A novel, homozygous mutation in desert hedgehog (DHH) in a 46, XY patient with dysgenetic testes presenting with primary amenorrhoea: a case report

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Abstract

Background: Desert hedgehog (DHH) mutations have been described in only a limited number of individuals with 46, XY disorders of sex development (DSD) presenting as either partial or complete gonadal dysgenesis. Gonadal tumours and peripheral neuropathy have been associated with DHH mutations. Herein we report a novel, homozygous mutation of DHH identified through a targeted, massively parallel sequencing (MPS) DSD panel, in a patient presenting with partial gonadal dysgenesis. This novel mutation is two amino acids away from a previously described mutation in a patient who presented with complete gonadal dysgenesis. Adding to the complexity of work-up, our patient also expressed gender identity concern.

Case presentation: A 14-year-old, phenotypic female presented with primary amenorrhoea and absent secondary sex characteristics. Investigations revealed elevated gonadotrophins with low oestradiol, testosterone of 0.6 nmol/L and a 46, XY karyotype. Müllerian structures were not seen on pelvic ultrasound or laparoscopically and gonadal biopsies demonstrated dysgenetic testes without neoplasia (partial gonadal dysgenesis). The patient expressed gender identity confusion upon initial notification of investigation findings. Formal psychiatric evaluation excluded gender dysphoria. Genetic analysis was performed using a targeted, MPS DSD panel of 64 diagnostic and 927 research candidate genes. This identified a novel, homozygous mutation in exon 2 of DHH (DHH:NM_021044:exon2:c.G491C:p.R164P). With this finding our patient was screened for the possibility of peripheral neuropathy which was not evident clinically nor on investigation. She was commenced on oestrogen for pubertal induction.

Conclusion: The evaluation of patients with DSD is associated with considerable psychological distress. Targeted MPS enables an affordable and efficient method for diagnosis of 46, XY DSD cases. Identifying a genetic diagnosis may inform clinical management and in this case directed screening for peripheral neuropathy. In addition to the structural location of the mutation other interacting factors may influence phenotypic expression in homozygous DHH mutations.

Keywords: Disorder of sex development, Desert hedgehog, DHH, Gonadal dysgenesis, Massively parallel sequencing
Male phenotypic development involves testis formation from the bipotential gonad (sex determination) directed by multiple genes that reside on sex and autosomal chromosomes (Fig. 1). Subsequently internal and external genitalia differentiation occurs controlled by factors secreted by the testis (sex differentiation) [1, 2] (Fig. 1). The gene, desert hedgehog (DHH) plays a role in testis determination [1, 3, 4] and its protein product, produced by Sertoli cells, promotes Leydig cell development by activating Hedgehog signalling [3, 5]. Thus, through this Sertoli-Leydig cell interaction, DHH also regulates androgen synthesis and is involved in sex differentiation.

Mutations in the genes involved in testis determination and male sex differentiation, such as DHH, cause 46, XY disorders of sex development (DSD). DSD may present in infancy with variable genital ambiguity and 46, XY DSD may present in adolescence with primary amenorrhoea. Historically, a specific diagnosis for 46, XY DSD has remained elusive for many patients. Hormonal testing has limitations with examination of the steroidogenic pathway to determine the adequacy of androgen production and action only yielding a diagnosis in approximately 30% of 46, XY DSD patients [6]. There is normal variation in androgen levels during the neonatal and infantile periods [7] and steroid biosynthesis may change with time in some pathogenic gene variants resulting in misdiagnosis [8]. The use of candidate gene testing for the diagnosis of 46, XY DSD is impeded by the extensive number of genes potentially implicated [9]. Recent advances in sequencing technologies, such as targeted massively parallel sequencing (MPS) of genes in DSD has facilitated molecular diagnosis in up to 43% of 46, XY DSD patients [10]. MPS, allows billions of DNA base-pairs to be sequenced in parallel, yielding substantially more throughput than other technologies, such as Sanger sequencing. Thus, while Sanger sequencing would target a candidate single gene or region, MPS can target all potentially responsible genes.
Herein we describe the clinical course of a patient diagnosed with a novel mutation in DHH using the recently described MPS DSD panel [10]. Homozygous mutations in DHH have been reported in partial and complete gonadal dysgenesis in only a limited number of 46, XY individuals [11–17]. Co-existence of peripheral neuropathy has been reported in some patients [11, 14–17] as have gonadal tumours [12, 14]. Identification of the genetic aetiology has informed our patient’s management and provides opportunity for genetic counselling for family members. This case was further complicated by gender identity concern. The reported incidence of gender dysphoria in DSD varies from 3.3% in a cohort involving individuals with a range of DSD presentations [18], up to 61.4% in individuals with 5α-reductase deficiency or 17β-hydroxysteroid dehydrogenase type III deficiency [19]. In addition to the underlying DSD, cultural and psychological factors are likely to influence the incidence rate [20].

