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MAP3K1-related Gonadal Dysgenesis: Six new cases and review of the literature

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Abstract

Investigation of disorders of sex development (DSD) has resulted in the discovery of multiple sex-determining genes. *MAP3K1* encodes a signal transduction regulator in the sex determination pathway and is emerging as one of the more common genes responsible for 46,XY DSD presenting as complete or partial gonadal dysgenesis. Clinical assessment, endocrine evaluation and genetic analysis were performed in six individuals from four unrelated families with 46,XY DSD. All six individuals were found to have likely pathogenic *MAP3K1* variants. Three of these individuals presented with complete gonadal dysgenesis, characterized by bilateral streak gonads with typical internal and external female genitalia, while the other three presented with partial gonadal dysgenesis, characterized by incomplete testicular development, resulting in clitoral hypertrophy with otherwise typical female external genitalia. Testing for *MAP3K1* variants should be considered in patients with 46,XY complete or partial gonadal dysgenesis, particularly in families with multiple members affected with 46,XY DSD. Identification of a *MAP3K1* variant should prompt an evaluation for DSD in female siblings of the proband.

Keywords

Disorders of sex development; MAP3K1; gonadal dysgenesis; 46; XY DSD

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INTRODUCTION

Disorders of sex development (DSD) are congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical and may affect up to 1:4500 infants [Lee et al. 2006]. Some of these disorders result from errors in sex determination, the process by which the male or female gonad is formed, and include 46,XX testicular DSD, 45,X/46,XY mixed gonadal dysgenesis, ovotesticular DSD, and 46,XY DSD with partial or complete gonadal dysgenesis [Ono and Harley 2013]. Sex determination is genetically controlled by the expression of the *SRY* gene on the Y chromosome, causing the undifferentiated gonad to develop into a testis [Ono and Harley 2013]. Sex differentiation follows when Sertoli cells in the developing testis produce Anti-Müllerian Hormone (AMH), leading to regression of the Müllerian ducts, while production of testosterone by the Leydig cells promotes differentiation of Wolffian duct structures. In the absence of a Y chromosome and expression of *SRY*, the undifferentiated gonad develops as an ovary and the Wolffian ducts regress [Ono and Harley 2013]. Gonadal dysgenesis results when the process of gonadal development is disrupted, leading to variable degrees of gonadal dysfunction [McCann-Crosby et al. 2014; Wolffenbuttel et al. 2016]. Multiple transcription factors and signaling molecules have been discovered to influence sex determination based on the identification of chromosomal abnormalities and identification of pathogenic variants in the genes encoding these factors in subjects with DSD. For individuals with 46,XY DSD, gonadal dysgenesis can result from loss of function mutations in *SRY*, *NR5A1(SF1)*, *SOX9*, *DHH*, *GATA4*, and *WT1*, single copy expression of *DMRT1*, *SOX 9*, *SF1*, and *WT1*, or duplication of *NR0B1* and *WNT4* [Baxter et al. 2015; Ono and Harley 2013]. The majority of individuals with DSD lack a known specific genetic etiology; however, more recently exome sequencing has been used to identify a likely genetic etiology in up to 43% of patients with 46,XY DSD [Baxter et al. 2015; Eggers et al. 2016].

The signal transduction gene, *MAP3K1*, is part of a network of genes responsible for gonadal development. *MAP3K1* mutations were first described in 2010 in two large families with 46,XY DSD and an autosomal dominant, sex-limited pattern of transmission as well as in 2 of 11 sporadic cases of 46,XY gonadal dysgenesis. In the large families that were reported, there were phenotypic presentations ranging from complete gonadal dysgenesis, sometimes with gonadoblastoma, to hypospadias and micropenis with cryptorchidism [Pearlman et al. 2010]. Recent studies suggest that *MAP3K1* is one of the more commonly mutated genes in 46,XY DSD, with mutations reported in 13–18% of patients [Ostrer 2014]. Functional studies of *MAP3K1* variants have demonstrated gain of function effects, causing increased phosphorylation of downstream targets resulting in decreased expression of *SOX9*, important for development of the testis, and increased expression of β -catenin. These gene expression changes mimic the signaling pathway in ovarian development and thus result in abnormal testicular development [Loke et al. 2014]. We report six individuals with heterozygous likely pathogenic *MAP3K1* variants from four unrelated families causing both partial and complete gonadal dysgenesis. In one family, the presence of the *MAP3K1* variant prompted testing of female siblings and identification of an affected sister. In a second family, the family history suggestive of possible sex-limited transmission prompted analysis of the *MAP3K1* gene followed by identification of an affected sister.

