA variant (NM 000348.3)	Protein variant
1	1982	Female	Infancy/ virilization	Maghreb	Y	N	1	Y	10 years/N	3.0	22.0	H	c.344G>A	p.(Gly115Asp)
2	1986	Female	Infancy/ virilization	Maghreb	Y	N	3	Y	13 years 6 months/ 13 years 19 months	32.0		H	c.344G>A	p.(Gly115Asp)
3	1988	Female	Amenorrhea	ND	N	N	2	N	18 years 7 months/ 18 years 9 months	15.7		H	c.377A>G	p.(Gln126Arg)
4	1994	Female	Amenorrhea	Iraqi Kurdish	N	Y	2	Y	13 years/ 13 years	18.5		H	c.453delC	p.(Phe152fs*8)
5	1997	Female	Infancy/ virilization	Iraqi Kurdish	Y	N	5	Y	19 years 5 months/ 19 years 6 months	28.8		H	c.453delC	p.(Phe152fs*8)
6	1997	Male	Infancy/ virilization	Turkish	Y	N	6	/	10 years 9 months/ 11 years	2.8	22.0	H	c.607G>A	p.(Gly203Ser)
7	1998	Female	Infancy/ virilization	Egyptian	N	N	3	Y	14 years 11 months/ 14 years			H	c.271T>C	p.(Tyr91His)
8	2001	Female	Neonatal, AD	Caucasian	N	N	3	N	11 months	7.5		CH	c.736C>T c.377A>G	p.(Arg246Trp) p.(Gln126Arg)
9	2004	Male-d	Neonatal	Caucasian	N	N	5.5	/	3 days/ 14 years 10 months	5.2		CH	c.311G>A c.644C>T	p.(Gly104Glu) p.(Ala215Val)
10	2005	Male	Neonatal	Turkish	N	Y	6	/	ND/ 2 months	3.8	5.7	H	c.607G>A	p.(Gly203Ser)
11	2007	Female	Neonatal	Caucasian	Y	N	2	N	1 year/ 1 month	26.8		H	c.622A>C	p.(Thr208Pro)
12	2007	Female	Infancy/ virilization, BIH	Iraqi Kurdish	N	Y	1.5	N	ND/ 4 months	7.4		H	c.453delC	p.(Phe152fs*8)
13	2007	Male	Neonatal	ND	N	Y	6	/	6 days/ 11 months			CH	c.42C>A + V89L	p.(Ser14Arg) Polymorphism
14	2008	Male	Neonatal	Caucasian	N	Y	8	/	2 years/ 2 years 10 months		9.2	CH	c.250C>A c.578A>G + V89L	p.(Leu84Met) p.(Asn193Ser) + Polymorphism
15	2009	Male	Neonatal	Turkish	N	Y	9	/	1.5 months/ 1 month 19 days 1.5 months	8.8	14.0	H	c.513G>C	p.(Arg171Ser)
16	2010	Female	Neonatal	Caucasian	N	N	3	Y	1 month/ 1.5 months	6.5		H	c.620C>A	p.(Ala207Asp)
17	2010	Male-d	Neonatal	Maghreb	Y	N	4.5	/	ND/ 11 days	5.1		CH	c.365delA c.578A>G	p.(Asn122Metfs*9) p.(Asn193Ser)

(Continued)

Table 1 Continued.

Case number	Year of birth	Sex of rearing	Phenotype at diagnosis	Ethnic group	Consanguinity	DSD in family	EMS	Clitoromegaly	Age at hormonal evaluation / molecular diagnosis	Basal testosterone/ DHT ratio	estosterone/ DHT ratio post-hCG test	Mutation	DNA variant (NM_000348.3)	Protein variant
18	2011	Male	Neonatal	Pakistan	Y	N	8	/	7 months/ 10 months	0.4	14.6	H	c.680G>A	p.(Arg227Gln)
19	2011	Female	Neonatal	Caucasian	N	N	3	Y	1 month/ 2 months	37.7		CH	c.377A>G	p.(Gln126Arg)
20	2012	Male-d	Neonatal	Maghreb	N	N	6	/	4 days/ 6 years	1.7		CH	c.704A>T	p.(Tyr235Phe)
21	2013	Female	Infancy/ virilization	Malian	Y	Y	ND	Y	4 years/ 11 months/ 4 years 11 months			H	c.578A>G	p.(Asn193Ser)
22	2013	Male-d	Neonatal	Maghreb	Y	Y	2	/	1 year 11 months/ 6 years			H	c.644C>T	p.(Ala215Val)
23	2013	Female	Infancy/ virilization	Ethiopian	N	Y	5	Y	3 years 9 months/ 3 years 10 months			CH	c.418T>G	p.(Trp140Gly)
24	2014	Female	Neonatal	Turkish	Y	N	3.5	N	3 months/ 4.5 months			H	c.332_333delTC	p.(Leu111Hisfs*24)
25	2015	Male	Neonatal	Turkish	N	Y	8	/	1 month 5 days/ 1.5 months	26.5		H	c.2T>G	p.(Met17)
26	2015	Male-d	Neonatal	Caucasian	N	N	3.5	/	3 days/ 1 month	14.1		CH	c.679C>T	p.(Arg227*)
27	2016	Male	Neonatal, AD	ND	ND	ND	6	/	1 month/ 1 month	26.5		CH	Deletion exon 2	
28	2016	Male	Neonatal	Kurdish	Y	N	6	/	16 days/ 4 days			H	c.513G>C	p.(Arg171Ser)
29	2017	Female > Male	Infancy/ virilization	Caucasian	N	N	3	Y	1 year 6 months/ 1 year 6 months			CH	c.168G>C	p.(Glu56His)
30	2018	Female	Neonatal	Malian	Y	Y	2	Y	3 days/ 4 days			H	c.377A>G	p.(Gln126Arg)
31	2019	Male-d	Neonatal	Maghreb	Y	N	4.5	/	15 days/ 8 months	>60		H	c.377A>G	p.(Gln126Arg)
					Y	N						H	c.586G>A	p.(Gly196Ser)
					N	N						CH	c.586G>A	p.(Gly196Ser)
					N	N						CH	c.603G>A	p.(Trp201*)
					Y	Y						H	c.692A>G	p.(His231Arg)
					Y	N						H	c.418T>G	p.(Trp140Gly)
					Y	N						H	c.678_684del7	p.(Arg227Phefs*50)

