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9p Partial Monosomy and Disorders of Sex Development: Review and Postulation of a Pathogenetic Mechanism

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Deletion of the distal segment of 9p causes a syndrome comprising trigonocephaly, minor anomalies, and intellectual disability. Patients with this condition also frequently present with genitourinary abnormalities including cryptorchidism, hypospadias, ambiguous genitalia, or 46,XY testicular dysgenesis. The region responsible for the gonadal dysgenesis has been localized to 9p24.3 with the likely responsible gene identified as *DMRT1*. Similar to patients with other molecular causes of 46,XY gonadal dysgenesis, patients with partial del 9p have an increased risk of gonadoblastoma. We present two patients with 46,XY gonadal dysgenesis due to partial 9p monosomy. Both patients were also diagnosed with gonadoblastoma following gonadectomy at an early age. Chromosomal microarray analyses refined the cytogenetic abnormalities and allowed potential genotype–phenotype relationships to be determined. We also review the literature as it pertains to partial 9p monosomy, genital abnormalities and gonadoblastoma and note that a large percentage of affected patients present with two copy number variations. We propose that a two-hit mechanism may be involved in the incomplete penetrance and variable expressivity of partial 9p monosomy and an abnormal genital phenotype. The significant percentage of gonadoblastoma in patients with 46,XY complete gonadal dysgenesis due to partial 9p monosomy also continues to support the necessity of gonadectomy in this patient population. © 2013 Wiley Periodicals, Inc.

Key words: distal monosomy 9p; 9p partial monosomy; disorders of sexual development; gonadoblastoma

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INTRODUCTION

In humans and other mammals, sex determination is initially made in the bipotential gonad with subsequently produced gonadal hormones responsible for the differentiation of male- and female-specific characteristics. Expression of the *SRY* (sex-determining region of Y) gene, located on the Y chromosome in mammals, is responsible for the initial determination step that yields a male gonad [Sekido and Lovell-Badge, 2009]. SRY, largely through its upregulation of *Sox9* expression, leads to the differentiation of Sertoli cells and an eventual male phenotype. In the absence of SRY and the failed upregulation of SOX9, the activation of beta-catenin signaling, through *Wnt4* and *Rspo1* activity, drives the bipotential precursor cells toward granulosa cell differentiation [Sekido and Lovell-Badge, 2009]. Abnormalities in the components of sex development, and in their downstream targets, clearly have implications on the functioning of this pathway and the resulting phenotype.

Disorders of sex development (DSD) are defined as any congenital condition in which the development of chromosomal, gonadal, or anatomical sex is atypical [Hughes, 2008]. These disorders are further divided into three categories: (1) sex chromosome DSD; (2) 46,XY DSD; and (3) 46,XX DSD [Hughes, 2008]. 46,XY gonadal dysgenesis occurs in the range of 1 in 3,000 births [Camerino

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et al., 2006]. Of these patients, 10–15% have a mutation in *SRY* and 10–15% have a mutation in *NR5A1* (*SF1*) [Hawkins et al., 1992; Philibert et al., 2010]. Other single gene causes have been identified in a few cases, and include mutations in *WT1*, *SOX9*, duplications of *NROB1* (*DAX1*), and 1p duplications containing *WNT4*. Cytogenetically visible aberrations have been known to cause gonadal dysgenesis in a number of instances as well, with the areas 2q, 9p, and 10q identified [Ostrer, 2004].

Partial monosomy for the distal segment of 9p (OMIM #158170), initially described by Alfi et al. [1973], results in a phenotype of trigonocephaly, minor anomalies, and intellectual disability. Ambiguous genitalia are estimated to be present in up to 70% of patients with partial 9p monosomy [De Grouchy and Turleau, 1982; Schinzel, 2001]. The critical interval for 46,XY complete gonadal dysgenesis has been localized between 9p24.3 and 9pter [Flejter et al., 1998; Guioli et al., 1998]. Further work has identified *DMRT1* to be the likely causative gene responsible for 46, XY complete gonadal dysgenesis in affected patients. Small intragenic *DMRT1* deletions have also been associated with 46,XY complete gonadal dysgenesis although point mutations were not identified in *DMRT1* when 46,XY female patients were evaluated [Raymond et al., 1999; Calvari et al., 2000; Vialard et al., 2002; Ledig et al., 2010, 2012].

Here, we present two patients with complete 46,XY gonadal dysgenesis found to have deletions of the distal segment of 9p. Gonadectomy documented gonadoblastoma in both patients. We present their clinical description as well as their molecular workup that includes detailed characterization of copy number breakpoints by array CGH. We review the literature regarding previously reported 46,XY patients with partial 9p monosomy and genital abnormalities, with special emphasis to 46,XY complete gonadal dysgenesis and the incidence of gonadoblastoma. We note that a large number of partial 9p monosomy DSD patients have a secondary copy number variation (CNV) and suggest a possible two-hit mechanism by which some 46,XY patients with partial 9p monosomy present with DSD and others present with no sex-related phenotype.

CLINICAL REPORT

Patient 1

Patient 1 has previously been reported elsewhere when she was 3 years old [McDonald et al., 1997; Flejter et al., 1998]. She was the first child of healthy, non-consanguineous parents, born at 42 weeks of gestation following a normal pregnancy. She had Apgar scores of 9 and 9 at 1 and 5 min, respectively, with a birth weight of 4.48 kg (1–2 SD above the mean). No concerns were noted neonatally.

She was referred at 10 months for a family history of recurrent miscarriages and a known balanced translocation in a paternal uncle. At 10 months she was developmentally normal but around 17 months was noted to have delays in speech and gross motor development. At 3 years her expressive language was at approximately an 18-month level. She sat independently at age 12 months and walked at age 18 months. In all grades, she qualified for special education and physical therapy. At 15 years she was reading at approximately a second grade level (age 7 years). She graduated from high school with the assistance of special education. Currently, at age 20 years, she is attending classes through a transitional school, focusing on life-skills.

Cardiac evaluation as a neonate was performed for unknown reason and showed a bicuspid aortic valve and patent foramen ovale (PFO); electrocardiogram showed a complete right bundle branch block. Renal ultrasound and a pelvic ultrasound study at 3 years showed a normal uterus and vagina without identifiable gonads.

At age 3 her weight and height were between the 50th and 75th centiles with a head circumference greater than the 95th centile. The patient was noted to have a single right palmar crease, bilateral 5th finger clinodactyly, mild metatarsus varus, and external female genitalia with no palpable gonads. Repeat evaluation at 19 years and 11 months of age revealed the patient's weight to be 100 kg (95–97th centile) with a height of 173.5 cm (90–97th centile) and a BMI of 33.4. She required corrective lenses.