SUBJECTS

Family 1

Patient 1 is a 6-year-old European Caucasian/Hispanic female who was diagnosed with 46,XY DSD in the neonatal period. Amniocentesis for advanced maternal age revealed a 46,XY fetal karyotype, which was discordant from phenotypic sex noted at birth. Patient 1 had female genitalia at birth, but developed clitoromegaly, first noticed around age 1 year. She presented to our clinic at the age of 4 for further evaluation and management due to parental concerns of progressive clitoral enlargement. Physical examination was significant for clitoromegaly, with a length of 2.5 cm and width of 0.8 cm, absent labia minora, a low confluence urogenital sinus with absent hymenal tissue, and a 1 cm gonad palpable in the right inguinal canal. A pelvic ultrasound showed bilateral hypoechoic masses within the subcutaneous soft tissues underlying the labia, which were thought to represent gonadal streaks. A uterus was not visualized. Laboratory studies revealed normal gonadotropins, undetectable gonadal sex steroids, and AMH in the normal male range, indicating the presence of testicular tissue (Table I). Her clinical picture, imaging, and laboratory assessment were consistent with partial gonadal dysgenesis. She underwent cystoscopy, vaginoscopy, diagnostic laparoscopy, and bilateral inguinal gonadectomy at age 5 years. Although a uterus was not identified on pre-operative imaging, a cervix and small uterus deviating to the right were seen intraoperatively. Pathology revealed bilateral dysgenetic gonads, predominantly comprised of testis with foci of intratubular germ cell neoplasia (ITGCN). DNA sequence analysis showed a maternally inherited variant in *MAP3K1* that results in insertion of an alanine residue in frame between codons 4 and 5 (c.14_16insCGG; p.Ala5dup), classified as a variant of uncertain significance.

Following interdisciplinary assessment of patient 1, karyotypes were obtained on her three older sisters and one of them, 10-year-old patient 2 was found to have a 46,XY karyotype and the familial *MAP3K1* variant (Fig. 1A). Unlike her sister, she had typical external female genitalia, including labia majora, labia minora, clitoris, hymenal opening, and urethra. Ultrasound of the pelvis showed a rudimentary uterus and small 1 cm gonads bilaterally. Laboratory studies revealed elevated gonadotropins, undetectable gonadal sex steroids, and undetectable AMH, consistent with gonadal failure (Table I). Her clinical picture, imaging, and laboratory assessment were consistent with complete gonadal dysgenesis. Patient 2 underwent laparoscopic bilateral gonadectomy and pathological findings revealed dysgenetic streak gonads with ovarian stroma, mixed Müllerian and Wolffian duct structures.

Family 2

Patient 3 is an 18-year-old European Caucasian female who was diagnosed with 46,XY DSD after presenting with primary amenorrhea and absent breast development at age 16. Family history was notable for a maternal first cousin with a similar presentation with surgical history of gonadectomy (Fig 1B). She had typical female external genitalia. MRI of the pelvis showed a rudimentary uterus and no identifiable gonadal tissue. Laboratory evaluation revealed elevated gonadotropins, undetectable gonadal sex steroids, and undetectable AMH, consistent with gonadal failure (Table I); thus, her clinical picture,

radiology studies, and laboratory assessment were consistent with complete gonadal dysgenesis. She underwent laparoscopic bilateral gonadectomy at age 16 and the pathological evaluation revealed bilateral streak gonads without any malignant transformation. Wolffian remnants and fallopian tubes were also identified.

Her sister, patient 4, is a 15-year-old female who presented after her sister's diagnosis with primary amenorrhea and minimal breast development. Her karyotype was 46,XY; however, unlike her sister, she had clitoromegaly, which was present since birth. Her physical examination was significant for a clitoris 2 cm in length and 0.6 cm in width and typical labia majora, labia minora, hymen, and urethra. A pelvic ultrasound and MRI demonstrated a prepubertal uterus and 2 cm left gonad. The right gonad was not visualized. Laboratory evaluation revealed elevated gonadotropins, detectable but low gonadal sex steroids, and undetectable AMH, consistent with gonadal failure (Table I). Her clinical picture, imaging, and laboratory assessment were consistent with partial gonadal dysgenesis. She underwent laparoscopic bilateral gonadectomy. Pathological findings were significant for a left streak gonad with gonadal-like stroma and right streak testes and streak ovarian-like stroma, with rudimentary Mullerian and Wolffian structures.