Neonatal, DSD during the neonatal period; Infancy/virilization, DSD during infancy/virilization; AD, antenatal diagnosis; BIH, bilateral inguinal hernia; CH, compound heterozygous variant; d, sex declaration delayed; DHT, dihydrotestosterone; DSD, differences of sex development; EMS, external masculinization score; H, homozygous variant; N, no; ND, not determined; Y, yes.

Table 2 Characteristics at diagnosis of patients with HSD17B3 deficiency.

Case number	Year of birth	Sex of rearing	Phenotype at diagnosis	Ethnic group	Consanguinity	DSD in family	EMS	Clinicosegaly	Age at hormonal evaluation/ molecular diagnosis	Basal testosterone/ androstenedione ratio	Testosterone/ androstenedione ratio after hCG test	Mutation	DNA variant (NM 000797.2)	Protein variant
32	1966	Female	Amenorrhoea	Maghreb	Y	N	/	N	52 years 9 months/ 53 years 2 months	0.2		H	c.155-1G>A	Splicing anomaly
33	1969	Female	Amenorrhoea	Maghreb	N	Y	/	Y	26 years/ 26 years 10 months	0.2		H	c.812A>G	p.(His271Arg)
34	1982	Female	Infancy/virilization	Turkish	Y	Y	2	Y	13 years 5 months/ 17 years 1 month	1.1	1.4	H	c.239G>A	p.(Arg80Gln)
35	1988	Female	Infancy/virilization	Caucasian	N	N	1	Y	14 years 6 months/ 14 years 10 months	0.4		CH	c.277+4A>T	Splicing anomaly
36	1994	Female	Infancy/virilization	Caucasian	N	Y	2	Y	5 months/ 10 months	0.3		CH	c.673 G>A	p.(Val1225Met)
37	1994	Female	Infancy/virilization	Caucasian	N	N	2	N	2 months/ 3 months	1.9	0.4	H	c.239G>A	p.(Arg80Gln)
38	1998	Female	Neonatal, AD	Caucasian	N	Y	1	Y	ND/ AD	0.6		CH	c.845C>G	p.(Pro282Arg)
39	1998	Female	Neonatal	Caucasian	N	Y	3	Y	26 days/ 2 months	0.2	0.2	H	c.277+4A>T	Splicing anomaly
40	1999	Female	Infancy/virilization	Caucasian	N	N	3	N	23 months/ 26 months	0.4	0.4	H	c.551C>T	p.(Ser184Phe)
41	2000	Female	Neonatal, AD	ND	Y	N	1.5	N	0 days/ AD	2.0	0.2	H	c.277+4A>T	Splicing anomaly
42	2001	Female	Infancy/virilization, BIH	Martiniq/ Benin	N	N	2	Y	5 months/ 9 months	0.7	0.3	CH	c.608C>A	p.(Ala203Glu)
43	2001	Female	Neonatal	Caucasian	N	Y	3	Y	2 months 9 days/ 1 month	0.2		H	c.389A>G	p.(Asn130Ser)
44	2002	Male	Neonatal, AD	Caucasian	N	N	5	/	4 months/ 16 years 2 months	0.2	0.9	CH	c.278-1G>C	Splicing anomaly p. (Arg45Trp)
45	2003	Male-d	Neonatal	Turkish	Y	N	6	/	1 month/ 12 years 5 months	1.6	4.5	H	c.133C>T	p.(Arg45Trp)
46	2005	Male	Neonatal, AD	Maghreb	Y	N	6	/	1 day/ AD	0.2	0.3	H	c.641A>G	p.(Glu214Gly)
47	2006	Female	Neonatal	Caucasian	N	N	3	N	20 days/ 4 months	0.2		CH	c.277+4A>T	Splicing anomaly p. (Arg45Trp)
48	2008	Female	Infancy/virilization	Caucasian	N	N	2	N	13 months/ 14 months	0.2		H	c.277+4A>T	Splicing anomaly
49	2011	Female>Male	Infancy/virilization	Burkinabe	ND	ND	5	/	9 years 3 months/ 9 years 4 months			CH	c.578C>A	p.(Pro193His)
50	2017	Female	Infancy/virilization	Maghreb	Y	N	3	Y	2 months/ 3 months	0.1		H	c.680C>A	p.(Thr227Asn)
51	2018	Female	Neonatal	Caucasian	N	N	2	N	4 days/ 3 months 20 days			H	c.490-6T>C	Splicing anomaly
52	2020	Male	Neonatal, AD	ND	N	N	3	/	2 months/ 12 day	0.3		CH	c.599C>T	p.(Ala200Val)
													c.694_698 delinsCCCATAC.557C>T	p.(Ser232Profs*18) p.(Ser184Phe)

Neonatal, DSD during the neonatal period; Infancy/virilization, DSD during infancy/virilization; AD, antenatal diagnosis; BIH, bilateral inguinal hernia; CH, compound heterozygous variant; d, sex declaration delayed; DHT, dihydrotestosterone; DSD, differences of sex development; EMS, external masculinization score; H, homozygous variant; hCG, human chorionic gonadotrophin; ND, not determined.