Case presentation
A 14-year-old girl was referred for evaluation of primary amenorrhoea and absent pubertal development. She is the oldest of four children born to consanguineous parents (first cousins) of Palestinian background. There were no perinatal issues and there was no past medical history of significance. A maternal sibling had transitioned from female to male as a teen; no further medical information regarding this family member was available.

On examination, our patient presented as a phenotypic female. She measured 154.5 cm in height (10 – 25th centile), weighed 51 kg (50th centile) and was normotensive. There were no dysmorphic features. Cardiovascular, respiratory and abdominal examinations were unremarkable. She had Tanner Stage 1 breast development; pubic hair was Tanner Stage 2. Genital examination demonstrated well-formed labia, a normal vaginal opening and no palpable gonads. There was a prominent clitoral structure.

Evaluation demonstrated low oestradiol with elevated gonadotrophins (oestradiol 84 pmol/L, follicle stimulating hormone 76 IU/L, luteinizing hormone 37 IU/L); this was confirmed on repeat testing one month later. Testosterone was 0.6 nmol/L. Urea and electrolytes, calcium and fasting glucose were normal. Karyotype revealed 46, XY. On pelvic ultrasound there were no Müllerian structures or gonads identified and there were no concerning mass lesions. On human chorionic gonadotrophin (HCG) stimulation test, baseline testosterone was 1.0 nmol/L and dihydrotestosterone (DHT) 0.2 nmol/L; post HCG testosterone was 0.9 nmol/L and DHT 0.2 nmol/L. Baseline cortisol was 200 nmol/L with cortisol 670 and then 730 nmol/L, 30 and 60 min post 250 mcg of Synacthen.

The diagnosis of a male genotype was difficult for the family. This was further complicated by the diagnosis not initially being disclosed to our patient by her parents. The patient’s mother was concerned about gender identity and assignment especially in view of her sibling’s history. Ultimately our patient was informed of the karyotype result following multidisciplinary review and parental counselling.

Examination under anaesthesia, laparoscopy, cystovaginoscopy and gonadal biopsies were performed. A blind ending vagina, approximately 6 cm in length from the introitus, was noted. There was no cervix, uterus, fallopian tubes or vasa. There were bilateral abnormal small gonads with a blind ending epididymal structure flanking each (Fig. 2).

Histopathology from the gonadal biopsies demonstrated bilateral dysgenetic testes with left para-gonadal biopsy showing Müllerian tissue resembling oviduct and the right para-gonadal biopsy showing vaso-epididymal tissue; there were no foci of gonadoblastoma or intratubular germ cell neoplasia. Our patient proceeded to gonadectomy five months later. Histopathology confirmed bilateral dysgenetic testes with no evidence of gonadoblastoma or germ cell neoplasia (Fig. 3).

When reviewing investigation findings, our patient expressed confusion regarding her gender identity stating she always felt that she was a boy. She was referred for psychiatric evaluation. At the time of psychiatric review (four months later), it was noted that our patient had not demonstrated pervasive gender discontent although she periodically expressed thoughts of the cultural advantages of being male. Our patient acknowledged feeling overwhelmed and confused when informed of investigation results. The reviewing psychiatrist concluded that our patient identified as female. Approximately fourteen months following presentation, the patient expressed her wish to proceed with oestrogen replacement therapy.