Whole exome sequencing was performed on patient 3 and her maternal cousin (Fig. 1B). Based on the family history suggestive of sex-limited autosomal dominant transmission and clinical phenotype of gonadal dysgenesis, a *MAP3K1* pathogenic variant was suspected as the underlying genetic etiology. Indeed, upon filtering of the variants, a heterozygous variant in *MAP3K1* (c.1760T>A; p.Leu587His) was identified in patient 3 and maternal cousin. The presence of the variant was confirmed by Sanger sequencing in the affected sister and unaffected maternal aunt. The variant was not present in the ExAC database or in dbSNP. It is predicted to be damaging by SIFT and PolyPhen2.

Patient 5

Patient 5 is a 3-year-old African American female referred for evaluation of clitoromegaly that was first appreciated at 6 months of age. Physical examination noted an enlarged clitoris that was 3 cm long and 1.5 cm wide and minimal labia minora. The external genitalia were otherwise typical female and gonads were not palpable. Pelvic ultrasound revealed a uterus and bilateral gonadal tissue located in the adnexal regions. Laboratory evaluation showed a normal 46,XY karyotype with FISH positive for *SRY*, slightly elevated testosterone for female, slightly increased FSH level, and low AMH (Table I). The presentation was most consistent with a diagnosis of partial gonadal dysgenesis. Family history was noncontributory. SNP chromosomal microarray did not detect any copy number variations. Whole exome sequencing was performed and revealed a variant of uncertain significance in the *MAP3K1* gene (c.2291T>G; p.L764R). This variant was not reported in the ExAC, 1000 genomes, or dbSNP databases. It was classified as possibly damaging by PolyPhen2 and deleterious by SIFT. The patient's unaffected mother was also found to carry the variant. Bilateral gonadectomy was performed, and pathology showed a right dysgenetic testicle with seminiferous tubules in the tunica and a left ovotestis with predominantly testicular differentiation and focal ovarian fibrous stroma. There was marked atrophy with mainly Sertoli only tubules and thick basement membranes. No germ cell neoplasia or

gonadoblastoma was identified. There were both Mullerian (fallopian tubes) and Wolffian duct (epididymis-like) structures present.

Patient 6

Patient 6 presented at 16-years-of age as a tall (180 cm; >99th centile) African American female with amenorrhea, absent breast development, normal pubic and axillary hair, typical female external genitalia, and a 46,XY karyotype. The family history was noncontributory. Laboratory evaluation ruled out steroidogenic disorders, showed an elevated LH and FSH, and low testosterone and AMH, making gonadal dysgenesis likely (Table I). Although initial pelvic ultrasound did not identify a uterus, a pelvic MRI revealed the presence of a small uterine structure, small cervix, probable small atretic or streak left gonad near left inguinal canal measuring 1.5 cm and no identifiable right gonadal tissue. The patient underwent bilateral gonadectomy. Pathological findings showed bilateral streak gonads lacking sex cord and germ cell elements. Wolffian remnants and small fallopian tubes were present, and no tumors were noted. SNP chromosomal microarray did not detect any diagnostic copy number changes, and *NR5A1* & *SRY* gene sequencing and deletion/duplication studies were negative for pathogenic variants. Whole exome sequencing revealed that the patient was heterozygous for a likely pathogenic variant in the *MAP3K1* gene (c.566T>A; p.L189Q), which affects the same amino acid previously reported by Perlman et al [Pearlman et al. 2010]. At the time of presentation, the patient was experiencing gender dysphoria from the assigned gender of rearing and is in the process of transitioning from female to male.