SRD5A2 deficiency (cases 8 and 27) and five had HSD17B3 deficiency (cases 38, 41, 44, 46, and 52). Overall, 33% ($n=17$) of patients were diagnosed during infancy, as they exhibited atypical genitalia or inguinal palpable gonads, and 9% ($n=5$) of patients were diagnosed during adolescence or adulthood, due to virilization or primary amenorrhea (Table 3).

The age at assessment and diagnosis clearly decreased over time, with a shift in favor of early assessment from the late 1990s on. Since 1998, only 15% ($n=8$) of the patients were older than 12 months at their first specialized consultation (Tables 1 and 2). This evolution was contemporary to the first molecular diagnoses that date back to 1995 for HSD17B3 deficiency and to 1999 for SRD5A2 deficiency, and it was followed by a generalization of early molecular diagnosis throughout the 2000s (Fig. 2). Patients born before 2007 were diagnosed at a median (range) age of 10.5 (0–53.2) years, while patients born in 2007 or beyond were diagnosed at a median (range) age of 0.4 (0–9.3) years ($P=0.029$).

Sex of rearing at diagnosis was female in 60% ($n=31$) of cases (15 with SRD5A2 deficiency and 16 with HSD17B3 deficiency) and male in 40% ($n=21$) of cases (16 with SRD5A2 deficiency and 5 with HSD17B3 deficiency). The initial decisions on sex of rearing shifted over time from female to male assignment, contemporary to the generalization of early assessment and diagnosis. The trend to favor a male assignment of affected newborns began in 2002; before this date, all but one patient (patient 6, born in Turkey in 1997 and diagnosed at the age of 10.5 years when he arrived in France) had been assigned at birth as females (Fig. 2). This means that the proportion of female-assigned patients

dropped from 95% ($n=19$) for those born before 2002 to 44% ($n=14$) for those born in 2002 or later ($P < 0.001$).

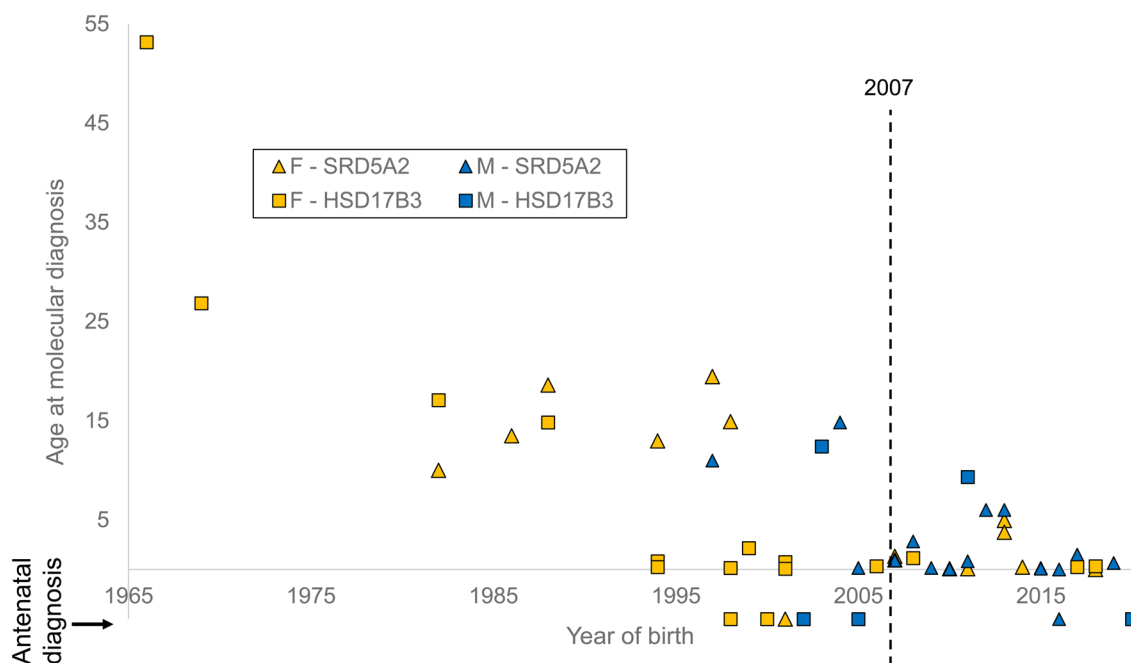
When the diagnosis was made in newborns, the degree of external virilization apparently influenced decisions on sex of rearing, as the median (range) EMS of patients assigned as females was significantly lower than that of patients assigned as males (females: 3.0 (1.0–3.5); males: 6.0 (2.0–9.0); $P < 0.001$; Fig. 3). However, since 2013, at least three patients with a low EMS have been assigned as males, suggesting that the influence of external virilization on the decision of sex of rearing weakened over time. In this cohort, when the conditions were diagnosed during the antenatal period, sex declaration was made at birth without delay, while the neonatal finding of atypical genitalia led to delayed sex declaration in seven cases. These seven patients were all reared as boys (Fig. 4), and their median (range) age at the time of declaration was 1.0 month (4 days–16 months). Among them, five had an EMS > 4 , while the two others had an EMS < 4 .