Patient 2

Patient 2 is a phenotypic female born at 33 weeks of gestation following a pregnancy complicated by preeclampsia and oligohydramnios. The patient's mother received no prenatal care until after 20 weeks gestation. She also reported use of marijuana and the prescription medications ondansetron, sertraline, bupropion, and fluconazole during the pregnancy. The patient's mother was 28 years old and had a history of developmental delay, cognitive impairment and depression with a known deletion of 9p24.1 and 22q11.21. Following delivery Apgar scores were 8 and 9 at 1 and 5 min, respectively. Birth weight was 2.05 kg (58th centile), length 43.5 cm (38th centile), and head circumference 28 cm (50th centile for a 29.5-week gestation infant). An echocardiogram showed a PFO and small-to-moderate restrictive apical muscular ventricular septal defect (VSD). Hearing was normal. Congenital hypothyroidism is being managed with levothyroxine.

Results of cranial ultrasonography were normal. A pelvic ultrasound study showed a normal uterus; gonads were not visualized. On renal ultrasonography kidneys were normal but with significant left hydronephrosis suggestive of ureteropelvic junction (UPJ) obstruction, confirmed on diuretic renal scan. This was corrected at age 1 year.

The patient was developmentally delayed early on and required developmental services. At age 4 months, she was meeting all developmental milestones. She began walking independently at age 15–16 months. At 17 months, her expressive language development was equivalent to that of a 14-month-old but with advanced receptive language.

At 4 months the patient weighed 5.14 kg (5th centile) was 56.1 cm long (1st centile) and had a head circumference of 36.8 cm (50th centile for 1 month). At that time we noted a small nose, mild micrognathia and right occipital plagiocephaly. She had an easily reducible umbilical hernia, female external genitalia, transitional palmar crease on the right hand, mild head lag but had an otherwise normal neurologic status. At age 17 months weight was 8.92 kg (3rd centile), height 75.2 cm (8th centile), and head circumference 42 cm (50th centile for a 5-month old). Results of eye examination and hearing test at age 1 year were normal.

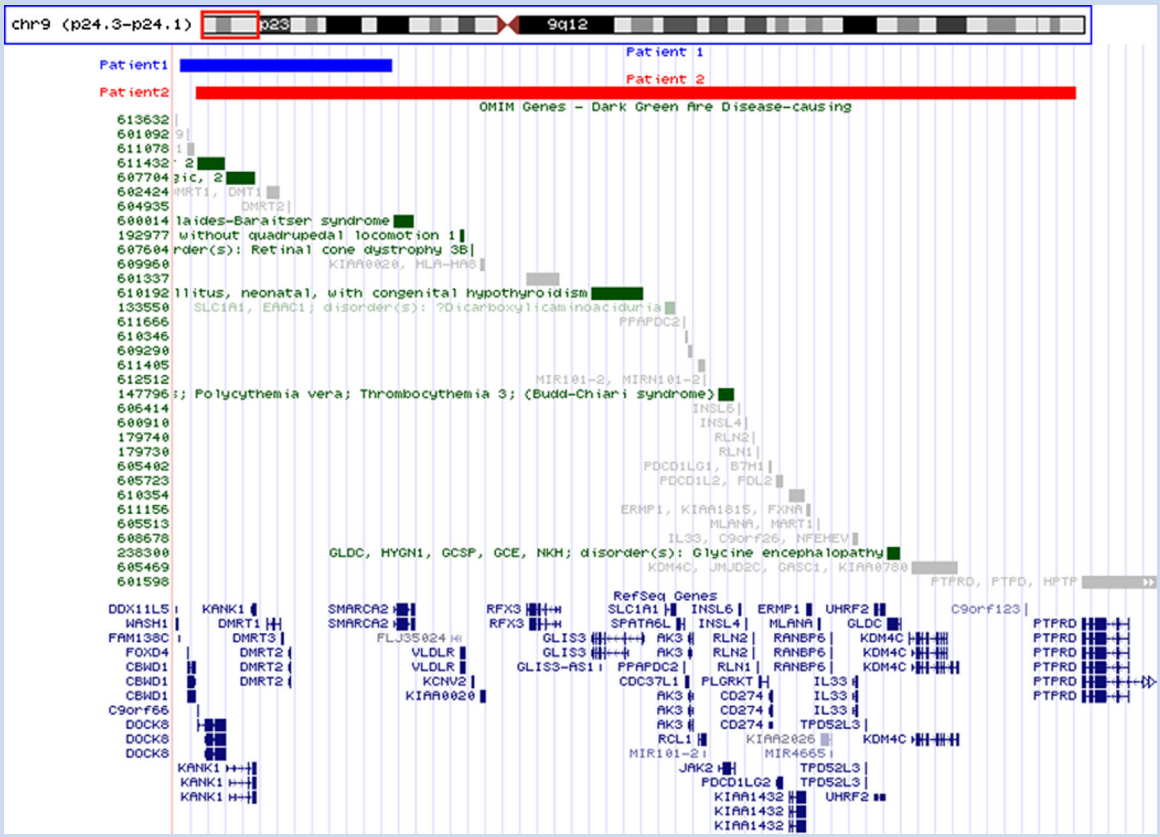

FIG. 1. Deleted region of chromosome 9 in Patients 1 and 2 shown in UCSC genome browser. The 9p haploinsufficient regions affecting Patients 1 and 2 are depicted in blue and red, respectively. OMIM and UCSC genes within the affected region are listed below deleted intervals.

RESULTS

Patient 1

At 10 months of age a karyotype obtained at the University of Utah showed a 46,XY,der(9)t(8;9)(p21;p24) unbalanced chromosome constitution with monosomy 9p24 and trisomy 8p21. At age 19 years, the boundaries of the deleted and duplicated regions were refined by microarray methods which identified a 25.3-Mb single copy duplication of 8p23.3p21.2 (176,818–25,510,851; hg 19) and a 2.0-Mb single copy deletion of 9p24.3 (46,587–1,994,144; hg 19) (Fig. 1). Father had a balanced translocation 46,XY,t(8,9)(p21;p24).

Given the increased incidence of gonadal malignancy in patients with gonadal dysgenesis, the patient underwent gonadectomy at age 3 years. Laparoscopic evaluation at that time showed the presence of a uterus and Fallopian tubes. Gonads were ovoid, white, firm and measured 2.5 × 0.6 × 0.8 cm. Both gonads had nearly identical histologic structure: They were dysgenic without ovarian follicles or seminiferous tubules. Cellular nests contained two cell types, large and round cells with clear cytoplasm and a large round nucleus and smaller comma-shaped cells. The histologic diagnosis was: gonadoblastoma.