DISCUSSION

Sex-specific gonadal development starts with the formation of the bipotential gonad, which differentiates into an ovary or testis. This process is dependent on the activation of the ovary-specific pathway or the testis-specific pathway. Transcription factors (*SRY*, *SOX9*, *SOX3*, *NR0B1*, *WT1*, *DMRT1*, *GATA4*, *NR5A1*) and signaling molecules (*WNT4*, *FGF9*, *DHH*, *RSPO1*, β -catenin) participate in regulatory networks to modulate these antagonistic pathways [Eggers et al. 2014; Loke et al. 2014; Ono and Harley 2013; Ostrer 2014]. Recently, cases of sporadic and familial 46,XY DSD have been attributed to pathogenic variants in the gene encoding *MAP3K1*, a signal transduction factor that is a key component of the network of transcription factors and signaling proteins that regulate testis-specific development [Baxter et al. 2015; Eggers et al. 2016; Pearlman et al. 2010]. Knockout of the *MAP3K1* gene in mouse embryos had only a minor effect on testis development [Warr et al. 2011]. Instead, *MAP3K1* variants have a gain of function effect by mimicking the ovary-specific pathway [Loke et al. 2014]. Specifically, increased phosphorylation of downstream targets, p38 and ERK1/2, and increased binding of cofactors RHOA, MAP3K4, FRAT1, and AXIN1 results in decreased expression of *SOX9* and its downstream targets, *FGF9* and *FGFR2*, that drive the male-specific pathway in a feed-forward loop, while blocking ovarian development by destabilizing β -catenin [Cool and Capel 2009; Ostrer 2014]. Increased p38 and ERK1/2 phosphorylation due to *MAP3K1* variants also results in increased expression of β -catenin (*CTNNB1*) and its downstream target, *FOXL2*, which by unknown mechanisms suppresses the *SOX9/FGF9* feed-forward loop [Eggers et al. 2014; Ostrer 2014]. Even though we were not able to perform functional studies, the presence of missense variants in

one family and two sporadic cases and duplication of a single amino acid in a second family could be consistent with a gain of function effect on the pathway, similar to previously reported pathogenic *MAP3K1* variants.

The pattern of inheritance of previously reported *MAP3K1* pathogenic variants is autosomal dominant and sex-limited based on familial cases [Ostrer 2014; Pearlman et al. 2010]. One family from France, of European descent, included six 46,XY females with complete or partial gonadal dysgenesis, three of whom had gonadal tumors [Pearlman et al. 2010]. In this family, there were also four affected males with 46,XY DSD who had genital abnormalities including first-degree hypospadias with chordee and perineal hypospadias. Affected individuals were found to have a c.634-8T> A variant, which resulted in aberrant splicing and segregated with the phenotype. *MAP3K1* pathogenic variants were also identified in another family from New Zealand, which included five 46,XY females with complete gonadal dysgenesis, and in two out of 11 unrelated sporadic cases of 46,XY complete gonadal dysgenesis [Pearlman et al. 2010]. In the original two families, there were eight and four obligate unaffected female carriers, respectively. Four sequence variants in the *MAP3K1* gene were identified a cohort of 10 Indian patients with 46,XY DSD and negative testing for *SRY*, *SFI*, and *DHH* pathogenic variants. However, all of the identified *MAP3K1* variants were found in dbSNP and in the ExAC database (rs702689, rs3822625, rs832575, rs34869245); thus, their pathogenicity in the reported cases is questionable [Das et al. 2013]. In a study by Baxter et al [2015], *MAP3K1* variants were identified in four sporadic cases with 46,XY DSD. Two patients were females with 46,XY complete gonadal dysgenesis, one patient had 46,XY ovotesticular DSD with ambiguous genitalia, and one patient was a male with 46,XY DSD and complex ambiguous genitalia (perineal hypospadias, small phallus, bifid scrotum, penoscrotal transposition, and no Müllerian structures) (Table II) [Baxter et al. 2015]. Eggers et al [2016] reported six *MAP3K1* variants in 11 patients following massively parallel sequencing and analysis of a targeted gene panel in a cohort of 278 patients with 46,XY DSD. The variants identified included one previously reported variant and five novel variants, with a range of phenotypes varying from complete gonadal dysgenesis to hypospadias [Eggers et al. 2016]. A summary of reported cases is presented in Table II. Taken together, these prior studies suggested that pathogenic *MAP3K1* variants explain 10–18% of 46,XY DSD and in particular, individuals with complete or partial gonadal dysgenesis.