Among patients whose DSD had not been suspected at birth ($n=22$), all but one (case 6, born in Turkey) were initially assigned as females. For two of these patients, change of sex of rearing (from female to male) was decided after diagnosis during infancy (cases 29 and 49).

Among patients reared as girls who were older than 15 years at the time of the study, only 10% ($n=2$) had expressed gender incongruence and requested female-to-male reassignment. One had SRD5A2 deficiency and had not been gonadectomized during childhood (case 5), while the other had HSD17B3 deficiency and had undergone bilateral gonadectomy and feminizing surgery during infancy (case 39). This latter patient's sister

Table 3 Clinical signs leading to diagnosis.

	<i>n</i>	%	SRD5A2	HSD17B3
Neonatal diagnosis	30	58	20	10
Clitoromegaly	5		3	2
Isolated micropenis	3		3	0
Micropenis + hypospadias	11		10	1
Female phenotype with palpable gonads without clitoromegaly	4		2	2
Antenatal diagnosis	7		2	5
Diagnosis during infancy	17	33	8	9
Clitoromegaly	9		5	4
Micropenis + hypospadias	3		2	1
Female phenotype with palpable gonads without clitoromegaly	2		0	2
Suspected inguinal hernia	3		1	2
Diagnosis during adolescence or adulthood	5	9	3	2
Amenorrhea with clitoromegaly	2		1	1
Amenorrhea without clitoromegaly	2		1	1
Isolated clitoromegaly	1		1	0



Patients are represented as triangles (SRD5A2 deficiency) or as squares (HSD17B3 deficiency); colors correspond to the initial sex-of-rearing (yellow: female; blue: male)

Figure 2
Sex of rearing and age at molecular diagnosis according to the year of birth.

(case 43), who had the same condition, never expressed gender incongruence.

Hormonal and genetic data

Patients with SRD5A2 deficiency

The baseline testosterone/DHT ratio was available for 68% ($n=21$) of patients. The median (range) baseline testosterone/DHT ratio was 8.8 (4.5–26.5). Among the 21 baseline ratios, 33% ($n=7$) were greater than 20, and among the 12 ratios established during mini-puberty, 75% ($n=9$) were greater than 7. The testosterone/DHT ratio after hCG stimulation test was available for 19% ($n=6$) of patients, and the median (range) ratio was 14.6 (5.7–22.0). Among the six ratios determined after an hCG stimulation test, 83% ($n=5$) were greater than 8.5 (Table 1).

Genetic analyses (NM_000348.4) identified SRD5A2 homozygous variants in 65% ($n=20$) of cases and compound heterozygous variants in 35% ($n=11$) of cases. A total of 27 different variants were identified: 74% ($n=20$) missense variants and 26% ($n=7$) frameshift variants, including eight variants that were – to our knowledge – not previously described (Table 4). All these variants were localized in exons, and most were located in exon 4 (Fig. 5; Supplementary Table 1, see section on supplementary materials given at the end of

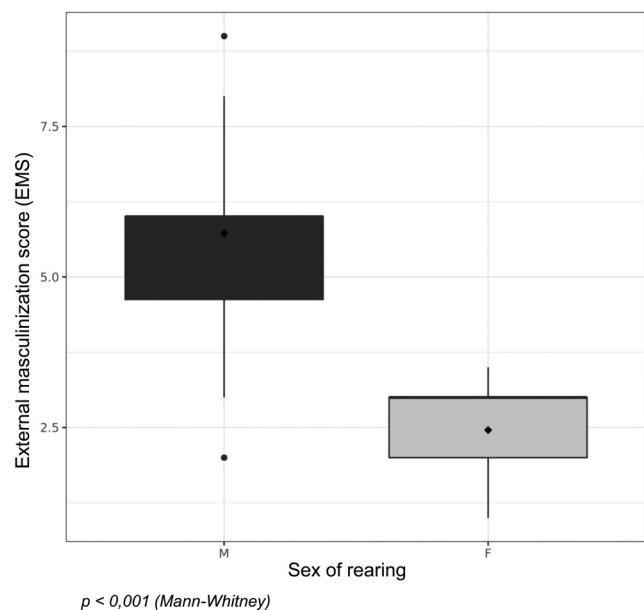
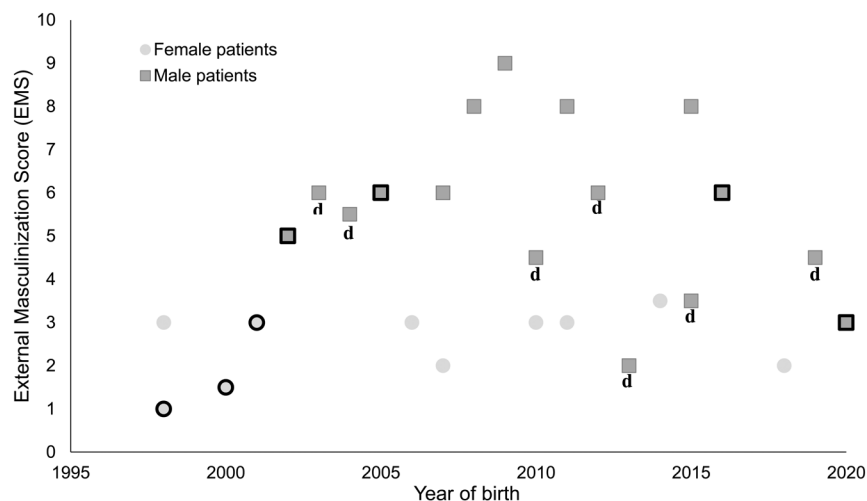


Figure 3
Comparison between EMS at birth according to the assigned gender.



d refers to delayed sex declaration; bordered squares and circles refer to antenatal diagnosis.