Patient 2

The patient's mother had a known history of 9p24.1 deletion and 22q11.21 deletion. A maternal chromosomal microarray study refined the boundaries of the 9p24.1 (194,104–8,256,492; hg 18) and 22q11.21 (18,989,547–19,835,417; hg 18) deletions measuring 8.3 Mb and 846 kb in size, respectively (Fig. 1). Amniocentesis of Patient 2's mother showed 45,X/46,XY mosaicism and the 9p deletion. Following delivery, metaphase FISH analysis of 15 cells identified the 22q11.21 deletion as well in Patient 2. Postnatal karyotype also confirmed the maternally inherited deletion of 9p24. Her karyotype was denoted as 46,XY,del(9)(p24.1)mat.ishdel(22)(q11.21q11.21)(b135h6-). Given the prenatal mosaicism, 30 metaphase cells were analyzed postnatally and showed low level mosaicism for a 45,X cell population. Of 500 interphase cells, FISH probes specific to X and Y centromeres showed 5.6% of the cells had a 45,X constitution and 94.4% of the cells had a 46,XY constitution.

Given the increased risk of gonadal malignancy, the patient underwent gonadectomy at 1 year of age. Laparoscopic evaluation showed a normal uterus and Fallopian tubes. Both gonads were "streak," measuring 1.4 × 0.5 × 0.3 cm and 0.9 × 0.3 × 0.3 cm (Fig. 2A). Grossly no tumor nodules were recognized. Microscopi-

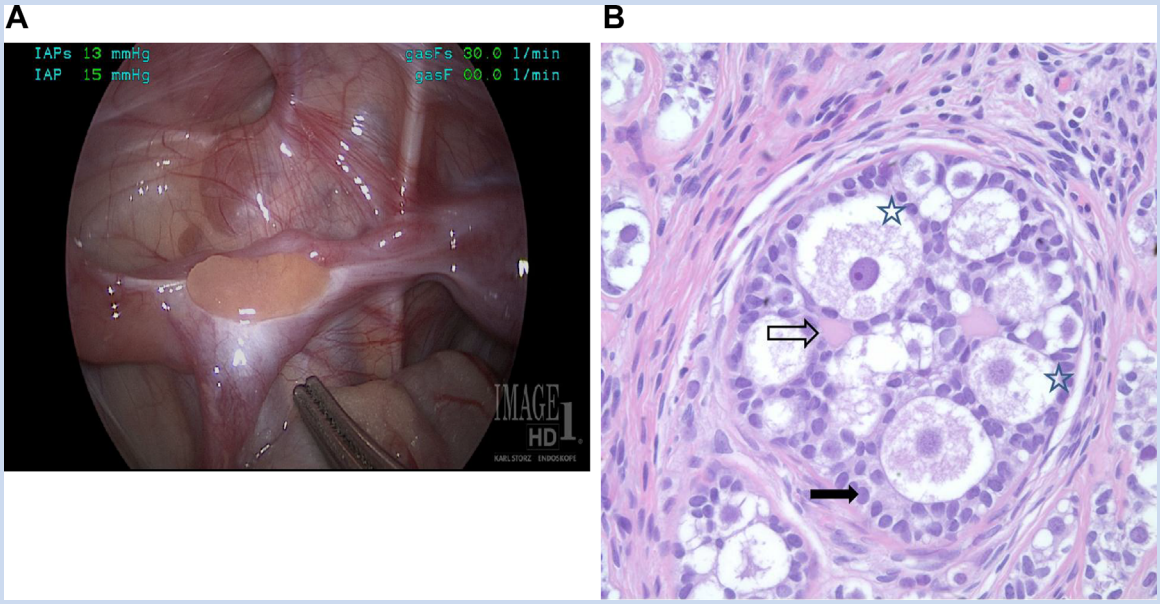

FIG. 2. Intraoperative and pathology images of Patient 2. A: Intraoperative photograph showing streak gonad. B: Gonadoblastoma focus containing large germ cells (star), small dark stromal cells (dark arrow), and eosinophilic hyaline bodies (open arrow).

cally, both gonads showed ovarian stroma with small foci of gonadoblastoma with microcalcifications (Fig. 2B). These foci contained nests of large germ cells with clear cytoplasm surrounded by smaller cells with dark hyperchromatic nuclei consistent with stromal sex cord type cells. Eosinophilic hyaline bodies composed of basement membrane material were also noted in the nests. No follicle formation or testicular differentiation was noted. No invasive tumor was seen. Cytogenetic analysis of the gonadal tissue showed mosaicism for 45,X and 46,XY cell lines and the previously identified deletion of 9p24.1. Following metaphase and interphase FISH analysis, shown in Figure 3, it was determined that one gonad contained 46% 45,X cells and 54% 46,XY cells with the other having 67% 45,X cells and 33% 46,XY cells.

DISCUSSION

DSD are a clinically and causally heterogeneous group of disorders. In patients with 46,XY complete gonadal dysgenesis, a cause is identified in less than half of the cases. Up to 20–30% of these are attributed to *SRY* and *SF1* mutations with other single gene causes contributing only a small proportion of the remainder [Hawkins et al., 1992; Philibert et al., 2010]. Array-comparative genomic hybridization has allowed clinicians to detect CNVs not visible cytogenetically and also allowed refinement of those previously detected karyotype aberrations. Ledig et al. [2010] estimated that the cause of 25% of syndromic and 5.6% of non-syndromic gonadal dysgenesis could be identified by array CGH. Hemizygosity of the distal segment of 9p is known to cause 46,XY gonadal dysgenesis and other milder genital phenotypes including ambiguous genitalia, hypospadias and cryptorchidism. Here we present two patients with a diagnosis of 46,XY complete gonadal dysgenesis found to have partial monosomy for 9p and other cytogenetic abnormalities.

The two patients reported here presented with classic findings consistent with complete 46,XY gonadal dysgenesis. Patient 1 was reported previously, with further molecular studies performed following the initial report [McDonald et al., 1997; Flejter et al., 1998]. As recommended by Flejter et al. [1998] the data reported here further characterize the deletion and duplication boundaries of this patient [Huret et al., 1988; Flejter et al., 1998; Muroya et al., 2000; Swinkels et al., 2008]. The patient is also trisomic for approximately 25 Mb of the short arm of chromosome 8. The phenotypic consequences of this aberration are unknown at this time. Of note, *GATA4* is within the duplicated region. Loss-of-function mutations and haploinsufficiency of *GATA4* has implications in sexual and cardiac development, with mutations causing 46,XY gonadal dysgenesis and heart septation defects, respectively [Reamon-Buettner and Borlak, 2005; Lourenço et al., 2011]. There has been debate as to whether *GATA4* duplication results in cardiac defects, but it remains an important consideration given the patient's bicuspid aortic valve [Yu et al., 2011]. No gain-of-function mutations or duplications of *GATA4* have been reported to cause gonadal dysgenesis or genital abnormalities, but patients with 8p duplications that include *GATA4* have presented with hypospadias [Yu et al., 2010, 2011]. The large number of genes involved makes an exact genotype–phenotype correlation difficult to establish.