Here we report six cases of 46,XY DSD with likely pathogenic *MAP3K1* variants in four unrelated families with phenotypes ranging from complete to partial gonadal dysgenesis. In two families, diagnosis of the proband led to identification of 46,XY DSD in a female sibling. The subjects presented in this report underwent gonadectomy given the increased risk of gonadal tumors in gonadal dysgenesis [Liu et al. 2014; Wolffenbuttel et al. 2016], and one of six patients demonstrated a premalignant change. Our findings confirm sex-limited autosomal dominant inheritance in both familial cases and one sporadic case. We were unable to perform maternal testing in one proband (Patient 6). To our knowledge, 46,XX individuals carrying pathogenic variants in *MAP3K1* are completely asymptomatic.

In our population of 16 patients (14 families) with 46,XY complete or partial gonadal dysgenesis, we have identified likely pathogenic *MAP3K1* variants in six patients from four

families. Of our remaining 10 patients, the majority have not yet been tested for *MAP3K1* variants either because they were evaluated prior to the recognition that pathogenic *MAP3K1* variants are a relatively common cause of gonadal dysgenesis or because of the limited availability of clinical testing for *MAP3K1* variants at the time of their evaluation. We suspect that there could be additional individuals in our remaining patient cohort who have *MAP3K1*-related gonadal dysgenesis. Even if our cohort contains no additional individuals with pathogenic *MAP3K1* variants, the four families described in this report represent 28% of our patient population with a diagnosis of complete or partial gonadal dysgenesis, which is higher than the previously reported findings [Baxter et al. 2015; Eggers et al. 2016; Pearlman et al. 2010]. Although larger numbers of patients would provide stronger evidence, our data suggest that *MAP3K1* pathogenic variants are the most common cause of 46,XY DSD with complete or partial gonadal dysgenesis. We propose routine testing for *MAP3K1* pathogenic variants in individuals affected with 46,XY DSD presenting as complete or partial gonadal dysgenesis. In families in which *MAP3K1* pathogenic or likely pathogenic variants have been identified, it is also important to obtain a peripheral blood karyotype on any prepubertal female siblings to determine whether there is more than one affected family member. Because clinical sequencing of *MAP3K1* is not widely available in the United States, whole exome sequencing may be the most effective method to test for *MAP3K1* pathogenic variants and obtain a genetic diagnosis. Identification of the underlying genetic etiology in two of these families directly led to changes in clinical management for the family members of the probands.

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Harry Ostrer, M.D. is a Professor of Pathology and Pediatrics at the Albert Einstein College of Medicine. He is a medical and molecular geneticist with a long-term interest in caring for patients with disorders of sex development (DSDs) as well as understanding the molecular pathogenesis for these disorders. His lab was the first to identify the role of the MAP kinase pathway in human DSDs.

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A. Family 1 **B. Family 2** **Figure 1.**

Pedigrees of two families with *MAP3K1*-related gonadal dysgenesis. Affected individuals with 46,XY karyotypes, complete or partial gonadal dysgenesis, and likely pathogenic *MAP3K1* variants are represented by black circles and + signs. Unaffected, presumably 46,XX females carrying *MAP3K1* variants are denoted by open circles and + signs. The probands are denoted by arrows.

Table I

Summary of clinical findings

	Family #1		Family #2		Patient 5	Patient 6
	Proband	Sister	Proband	Sister	Proband	Proband
Presentation	Amniocentesis discordant from phenotypic sex at birth. Clitoromegaly noted at age 1 year	46,XY karyotype identified following evaluation of sister	Absent secondary sex characteristics and primary amenorrhea	Primary amenorrhea and minimal breast development	Clitoromegaly noted at age 6 months	Absent secondary sex characteristics and primary amenorrhea
Exam	Enlarged clitoris with otherwise typical external female genitalia	Typical external female genitalia	Typical external female genitalia	Enlarged clitoris with otherwise typical external female genitalia	Enlarged clitoris with otherwise typical external female genitalia	Typical external female genitalia
Labs [§]	AMH 44 ng/mL FSH 4.7 mIU/mL LH 0.1 mIU/mL Test < 0.2 ng/mL E2 < 12 pg/mL	AMH < 0.3 ng/mL, FSH 85.9 mIU/mL LH 28 mIU/mL Test < 0.2 ng/mL	AMH < 0.3 ng/mL FSH 83.7 mIU/mL LH 25.12 mIU/ml Test 0.19 ng/mL E2 < 20 pg/mL	AMH < 0.3 ng/mL FSH 129.4 mIU/mL LH 22.1 mIU/mL Test 0.26 ng/mL E2 19 pg/mL	AMH 0.5 ng/mL FSH 12.2 mIU/mL LH 0.4 mIU/mL Test 0.69 ng/mL E2 19 pg/mL	AMH < 0.3 ng/mL FSH 67.4 mIU/mL LH 33.8 mIU/ml Test 13 ng/mL E2 < 12 pg/mL
Diagnosis	46,XY partial gonadal dysgenesis	46,XY complete gonadal dysgenesis	46,XY complete gonadal dysgenesis	46,XY partial gonadal dysgenesis	46,XY partial gonadal dysgenesis	46,XY complete gonadal dysgenesis
Surgical management	Laparoscopy and bilateral inguinal gonadectomy	Laparoscopic bilateral gonadectomy	Laparoscopic bilateral gonadectomy	Laparoscopic bilateral gonadectomy	Laparoscopy and bilateral inguinal gonadectomy	Laparoscopic bilateral gonadectomy
MAP3K/ variant	c.14_16insCGG (p.A5dup)		c.1760T>A (p.L587H)		c.2291T>G (p.L764R)	c. 566T>A (p.L189Q)