Figure 4

EMS according to the year of birth.

this article). The pathogenicity of all variants according to the American College of Medical Genetics (ACMG) classification is reported in supplementary data (Supplementary Table 1).

Patients with HSD17B3 deficiency

The baseline testosterone/androstenedione ratio was available for 86% ($n = 18$) of patients. The median (range) baseline testosterone/androstenedione ratio was 0.2 (0.2–0.7). The testosterone/androstenedione ratio after hCG stimulation test was available for 43% ($n = 9$) of patients: the median (range) ratio was 0.4 (0.2–4.5) and 67% ($n = 6$) of ratios were less than 0.8 (Table 2).

Genetic analyses (NM_000197.2) identified *HSD17B3* homozygous variants in 62% ($n = 13$) of cases and compound heterozygous variants in 38% ($n = 8$) of cases. A total of 18 different variants were identified: 72% ($n = 13$) missense variants, 22% ($n = 4$) splicing anomalies, and 6% ($n = 1$) frameshift variant; 78% ($n = 14$) of variants

were located in exons and 22% ($n = 4$) were located in introns. The most frequent variant was located in intron 3 (c.277+4A>T) as 29% ($n = 6$) of patients harbored it, and it resulted in a splicing anomaly (Fig. 6, Supplementary Table 2). To our knowledge, eight variants were not previously described (Table 5). The pathogenicity of all variants according to the ACMG classification is reported in supplementary data (Supplementary Table 2).

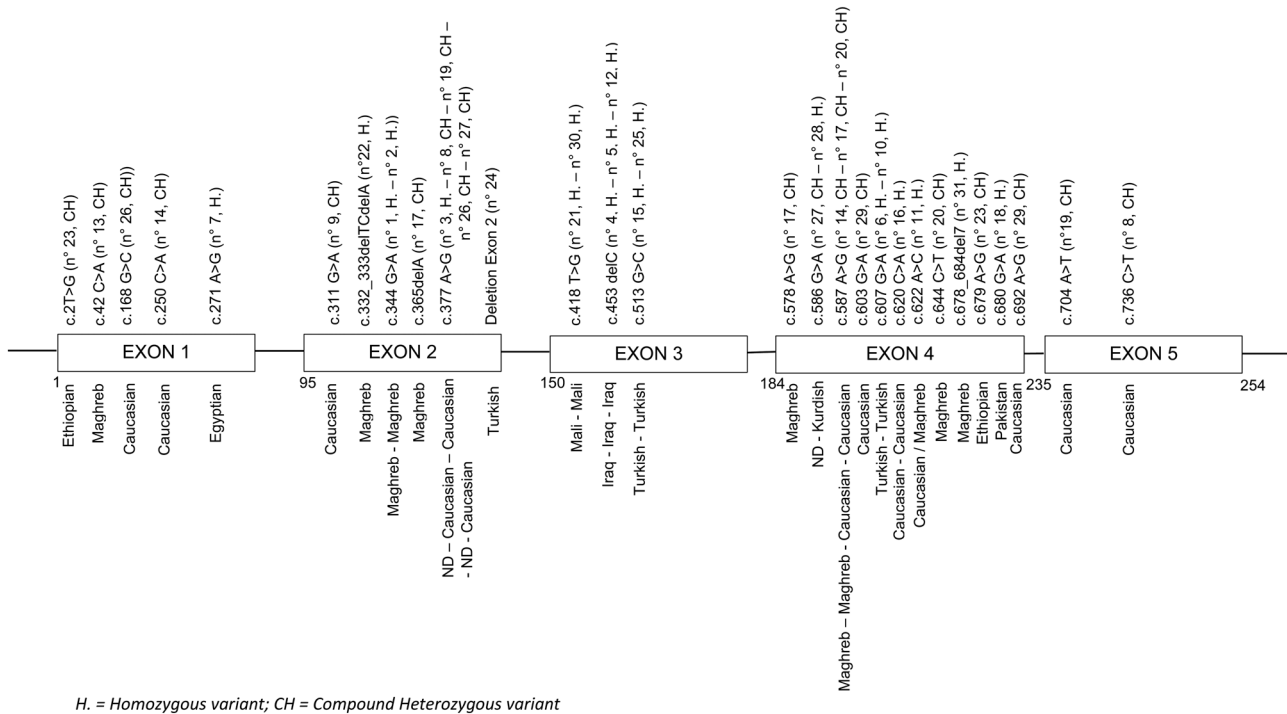
Therapeutic interventions

Hormonal treatment and surgical management were similar for both conditions but obviously differed according to the patients' sex of rearing. Overall, 71% ($n = 22$) of patients reared as girls underwent gonadectomy, which was bilateral in all but one case. The median (range) age at gonadectomy was 1.9 years (14 days–27 years). Since 2010, no gonadectomy had been performed during the neonatal period or infancy, with one exception (case 24, unilateral gonadectomy). Overall, 36% ($n = 8$) of girls

Table 4 Genetic variants of patients with SRD5A2 deficiency.