Patient 2 also presented with findings of complete gonadal dysgenesis. Her mosaic karyotype contained both 45,X and 46, XY cell lines. The external phenotype in patients with 45,X/46,XY mosaicism can include normal male or female genitalia or ambiguous genitalia with gonadal pathology also variable, ranging from

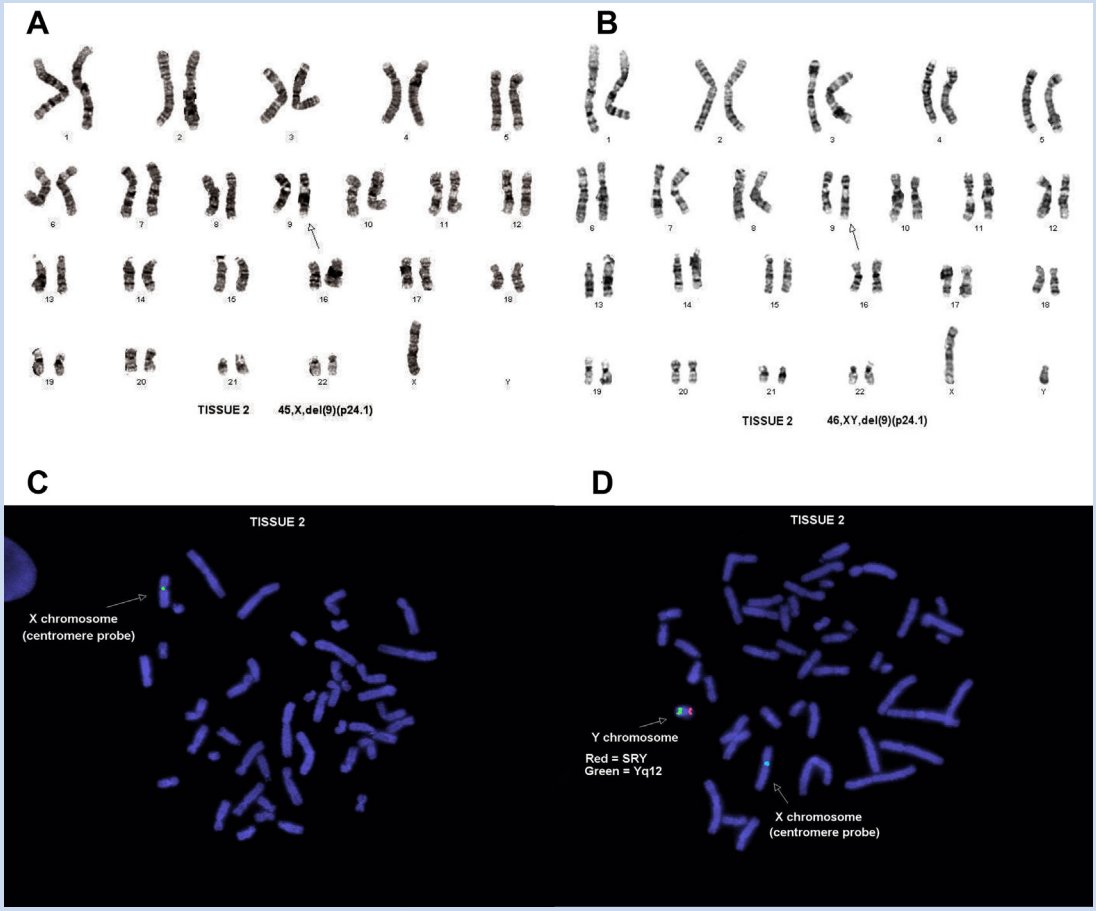

FIG. 3. Cytogenetic results of Patient 2's mosaic gonadal tissue using X chromosome centromeric (green), SRY (red), and Yq12 (green) probes of gonadal tissue. A: 45,X,del(9)(p24.1) karyotype. B: 46,XY,del(9)(p24.1) karyotype of gonadal tissue 2. C: FISH analysis showing only one X chromosome signal and absent hybridization of Y chromosome probes. D: FISH analysis confirming mosaicism with hybridization of both X and Y probes.

apparently normal testes to dysgenetic gonads [Farrugia et al., 2013; Tosson et al., 2012]. Similar to Patient 2, individuals with 45,X/46,XY mosaicism can have significant differences in the percentage of 45,X and 46,XY cell lines present in different tissues [Tosson et al., 2012]. This has clear implications in gonadal development, with the elevated percentage of 45,X cells (67%) present in Patient 2's gonadal tissue likely contributing to their dysgenetic development. Determining the exact contribution that each cytogenetic aberration (partial 9p monosomy and the 45,X cell line) has on Patient 2's phenotype is difficult to establish. The patient will require management for Turner syndrome as she grows.

Patient 2 also inherited an 846 kb deletion of 22q11.21 from her mother. This deletion lies within the distal half of the common 3 Mb deletion associated with DiGeorge syndrome (OMIM #18440) and velocardiofacial syndrome (VCFS; OMIM #192430). The proximal region of the long arm of chromosome 22 has a large number of low copy repeats that increase the risk of rearrangements caused by non-allelic homologous recombination. The most common rearrangement, seen in DiGeorge syndrome/VCFS, occurs as a result of non-allelic homologous recombination between low copy repeats 2 and 4, as defined by Edelmann et al. [1999] and McDermid and Morrow [2002]. Patients have been described with deletions of the surrounding genomic area [Garcia-Miñaur et al., 2002; Rauch et al., 2005; Ogilvie et al., 2009; Breckpot et al., 2012]. Our patient's deletion contains 19 genes including three OMIM disease genes (*ZNF74*, *HCF2*, and *SNAP29*) but does not include *TBX1*. It is nearly identical to the deletions reported by Garcia-Miñaur et al. [2002] and Rauch et al. [2005], and lies between low copy repeat 3 and low copy repeat 4. The patient reported by Garcia-Miñaur et al. [2002], a male who inherited his deletion from an asymptomatic father, had Tetralogy of Fallot, microcephaly and minor anomalies. Rauch et al. [2005] reported on a patient with a similar deletion who also presented with congenital heart disease (CHD), mild hypotonia, frequent infections and facial features consistent with mild DiGeorge syndrome. This deletion may provide a partial explanation of the VSD in Patient 2 with haploinsufficiency for *CRKL* (within the deleted segment) suggested as a candidate gene responsible for the CHD in these patients

[Breckpot et al., 2012]. 46,XY gonadal dysgenesis has not been reported in these patients, but two patients have been reported with 46,XX testicular DSD who were found to have the DiGeorge deletion [Phelan et al., 2002; Erickson et al., 2003]. Similar to the presence of the 45,X cell line, this deletion makes assigning responsibility to any one causative cytogenetic aberration difficult.