Our patient had DNA collected under a research protocol examining the molecular genetics of sex determination and gonad development using a MPS targeted DSD gene panel as described by Eggers et al. [10]; consent was obtained from the patient and her mother for this gene analysis. Of the 64 diagnostic and 927 research candidate DSD genes covered in this panel, our patient had a single, rare, non-synonymous variant. This was a novel, homozygous, missense mutation in exon 2 of DHH (DHH:NM_021044:exon2:c.G491C:p.R164P). This was confirmed on Sanger sequencing using the primers gccggaataacaaagaatcaac and ggcaacagtactactgcakit.

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damaging by FATHMM (score −6.31) [23]. Furthermore, this variant is not present in the ExAC [24], 1000 Genomes Project [25], and NHLBI GO Exome Sequencing Project databases [26], supporting the putative damaging effect of the mutation.

We generated a three-dimensional protein model of DHH (Fig. 4) using SWISS-MODEL (template ID 3n1g.1.A) [27] and we used HOPE [28] to analyse the structural and functional effects of the mutation. HOPE revealed that the mutated residue is located on a highly conserved position and overlapped three function domains: Hedgehog Protein (InterPro IPR001657), Hedgehog, N-Terminal Signalling Domain (InterPro IPR000320), and Hedgehog Signalling/Dd-Peptidase Zinc-

![Fig. 2 Surgical photos. a Laparoscopic view of left and right gonad within the pelvis. b Blind ending vagina at vaginoscopy. c Left gonad and epididymal flanking structure. d Right gonad and epididymal flanking structure](image)

![Fig. 3 Histopathology. a Right gonad excision biopsy, H&E stain, demonstrating seminiferous tubules lined by Sertoli cells without spermatogenesis. b Left gonad excision biopsy, H&E stain, demonstrating seminiferous tubules lined by Sertoli cells without spermatogenesis. There is intervening fibrosis with occasional, unusually large clusters of Leydig cells. c Left gonad excision, inhibin stain, demonstrating Sertoli and Leydig cell appearance. d Normal testis of 15-year-old, showing seminiferous tubules with spermatogenesis](image)
Binding Domain (InterPro IPR009045). The difference in charge and amino acid size between the wild-type and mutant amino acid likely results in loss of interactions with other molecules.

Follow-up and outcomes
After her psychiatric evaluation, our patient commenced transdermal estrogen in gradually increasing doses. On follow-up out to twelve months post estrogen initiation, breasts had increased in size and were Tanner stage 3. She was pleased with progress of pubertal induction and accepted further escalation in estrogen dose. She no longer expressed gender confusion.

Following the finding of a homozygous DHH mutation our patient was specifically evaluated considering the possibility of a peripheral neuropathy. There was no history suggestive of neurological impairment and clinical neurological examination (cranial nerves, gait, co-ordination, tone, power, deep tendon reflexes, touch, vibration and joint position sensation) was normal. Limited nerve conduction studies including left median nerve motor, sensory and F wave response as well as right upper limb somatosensory evoked potential study with stimulation of the median nerve at the wrist were all normal.

Our patient’s family was offered referral for genetic counselling but this has been declined to this point.

Discussion
Our patient presented with absent puberty and amenorrhea in the setting of a 46, XY karyotype (46, XY DSD). Although an understanding of male sex development (Fig. 1) and the results of biochemical and anatomical evaluation help narrow the possible diagnoses [29, 30], without gene testing the differential diagnoses in our patient remained broad. In our patient, possible underlying etiologies included the numerable genetic defects causing testicular development disorders (as suggested by Fig. 1), a milder phenotype of steroidogenic factor-1 (SF-1) under-expression, luteinizing hormone receptor defects and homozygous mutation in DHH (a disorder of potentially both testicular development and androgen synthesis) [1, 29]. In similar scenarios, candidate gene testing provides a molecular diagnosis in only approximately 20% of cases [9]. MPS is more efficient than candidate gene testing (such as Sanger sequencing), its sensitivity allows detection of cases of mosaicism, and using current panels it is more likely to provide a diagnosis [10]. In comparison to whole exome or whole genome sequencing, MPS with a targeted gene panel offers the advantage of shorter processing time with less...
DHH is a member of the Hedgehog family of signalling proteins which exerts its action through the receptor Patched [32]. Work in mouse models indicates that DHH expression is limited primarily to Sertoli cells in the developing testes and to Schwann cells in peripheral nerves [32, 33]. Whilst Dhh-null female mice show normal reproduction, Dhh-null male mice are sterile [31] with the majority having a feminized appearance [5]. Testes have few Leydig cells, an interstitium filled with fibroblast-like tissue and Sertoli-peritubular cell dysfunction [5], findings similar to that observed in our patient. In nerves, Dhh-null mice demonstrate impaired nerve sheath formation with susceptibility to mechanical assault and inflammation-related damage leading to minifascicle formation [32].