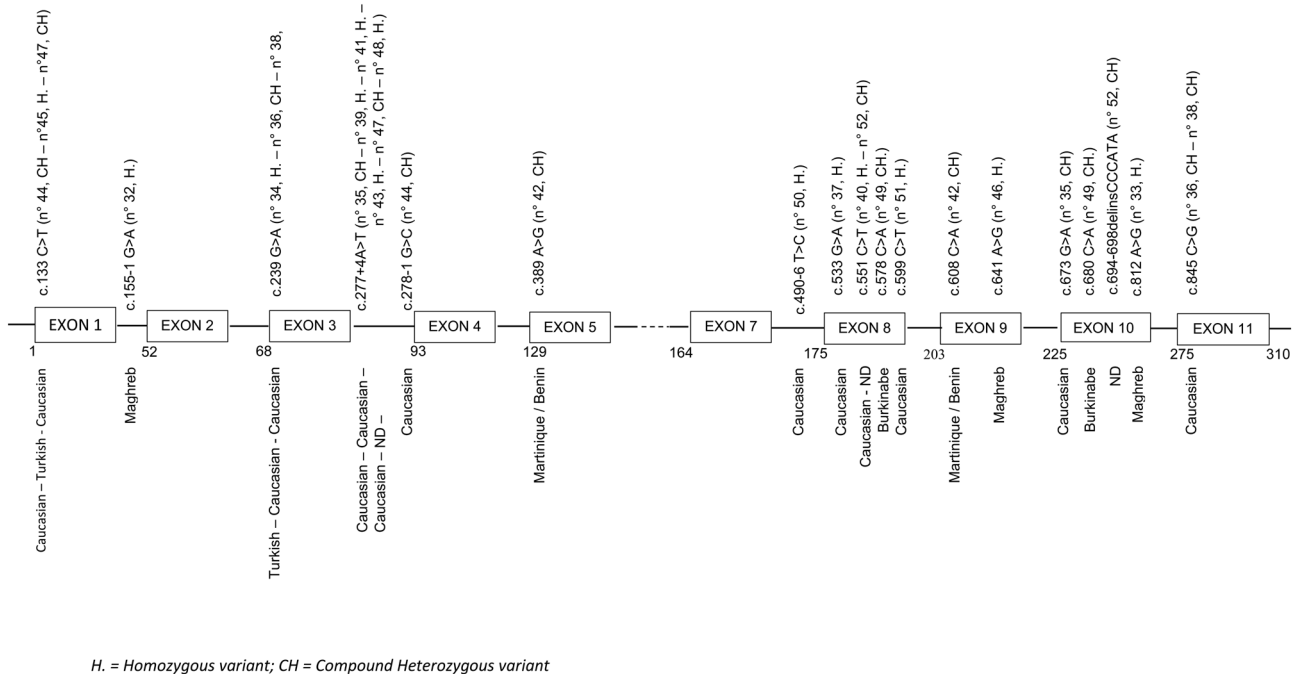
SRD5A2 DNA variant (NM_000348.4)	Protein variant	Location	Classification ACMG	Case number
c.2T>G	p.(Met1?)	Exon 1	4	23
c.168G>C	p.(Glu56His)	Exon 1	4	26
c.250C>A	p.(Leu84Met)	Exon 1	3	14
c.365delA	p.(Asn122Metfs*9)	Exon 2	5	17
c.418G>T	p.(Trp140Gly)	Exon 3	4	21, 22
c.622C>A	p.(Thr208Pro)	Exon 4	3	11
c.678_684del7	p.(Arg227Phefs*50)	Exon 4	4	31
c.603G>A	p.(Trp201*)	Exon 4	5	29

ACMG, American College of Medical Genetics (3 = uncertain significance variant; 4 = likely pathogenic; 5 = pathogenic).



H. = Homozygous variant; CH = Compound Heterozygous variant

Figure 5
Genetic variants of patients with SRD5A2 deficiency.



H. = Homozygous variant; CH = Compound Heterozygous variant

Figure 6
Genetic variants of patients with HSD17B3 deficiency.

Table 5 Genetic variants of patients with HSD17B3 deficiency.

HSD17B3 DNA variant (NM_000197.2)	Protein variant	Location	Classification ACMG	Case number
c.155-1G>A	Splicing anomaly	Intron 2	4	32
c.490-6T>C	Splicing anomaly	Intron 7	4	50
c.533G>A	p.(Gly178Asp)	Exon 8	3	37
c.551C>T	p.(Ser184Phe)	Exon 8	3	40, 52
c.578C>A	p.(Pro193His)	Exon 8	4	49
c.641A>G	p.(Glu214Gly)	Exon 9	3	46
c.680C>A	p.(Thr227Asn)	Exon 10	4	49
c.694delinsCCCATA	p.(Ser232Profs*18)	Exon 10	4	52

ACMG, American College of Medical Genetics (3 = uncertain significance variant; 4 = likely pathogenic; 5 = pathogenic).

underwent gonadectomy after 13 years of age; among them, six had experienced adolescent virilization, while this information was missing for two others.