Both patients presented with 9p monsomy as well as other significant chromosomal abnormalities that make establishing an exact genotype–phenotype relationship difficult. To gain additional insights, we reviewed the literature and identified previous reports of partial 9p monosomy causing haploinsufficiency of *DMRT1*, the leading candidate gene for 46,XY complete gonadal dysgenesis in these patients (see below). Specific emphasis was paid to patients with 46,XY karyotypes and any genital-related phenotypic abnormalities (Table I). The reported genital phenotypes ranged from complete gonadal dysgenesis to cryptorchidism, hypospadias, and micropenis. Though Table I is limited to those patients with genital abnormalities, multiple 46,XY patients with no abnormal genital phenotype or complete gonadal dysgenesis have been described with monosomy for near-identical segments of 9p (Table II). This is in contrast to a number of patients with complete or partial 46,XY gonadal dysgenesis found to have small intragenic deletions in *DMRT1* [Ledig et al., 2010, 2012].

Review of Table I shows that 60% (43/72) of those patients with genital abnormalities and/or complete gonadal dysgenesis have at least one additional CNV/karyotype abnormality besides monosomy for a portion of 9p. Most of these are trisomies caused by an unbalanced translocation. Given the variable penetrance and expressivity of the genital phenotype, this may suggest a second hit is needed for the 46,XY complete gonadal dysgenesis and/or genital abnormalities to develop. Huret et al. [1988] evaluated 80 cases of partial 9p monosomy and compared those with other unbalanced segments (41 cases) with those containing only partial 9p monosomy (39 cases). They found 42% of both groups presented with external genitalia abnormalities. It should be noted though that both groups included both 46,XY and 46,XX patients. Given that partial 9p monosomy, especially *DMRT1* haploinsufficiency, affects 46,XX individuals much less significantly (no testicular DSD/gonadal dysgenesis or genitalia ambiguity) than those with 46,XY karyotypes, the data in Table I should prove more useful when considering the genotype–phenotype relationships of partial 9p monosomy. Comparing the patients in Table I to those patients without external genital abnormalities (Table II) reveals statistically significant support for a two-hit hypothesis as 81% (13/16) of those patients with no genital phenotypes have only one noted CNV/cytogenetic abnormality (Fisher's exact test, $P = 0.0047$). Further comparison of both groups of patients reveals that the three patients with no genital abnormalities and a second hit have similar additional CNVs to three patients listed in Table I (trisomy for portions of 6p, 10q, and 20p). This suggests further variable expressivity or incomplete penetrance of these duplicated regions versus an unknown alternative locus contributing to the genital phenotype in the affected patients. It should also be mentioned that a significant percentage of the patients evaluated have only had karyotype analysis. Chromosomal microarray would likely identify the presence of additional copy number abnormalities undetectable by cytogenetic techniques. A potential reporting bias should also be considered as patients with a more severe phenotype and/or multiple copy number abnormalities are more likely to be reported. Regardless though, given the significant differences between both groups, further evaluation of a two-hit mechanism is warranted.

This two-hit hypothesis is similar to the previously suggested second-hit models involving other developmental abnormalities including a cardiac phenotype in *GATA4* duplications [Giririjan et al., 2010; Yu et al., 2011; Lupski, 2012]. Though chromosomal duplications, which represent most of the second-hits in our patients, are better tolerated when compared to deletions, duplication of *DAX1* can lead to 46,XY complete gonadal dysgenesis [Barbaro et al., 2007], and dosage sensitivity is well described in mouse sex reversal [Bouma et al., 2007; Buaas et al., 2009; Correa et al., 2012]. Overall, this may suggest a role for other duplicated regions and dosage-sensitive genes in providing the second-hit responsible for the gonadal dysgenesis phenotype in these patients. Review of the genomic regions reported as second hits in Table I failed to identify any strong candidate genes that could be implicated in the abnormal genital phenotype. Although there are genes that have been implicated in abnormal sex development within duplicated regions of the 9p monosomy patients, including *CYP11A* and *SRD5A2*, the genital abnormalities are associated with loss of function rather than gain of function.

As previously mentioned, *DMRT1* is the gene likely responsible for gonadal dysgenesis in a subset of 9p monosomy patients. Localized to the 9p24.3 region are three *DMRT* (Doublesex-Mab3-Related Transcription factor 1–3) genes. These genes were initially identified as strong candidate genes for 46,XY complete gonadal dysgenesis based on their *Caenorhabditis elegans* and *Drosophila melanogaster* homologues' role in sexual development [Raymond et al., 1998, 1999]. *DMRT* genes contain a DNA-binding motif domain, a zinc containing DNA-binding module [Zhu et al., 2000]. In mammals, *DMRT1* is expressed only in the gonad and following sex determination, only in the testis [Raymond et al., 1998; Matson and Zarkower, 2012]. *DMRT1*-null male mice have normal external genitalia with functional Sertoli cells, but have hypoplastic testes, disorganized seminiferous tubules and lack germ cells [Raymond et al., 2000]. Heterozygous males are phenotypically normal with normal testes and retained fertility [Raymond et al., 2000]. However, in homozygous null male mice, at 2 weeks following birth, the Sertoli cell expression pattern changes; there is decreased expression of *SOX9*, increased expression of *FOXL2*, and overall reprogramming of Sertoli cells into a granulosa-like cell type [Matson et al., 2011]. This, and data regarding the function of granulosa cells, suggests that following determination and differentiation, both Sertoli and granulosa cells require the presence of certain proteins to maintain their identity and function [Matson and Zarkower, 2012]. This principle, termed sex maintenance, is achieved in males through the function of *DMRT1*, and in females through *FOXL2* [Uhlenhaut et al., 2009; Matson et al., 2011].