[§]Normal reference ranges: AMH: female <8.8 ng/mL.; male 7.4 – 243 ng/mL. FSH: prepubertal ref range not given; post-menopausal range 21 –131 mIU/mL. LH: prepubertal ref range not given; post-menopausal range 16 – 64 mIU/mL. Total testosterone (Test): female and prepubertal 0 – 0.2 ng/mL, Estradiol (E2) prepubertal: <20 pg/mL.

Table IISummary of reported cases with *MAP3K1*-related phenotypes

	Familial or Sporadic	Gender	Clinical Diagnosis	<i>MAP3K1</i> variant
Pearlman et al [2010]	Familial	6 Females	Complete gonadal dysgenesis (2) Partial gonadal dysgenesis (4) Gonadal tumors (3)	c.634-8 T>A
		4 Males	First degree hypospadias with chordee (1) Micropenis, cryptorchidism, perineal hypospadias (1) Perineal hypospadias only (2)	
	Familial	5 Females	Complete gonadal dysgenesis	c.1846G>A [p.Gly616Arg]
	Sporadic	Female	Complete gonadal dysgenesis	c.566T>C [p.Leu189Pro]
	Sporadic	Female	Complete gonadal dysgenesis	c.566T>G [p.Leu189Arg]
Loke et al [2014]	Sporadic	Female	Gonadal dysgenesis	p.Pro153Leu
	Familial	Female	Gonadal dysgenesis	c.2180-2A>G
Baxter et al [2015]	Sporadic	Female	Complete gonadal dysgenesis	c.1846G>A [p.Gly616Arg]
	Sporadic	Female	Complete gonadal dysgenesis	c.1016G>A [p.Arg339Gln]
	Sporadic	Male	Micropenis, chordee, incompletely fused scrotum, hypospadias, and ovotestis	c.1846G>A [p.Gly616Arg]
	Sporadic	Male	Small phallus, hypospadias, bifid scrotum, penoscrotal transposition	c.770C>T [p.Pro257Leu]
Eggers et al [2016]	2 Sporadic	Female	Complete gonadal dysgenesis	c.566T>G [p.Leu189Arg]
	Sporadic	Female	Complete gonadal dysgenesis	c.2071T>C [p.Cys691Arg]
	2 Sporadic	NR	46,XY DSD (1) Partial gonadal dysgenesis (1)	c.4328C>T [p.Ala1443Val]
	4 Sporadic	3 Male	46,XY DSD (2) Hypospadias (1)	c.934A>T [p.Met312Leu]
		1 Female	Complete gonadal dysgenesis (1)	
	Sporadic	NR	46,XY DSD	c.710A>G [p.Gln237Arg]
	Sporadic	Male	Hypospadias	c.394G>C [p.Asp132His]
Current report	Familial	2 Females	Complete gonadal dysgenesis (1) Partial gonadal dysgenesis (1) Gonadal tumor (1)	c.14_16insCGG [p.Ala5dup]
	Familial	2 Females	Complete gonadal dysgenesis (1) Partial gonadal dysgenesis (1)	c.1760T>A [p.Leu587His]
	Sporadic	Female	Complete gonadal dysgenesis	c.566T>A [p.Leu189Gln]
	Sporadic	Female	Partial gonadal dysgenesis	c.2291T>G [p.Leu764Arg]