Pubertal induction treatment was administered to 83% ($n=20$) of adolescent or adult girls. An 11-year-old patient had not yet initiated estrogen therapy at the time of the study, while information was missing for the last three patients. The median (range) age at pubertal induction was 11.9 (10.3–36.0) years. No puberty blockade was reported in this group.

Overall, 23% ($n=7$) of girls underwent clitoral or perineal surgery, at a median (range) age of 15.1 (1.9–36.0) years; 13% ($n=4$) underwent vaginoplasty, at a median (range) age of 17.9 (14.4–36.0) years. Also, 23% ($n=7$) of patients had vaginal dilatations during adolescence and one during infancy (for four patients dilatations were necessary for vaginal stenosis after vagina surgery; for four other patients, auto-dilatations were performed in order to develop a vagina without surgery). The median (range) age at first vaginal dilatation was 17 (6.0–18.6) years. In addition, breast prostheses were requested by 10% ($n=3$) of patients, at a median (range) age of 18.0 (16.0–19.0) years. One patient who had undergone bilateral gonadectomy and feminizing surgery (clitoral reduction and perineoplasty but no vaginoplasty) during infancy expressed a gender incongruence during adulthood and requested a female-to-male reassignment treatment (case 39).

All patients reared as boys ($n=21$) received androgen therapy: except for one patient (case 13), penile length before treatment was less than the 5th percentile (40). This treatment was initiated at a median (range) age of 5.0 months (18 days–10.9 years): 62% ($n=13$) of patients were treated during their first year of life, 28% ($n=6$) of patients between 1 and 3 years of age, and 10% ($n=2$) of patients after 9 years of age (Supplementary Table 3).

Among the 16 male patients with SRD5A2 deficiency, 56% ($n=9$) received transdermal DHT, 19%

($n=3$) injectable testosterone enanthate, and 25% ($n=4$) testosterone enanthate and DHT successively. A quarter ($n=4$) received androgen therapy only, and 75% ($n=12$) of patients underwent both hormonal treatment and penile surgery. All male patients ($n=5$) with HSD17B3 deficiency received testosterone enanthate, with additional DHT for one of them (case 49); among them, four were also treated surgically (Supplementary Table 3).

Overall, 90% ($n=19$) of patients underwent genital surgery, at a median (range) age of 1.5 (0.4–5.9) years: undescended testis surgery was performed in 42% ($n=8$) of cases, at a median (range) age of 3.3 (1.3–6.0) years, and surgery of hypospadias was performed in 79% ($n=15$) of cases, at a median (range) age of 1.5 (0.5–12.4) years, with a median (range) number of interventions per patient of 2 (1–10) (Table 6). Before hypospadias surgery, the penile length was between the 5th and 50th percentiles according to the patients' age in 53% ($n=8$) of cases and under the 5th percentile in 14% ($n=2$) of cases; these data were missing in 33% ($n=5$) of cases. At the last reported visit, the penile length was over or equal to the 5th percentile according to the age in 62% ($n=13$) of patients and lower than the 5th percentile in 33% ($n=7$) of patients; data were missing in one case (Supplementary Table 3). None of the adult male patients ($n=3$) had expressed desire of paternity nor underwent sperm analysis at the time of the study.

Discussion

This study was the first to describe a cohort of patients with a molecular diagnosis of SRD5A2 or HSD17B3 deficiency in France and clearly showed how the changes in diagnostic and clinical practices over the past two decades have impacted the general picture of these conditions. First, in contrast with previous studies (1,

Table 6 Surgical management and complications for patients reared as boys.

Case number	Year of birth	EMS	Undescended testicle surgeries: age (years)		Hypospadias surgeries: technique/age (years)		Number of genital surgeries
6	1997	6	N	/	TIP	11.3	2
					then TP	12.5	
9	2004	5.5	Y, L	5.9	Koyanagi	1.5	1
10	2005	6	Y, L then R	5.0, 6.0	PIF	1.5	3
13	2007	6	N	/	Koyanagi	1.8	4
					Urethroplasty (fistula)	3.0, 7.0	
					Urethroplasty (stenosis)	4	
14	2008	8	N	/	N	/	0
15	2009	9	N	/	PIF	2.1	1
17	2010	4.5	Y, L then R	2.6, 5.0	Koyanagi	1.5, 6.0	5
					Urethroplasty with buccal mucosa graft	8.0	
18	2011	8	Y, bilateral	2.0	N	/	1
20	2012	6	N	/	Splangioplasty, prepuce reconstruction	0.9	1
22	2013	2	N	/	N, refused by patient	/	0
25	2015	8	Y, bilateral	1.4	N	/	1
26	2015	3.5	N	/	Koyanagi (two stages)	1.0, 1.5	4
					Urethroplasty (fistula)	2.5, 4.0	
27	2016	6	N	/	PIF	0.9	1
28	2016	6	N	/	PIFDF	1.2	1
29	2017	3	N	/	Urethroplasty (first stage)	2.8	2
					Urethroplasty (stenosis)	4.0	
31	2019	4.5	N	/	Koyanagi	2.0	1
44	2002	4.5	N	/	Koyanagi	2.0	2
45	2003	6	N	/	Two-stage urethroplasty	0.5	10
					Urethral prosthesis (stenosis)	0.8	
					Urethral prosthesis extraction	1.0	
					Revision urethroplasty	3.5, 4.8	
					Urethroplasty with buccal mucosa graft	10.3, 11.5	
					Urethroplasty (stenosis)	12.5, 12.6, 12.7	
46	2005	6	Y, R	4.0	ND	0.4	3
					PIF	3.3	
49	2011	5	Y, bilateral R	4.1 9.0	TIP (two stages)	4.1, 5.9	4
					Revision genitoplasty (suture dehiscence)	8.0	
					Urethroplasty (fistula)	9.0	
52	2020	3	Y, bilateral	1.3	N	/	1

EMS, external masculinization score; L, left; N, no; ND, not determined; PIF, preputial island flap; PIFDF, preputial island double face; R, right, TIP, tubularized incised plate; TP, tubularized plate; Y, yes.