Review of Patient 2's history reveals the presence of congenital hypothyroidism diagnosed on newborn screening. Though there are multiple genetic causes of congenital hypothyroidism, it is interesting to note that Patient 2 is haploinsufficient for *GLIS3*, which lies within the deleted 9p interval. *GLIS3* loss-of-function mutations cause an autosomal recessive syndrome termed Neona-

TABLE I. Chromosomal Imbalances in 46,XY Patients with 9p Deletions and Genital Abnormalities

Case	Karyotype or chromosomal region[a]	CNV size	External genitalia	Pathology	Refs.
1	46,XY,der(9)t(8;9)(p21;p24)	9p: 2 Mb[b] 8p: 25.3 Mb[b]	Female	Dysgenetic tissue, *gonadoblastoma*	Patient 1
2	45,X/46,XY,del(9)(p24.1)mat.ishdel(22)(q11.21q11.21)(b135h6-)	9p: 8.3 Mb[c] 22q: 846 kb[c]	Female	Dysgenetic tissue, *gonadoblastoma*	Patient 2
3	46,XY,del(9)(pter-p22)	—	Cryptorchidism	—	Chen et al. [2012]
4	del9p24.3p22.2 dup9p22.2p11.2	del9p: 18.3 Mb[d] dup9p: 21.5 Mb[d]	Cryptorchidism	—	Recalcati et al. [2012]
5	46,XY,del 9p24.1pter	6.5 Mb[e]	Ambiguous genitalia	1 gonad with dysgenetic tissue and *gonadoblastoma*	Onesimo et al. [2012]
6	del9p24.3 dup11q24	9p: 35 kb[f] 11q: 8.5 Mb[f]	Ambiguous genitalia	Dysgenetic uterine tissue	Ledig et al. [2012]
7	46,XY.arr 9p13.3p23(12,439,651–36,100,991)x3, 9p23p24.3-(36,587–12,432,345)x1 dn	del9p: 12.3 Mb[g] dup9p: 23 Mb[g]	Ambiguous genitalia	Prepubertal testicles and fallopian tissue	Neira et al. [2012]
8	46,XY, der9 t(Y;9)(q12; p23).ish der(Y;9)(q12;p23)(wcpY, RP11-518K17, RP11-109G22).arr 9p24.3p23(201,086–12,993,711)x1 dn	9p: 12.8 Mb[h]	Ambiguous genitalia	Germ cell hypoplasia of seminiferous tubules	Lee et al. [2011]
9	46,XY,der(9)t(9;20)(p24;p12)	del9p: 6.36 Mb dup20p: 14.8 Mb	Hypospadias and shawl scrotum	—	Freitas et al. [2011]
10	46,XY,der(9)t(5;9)(q34;p23)	del9p:12 Mb[i] dup5q: 17 Mb[i]	Micropenis and cryptorchidism	—	Vásquez-Velásquez et al. [2011]
11	46,XY,der(9)t(9;15)(p23;q25.3)	del9p: 11.5 Mb[j] dup15q: 16.5 Mb[j]	Female	Fibrous tissue with testicular morphology	Argyriou et al. [2010]
12	del9p23.3-p23	10.6 Mb[k]	Clitoral hypertrophy	Partial gonadal dysgenesis, *dysgerminoma*	Ledig et al. [2010]
13	del9p24.2-p23 dup16p13.3-p13.13	9p: 9.7 Mb[l] 16p: 11.41 Mb[l]	Female	—	Ledig et al. [2010]
14	del9p24.3	821.6 kb[m]	Female	—	Ledig et al. [2010]
15	del9p24.4	103.2 kb[n]	Female	—	Ledig et al. [2010]
16	del9p24.3	~700 kb[o]	Female	Dysgenetic tissue	Barbaro et al. [2009]
17	46,XY,del(9)(p23)	11.5 Mb[p]	Female	Fibrovascular tissue with Mullerian glandular-tubular structures	Barbaro et al. [2009]
18	46,XY,der(9)t(9;16)(p22;q24)	—	Hypospadias and/or micropenis	—	Swinkels et al. [2008]

TABLE I. (*Continued*)

Case	Karyotype or chromosomal region[a]	CNV size	External genitalia	Pathology	Refs.
19	46,XY,del(9)(p24)	—	Hypospadias and/or micropenis	—	Swinkels et al. [2008]
20	46,XY,del(9)(p23)	—	Hypospadias and/or micropenis	—	Swinkels et al. [2008]
21	del9pter-p23 dup9p23 dup20p13	del9p: 10.4 Mb[q] dup9p: 1.2 Mb[q] dup20p: 4.2 Mb[q]	Chordee and cryptorchidism	—	Hauge et al. [2008]
22	46,XY,der(9)t(7;9)(p21.2;p24.1)	—	Cryptorchidism and hypospadias	*Seminoma*	Velagaleti et al. [2007]
23	46,XY,del(9p24)	~7 Mb	Genital bud with striated non-fused labioscrotal folds	Both dysgenetic and seminiferous tubule-like structures with rare Sertoli cells	Vinci et al. [2007]
24	45,X,der(Y;9)(q12;p24).ish der(Y;9)(DYZ3 + ,SRY + ,9ptel−) dn	—	Ambiguous genitalia	—	Vásquez-Velásquez et al. [2005]
25	del9pter-p24 dup1p34.3-p33	9p: 4 Mb 1p: 7.9 Mb	Cryptorchidism	—	Hayashi et al. [2005]
26	46,XY,t(7;9)(q32;p24)	9p: ~4–6 Mb 7q: ~25 Mb	Female	Bilateral ovotestes	Ounap et al. [2004]
27	46,XY,del(9)(p22)	—	Female	Dysgenetic tissue, *gonadoblastoma*	Livadas et al. [2003]
28	45,X,der(Y;9) (Ypter-Yq12::9p21.1–9p22.2::9p22.2–9qter)	del9p: ~15 Mb dup9p: ~16 Mb	Female	Dysplastic, *gonadoblastoma*	de Ravel et al. [2004]
29	46,XY,der(9)t(3;9)(p14;p24)	—	Ambiguous	—	Witters et al. [2004]
30	46,XY,del(9)(pter-p22)	—	Ambiguous genitalia	Dysgenetic tissue	Vialard et al. [2002]
31	46,XY,add(9)(p24) = 46,XY,inv dup(9)(p12p24)	del9p: 2.1–3.8 Mb dup9p: 30 Mb	Female	—	Muroya et al. [2000]
32	46,XY,r(9)(p24q34.3)	~20 Mb	Female	—	Muroya et al. [2000]
33	46,XY,der(9)t(4;9)(p15;p23)	~27 Mb	Female with hypoplastic labia majora	Dysgenetic tissue, *gonadoblastoma*	Muroya et al. [2000]
34	46,XY,del(9)(p23)	3.9–10.5 Mb	Ambiguous genitalia	Hypoplastic testes with Wolffian structures	Muroya et al. [2000]
35	46,XY,der(9)t(4;9) (p13;p24)	0.5–2.8 Mb	Male with cryptorchidism	—	Muroya et al. [2000]
36	46,XY,der(9),t(8;9)(q23.1;p23)	del9p: ~17 cM dup8q: NR	Ambiguous genitalia	Testicular morphology with few spermatocytes and rare gonocytes	Shan et al. [2000]
37	46,XY,der(9),t(9;13)(p22;q14)	del9p: ~23 cM dup13q: NR	Female	—	Shan et al. [2000]
38	46,XY,r(9)(p23q34.3)	—	Ambiguous genitalia	—	Raymond et al. [1999]
39	46,XY,der(9)t(4;9)(q27;p24)	—	Cryptorchidism	—	Wouters et al. [1999]
40	46,XY,der(9),t(9;15)(p22;q22.3)	—	Female	—	Flejter et al. [1998]
41	46,XY,der(9)t(9;11)(p24;q14.2)mat	—	Ambiguous genitalia	—	Flejter et al. [1998]