4, 6, 21, 41), the majority of the cases reported herein were diagnosed in newborns, or prenatally. Since the beginning of 2000s, making a diagnosis during adolescence has become the exception rather than the rule. The generalization of early diagnosis has been accompanied by a radical change in decision-making regarding the patients' sex of rearing. Except for one case (patient not born in France), all patients born before 2002 were reared as girls, whereas a large majority of those born later were reared as boys. A major consequence of this evolution is the radical decrease in the number of early gonadectomies. However, the shift in favor of male assignment has increased the number of therapeutic interventions, either hormonal or surgical, throughout the patients' childhood.

These findings are in line with the international trend that has been clearly reported by Kolezinska *et al.* about patients with 46,XY DSD, and in particular those with disorders of androgen synthesis (37). These authors have noticed that several reasons may have led to changes in early sex-assignment policies for patients with 46,XY DSD, in particular the relatively better outcomes for patients initially assigned as males, the technical improvements of masculinizing surgery, as well as a more general shift in 'social attitudes' (37). They also evoked the greater emphasis placed by clinicians on the karyotype but reported that at the time of their study (2013), confirmatory genetic diagnosis was still 'rarely sought' but would likely play a greater role in assisting sex-assignment decisions in the future (37). The present

study showed that this has in fact been the case in France over the last years. For more than half of the patients reared as boys, sex-of-rearing decisions benefitted from a longer time of reflection, as diagnosis was made during the antenatal period or as the sex declaration was delayed until diagnostic confirmation. Also, while decision-making regarding sex assignment at birth used to be guided, at least partly, by the degree of external virilization, this study reported three patients with a low EMS who were reared as boys since 2013. This was contemporary to a new step in the generalization of early molecular diagnosis, with the spread of next-generation sequencing. Thus, it seems that such molecular diagnosis has acquired a growing importance in sex-assignment decisions and reinforced the trend toward the systematic assignment of newborns with disorders of androgen synthesis as males.

Another consequence of the widespread availability of molecular diagnosis is the partial decline of the clinicians' reliance on steroid level evaluations and ratios. These evaluations encounter several limitations in current practice, as they should be performed at the same time and in the same laboratory to be interpretable and as the determination of DHT concentration can only be performed in a few laboratories. In this study, steroid evaluations were not always fully reported in patient files, for example for cases in which a familial history of the condition had oriented the diagnostic investigations. However, hormonal evaluations remained crucial when the molecular diagnosis was not available or conclusive. Excluding these cases was a limitation of the present study, although this does not question the relevance of the reported generalization of early genetic diagnosis.

The reliance on a retrospective calculation of the EMS was another limitation of the present study. This score is imperfect as it does not provide a complete clinical picture and as clinical descriptions may vary among clinicians, especially in case of partial fusion. Here, its calculation was based on clinical notes, which constitutes an additional limitation. Although approximate, this method remains useful to retrospectively compare patient phenotypes, and it has been used in the same manner elsewhere (37).

Finally, another limitation of the study lies in the paucity of data on patient medium- and long-term outcome, due to a focus on medical records in which information was often scarce regarding the psychosocial aspects and follow-up information after adolescence. It is however worth noticing that this cohort reported only two cases of adult patients who have requested female-to-male reassignment. The overall 10 % rate of post-pubertal

female-to-male reassignment was thus relatively low, but similar to that reported in some other samples of patients with SRD5A2 deficiency (4) and HSD17B3 deficiency (41). The contrast with studies reporting high rates of sex reassignment in patients with these conditions may be explained by cultural factors (10, 41) but also by the fact that high rates of sex reassignment used to concern mostly patients who were not diagnosed during infancy and thus underwent unexpected virilization at adolescence (11, 42). However, in this cohort, one of the patients who requested female-to-male reassignment had been diagnosed early and underwent gonadectomy during infancy, which confirms that the development of a male gender identity does not strictly rely on such virilization (43). The fact that this patient's sister, who had the same condition and treatment history, never expressed gender dissatisfaction also confirms the implication of several factors in the development of gender identity (10, 11, 35). The follow-up of an increasing number of patients with disorders of androgen synthesis reared as boys may certainly bring new insights to this area of research.

Conclusion

This study provided the first description of a French cohort of patients with a genetically confirmed diagnosis of SRD5A2 deficiency or HSD17B3 deficiency. Besides bringing new insights on the genetic underpinnings of these conditions and detailed information on therapeutic trajectories, it clearly showed that the generalization of early diagnosis seemingly reinforced the growing trend in favor of patients' initial assignment as males. The overall presentation of disorders of androgen synthesis has thus changed, together with their clinical management. There is still a major need to assess the consequences of these transformations on patients' outcome, particularly regarding their psychosocial functioning and personal fulfillment.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-22-0227>.

Declaration of interest

Lise Duranteau is on the editorial board for *Endocrine Connections* but has not been involved with any editorial or peer review process of this manuscript.

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