TABLE I. (*Continued*)

Case	Karyotype or chromosomal region[a]	CNV size	External genitalia	Pathology	Refs.
42	46,XY,del(9)(p23)	~17–23 cM	Ambiguous genitalia	—	Guioli et al. [1998]
43	46,XY,del(9)(p23;p24.3)	~18.6–21 cM	Ambiguous genitalia	—	Guioli et al. [1998]
44	46,XY,del(9) (p23.05)	~11–21 cM	Female	Wolffian duct remnants in streak gonads	Guioli et al. [1998]
45	46,XY,(9),der(9) t(7;9)(q21.1;p24)	~2.9–4.8 cM	Ambiguous genitalia	—	Guioli et al. [1998]
46	46,XYdel(9)(pter-p22)	—	Micropenis	—	Shashi et al. [1998]
47	46,XYdel(9)(pter-p23)	~9.5–12.9 Mb	Clitoromegaly	Fibrous stroma without primary follicles, rare Leydig-like cells	Veitia et al. [1998]
48	46,XYdel(9)p24.3	—	Ambiguous genitalia	Syncytial Sertolian cords and some spermatogonia	Veitia et al. [1998]
49	46,XY,der(9)t(7;9)(p21.2;p23.5)	—	Hypospadias and cryptorchidism	—	Back et al. [1997]
50	46,XY,del(9)(p23)	~8–10.5 Mb	Ambiguous genitalia	Seminiferous tubules present with Sertoli cells and spermatogonia	Ogata et al. [1997]
51	46,XYinv dup(9)(p12p23)del(9)(p24)	~9.5–11 Mb	Female	—	Veitia et al. [1997]
52	46,XY,t(9,14)(p23; q12),-der(14)t(9;14),+r(14) 45,XY,t(9; 14)(p23; q12),-der(14)t(9;14)	~9.5–10.5 Mb	Ambiguous genitalia	Reduced number of tubules but with normal constitution. No Mullerian structures present	Veitia et al. [1997]
53	46,XY,-9,+der(9)t(5;9)(q32;p24) mat	—	Hypospadias, chordee, bifid scrotum	—	Schimmenti et al. [1995]
54	46,XY,del(9)(p2305)	—	Female	Few epididymal tubules, islands of interstitial cells and Wolffian duct remnants	Bennett et al. [1993]
55	46,XY,der(9),t(4;9)(?;p24)pat	—	Female	—	Magenis et al. [1990]
56	46,XY,der(9),t(2;9)(p21;p24)	~9–11 cM	Female	—	Hoo et al. [1989]
57	46,XY,der(9)t(9;6)(p24;p11)	—	Ambiguous genitalia	—	Lytle et al. [1989]
58	46,XY,der(9),t(9;12)(p21;q24)mat	—	Hypospadias	—	Huret et al. [1988]
59	46,XY,del(9)(p22)/46,XY,r(9)(p22;q34)	—	Micropenis	—	Leung and Rudd [1988]
60	46,XY,der(9),t(7;9)(q31.1;p23)pat	—	Female	Testicular with seminiferous tubules lined by Sertoli cells	Crocker et al. [1988]
61	46,XY,der(9),t(3;9)(p21.33;p22.1)mat	—	Female	—	Fryns et al. [1986]
62	46,XY,-9,+der(9)t(9;10)(p22;q25.2)	—	Cryptorchidism	—	Hoo [1986]
63	46,XY,del(9)(pter-p22)	—	Micropenis, cryptorchidism, hypospadias	—	Kadotani et al. [1984]
64	46,XY,del(9)(pter-p22)	—	Micropenis	—	Szymańska et al. [1984]
65	46,XY,del(9)(pter-p22)	—	Hypospadias	—	Wilhelm and Osztovics [1982]
66	46,XY,del(9)(pter-p22)	—	Micropenis and underdeveloped scrotum	—	Monaghan and Howard [1981]
67	46,XY,der(9)t(9;13)(p23;q21)	—	Hypospadias and micropenis	—	Prieto et al. [1980]

TABLE I. (*Continued*)

Case	Karyotype or chromosomal region[a]	CNV size	External genitalia	Pathology	Refs.
68	46,XY,del(9)(pter-p22)	—	Cryptorchidism	—	Fryns et al. [1980]
69	46,XY,del(9)(pter-p22)	—	Hypospadias	—	Funderburk et al. [1979]
70	46,XY,del(9)(pter-p21)	—	Micropenis	—	Pavone et al. [1978]
71	46,XY,der(9),t(9;13)(p21;q21)mat	—	Ambiguous genitalia	Immature testicular tissue (left) and fibro-adipous tissue (right)	Jotterand and Juillard [1976]
72	46,XY,del(9)(pter-p22)	—	Hypospadias and cryptorchidism	—	Alfi et al. [1973]

NR, not reported.
[a]All karyotypes of 46,XY constitution.
[b]9p: 46,587–1,994,144, 8p: 176,818–25,510,851; hg19.
[c]9p: 194,104–8,256,492, 22q: 18,989,547–19,835,417; hg 18.
[d]del9p: 194,193–18,341,167, dup9p: 18,368,491–39,884,938; hg18.
[e]9p: 204,367–6,582,172; hg18.
[f]9p: 883,300–918,342, 11q: 1,256,069,874–125,895,030; hg18.
[g]del9p: 36,587–12,432,345, dup9p: 12,439,651–36,100,991 (hg 19).
[h]9p: 201,086–12,993,711 (build NR).
[i]9p: 194,000–12,664,000, 5q: 163,328,000–180,629,000; hg 18.
[j]del9p: 0–11,447,000, dup 15q: 83,721,000–100,283,000; hg 18.
[k]9p: 152,931–10,776,275 (build NR).
[l]9p: 229,226–9,933,540, 16p: 45,058–11,454,770; hg18.
[m]9p: 270,055–1,091,607; hg18.
[n]9p: 72,747–855,979; hg 18.
[o]9p: 107,982–776,954 (build NR).
[p]9p: 107,982–11,547,363 (build NR).
[q]del9p: pter-10,430,655, dup9p: 10,571,443–11,808,291, 20p: 18,580–4,307,012 (build NR).

TABLE II. Chromosomal Imbalances in 46,XY Patients With 9p Deletions and No Genital Abnormalities

Case	Karyotype or chromosomal region[a]	CNV size	Refs.
1	del9pter-p22 dup10q26-qter	—	Akbas et al. [2011]
2	del9pter-p23	11.1 Mb	Shimojima and Yamamoto [2009]
3	46,XY,del(9)(p24.3)	1.17–1.23 Mb[b]	Hauge et al. [2008] (Case 3)
4	del9pter-p23	del9p: 10 Mb	Hauge et al. [2008] (Case9)
	dup20pter-p12.1	dup20p: 14 Mb	
5	del9pter-p22.3	~15 Mb	Swinkels et al. [2008] (Case 8)
6	46,XY,del(9)(pter-p22)	—	Huret et al. [1988] (Case 2)
7	46,XY,del(9)(qter-p220	—	Boby et al. [1994]
8	46,XY,del(9)(qter-p2304)	—	Taylor et al. [1991]
9	46,XY,der(9)t(6:9)(p211;p24)	—	Eden et al. [1985]
10	46,XY,del(9)(pter-p22)	—	Ioan et al. [1985]
11	46,XY,del(9)(pter-p12)	—	Young et al. [1983]
12	46,XY,del(9)(pter-p22)	—	Bricarelli et al. [1981]
13	46,XY,del(9)(pter-p12)	—	Hernandez et al. [1979]
14	46,XY,del(9)(pter-p22)	—	Nielsen et al. [1977]
15	46,XY,del(9)(pter-p22)	—	Alfi et al. [1976]
16	46,XY,del(9)(pter-p21)	—	Serville et al. [1976]

[a]All karyotypes of 46,XY constitution.
[b]p: pter-1,167,143–1,233,178 (build NR).

tal diabetes mellitus with congenital hypothyroidism (OMIM #610199) [Senée et al., 2006]. This condition has been seen in consanguineous Saudia Arabian families and can include hepatic fibrosis, congenital glaucoma and polycystic kidneys. Though Patient 2 has loss of only one copy of the gene, it is possible that haploinsufficiency results in the congenital hypothyroidism but none of the other features that are part of the condition. Multiple other patients have been reported with partial 9p monosomy and hypothyroidism [Ioan et al., 1985; Kozma et al., 2000; Velagaleti et al., 2008]. Review of Patient 1's deleted 9p interval shows *GLIS3* not to be deleted. It is also possible that the deletion of *GLIS3* in Patient 2 uncovered an autosomal recessive mechanism leading to her congenital hypothyroidism, leading to speculation that she may carry a deleterious mutation of her other *GLIS3* allele. Further testing would be required to prove this hypothesis. Regardless, we recommend evaluation for hypothyroidism in patients with partial 9p monosomy, especially if *GLIS3* is within the deleted interval.

Patients with DSD, specifically those with dysgenetic gonads and/or hypovirilization, have an increased risk of type II germ cell tumors [Looijenga et al., 2010]. Gonadoblastomas are estimated to occur in up to 30% of 46,XY patients with dysgenetic gonads [Sultana et al., 1995]. The presence of Y chromosome material has been implicated in the oncogenesis in these patients, with the locus mapped to the Y centromeric region [Page, 1987]. *TSPY* has arisen as the leading candidate for the responsible gene [Lau, 1999]. Given this increased risk, both of the patients reported here underwent gonadectomy with pathology showing the presence of dysgenetic gonads and gonadoblastoma. Additional immunohistochemical stains were not performed on our two patients' samples because both lacked identifiable seminiferous tubules, making specific staining to differentiate delayed germ cell maturation from intratubular germ cell neoplasia unnecessary. Review of Table I shows that multiple patients reported in the past developed gonadoblastoma as well. Livadas et al. [2003] previously reviewed the literature as it pertained to gonadoblastoma in patients with 9p deletions and other 46,XY complete gonadal dysgenesis loci. Review of Table I shows that of those patients with 46,XY karyotypes, complete gonadal dysgenesis and partial 9p monosomy, 11% (8/72) developed a gonadal malignancy. If only those patients with pathology data are considered, this percentage increases to 30% (8/27). It is also important to note that most gonadal malignancies occurred in patients with complete gonadal dysgenesis (with the exception of Cases 3 and 8 who presented with ambiguous genitalia and clitoral hypertrophy, respectively). This supports the recommendation that gonadectomy be performed in patients with gonadal dysgenesis, especially those with partial 9p monosomy. Specific recommendations regarding gonadectomy and surveillance of 9p monosomic individuals with less severe genital phenotypes are difficult to make at this time given that the natural history of this cohort is currently unknown. Empirically, for these patients we recommend annual testicular examinations and consideration of scrotal ultrasound until adult age. Clinicians should have a low threshold for biopsy if suspicious findings are identified.

While the presence of *TSPY* can contribute to the increased risk of malignancy in these patients, loss of *DMRT1* activity has also been linked to an increased risk of cancer given its proposed tumor suppressor properties [Krentz et al., 2009]. Krentz et al. [2009] reported an increased incidence of testicular teratoma (Type I germ cell tumor) with loss of *DMRT1* in the male mice of the 129Sv strain. This incidence was noted to be around 90% in homozygous null

mutants and 4% in heterozygous mice with no noted increased tumor incidence in female mice. This increased teratoma risk was shown to result from a disruption of cell cycle pluripotency and cell cycle control [Krentz et al., 2009]. Genome wide association studies have also shown an increased susceptibility to testicular germ cell cancer in or around *DMRT1* [Turnbull et al., 2010; Kanetsky et al., 2011; Kratz et al., 2011]. It remains difficult to determine the exact oncogenic contribution that haploinsufficiency for *DMRT1* has, but further evaluation of this evolutionarily conserved pathway is clearly needed.

In conclusion, we report two patients with 46,XY complete gonadal dysgenesis caused by partial 9p monosomy. Both patients underwent gonadectomy, which revealed the presence of gonadoblastoma. The deletion breakpoints of Patient 1, who has previously been reported, were further characterized. Both patients' deletions resulted in *DMRT1* haploinsufficiency, which is likely contributing to their gonadal dysgenesis. Review of the literature shows that haploinsufficiency for *DMRT1* results in gonadal dysgenesis and abnormal sex development with variable penetrance and expressivity. We suggest this variability may be due to the presence of a second-hit (CNV or other molecular mechanism), which may be needed for subsequent abnormal sex development. Gonadoblastoma was also present in a significant percentage of patients with partial 9p monosomy, specifically those with gonadal dysgenesis, further supporting the recommendation that gonadectomy be performed in these patients. Further investigation will hopefully elucidate the relationship between *DMRT1* loss-of-function/haploinsufficiency and oncogenesis.

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