A clinical case with features similar to Dhh-null mice (46, XY gonadal dysgenesis and minifascicular neuropathy) was first described by Umehara et al. in 1999 [34]. This case was subsequently confirmed to have a homozygous DHH mutation [11]. The clinical details of a further eleven individuals with 46, XY karyotype and homozygous DHH mutations have been described [11–17] (Table 1). Another two individuals with heterozygous mutations on the background of a 45,X/46, XY karyotype have also been reported [35].

Previously reported individuals with 46, XY karyotype and homozygous DHH mutations all had female external genitalia and presented with primary amenorrhoea and lack of pubertal development. Internal reproductive anatomy varied with complete gonadal dysgenesis [12, 13, 15, 16] and partial gonadal dysgenesis with [11] or without [14, 15, 17] Müllerian structures described. Cases of complete gonadal dysgenesis tended to have more damaging mutations (failure of translation or premature termination) [12, 13] than the reported sisters with partial gonadal dysgenesis and an associated missense mutation [14], although a case of complete gonadal dysgenesis in a patient with a homozygous missense mutation is reported [12]. Our patient proceeded to gonadectomy due to the increased risk of gonadal tumours with gonadal dysgenesis. Gonadal tumours have been reported in DHH mutations [12, 14]. Of the 12 described 46, XY homozygous DHH mutation cases, six developed a peripheral neuropathy between 20 and 43 years of age [11, 14–17], with no clear genotype-phenotype correlation. It is possible that the cases who did not have evidence of peripheral neuropathy at the time of reporting may still develop symptoms, particularly given that several of these cases were younger than 20 years of age. More recently, a case of minifascicular neuropathy associated with homozygous DHH has been reported in a phenotypic female with a 46, XX karyotype [15]. It is only with the diagnosis of DHH mutation that we were prompted to consider peripheral neuropathy in

data handling and analysis without the risk of identifying variants in unrelated areas of the genome ( incidental findings) [9, 10]. As the price of MPS technologies decrease, the clinical use of targeted gene panels becomes a better option than Sanger sequencing one or more candidate genes. Where MPS targeted gene panels are not readily available or cost prohibitive, an alternative approach in a suspected autosomal recessive condition (i.e. in the case of consanguineous union) would be microarray and subsequent candidate gene sequencing of potential pathogenic genes within regions of homozygosity.

In our patient, a novel, homozygous DHH mutation was detected using the MPS targeted DSD gene panel described by Eggers et al. [10]. This MPS targeted DSD gene panel was conducted as part of a research protocol. DNA from 326 DSD patients has been analysed with this panel [10]; seven new patients with eight novel DHH mutations have been identified. Whilst four patients (including our patient) had homozygous or compound heterozygous DHH mutations and presented as 46, XY females, three individuals had heterozygous mutations, two of whom were 46, XY undervirilised males. These heterozygous mutations were deemed variants of uncertain significance but suggest DHH mutations may explain a broader spectrum of 46, XY DSD. On the other hand, as evidenced by fathers of the reported homozygous DHH mutation patients, individuals with a heterozygous DHH mutation may be asymptomatic [11]. Functional studies are now being carried out to ascertain the pathogenicity of these variants [Ayers et al. Unpublished]. With these studies and with wider use of MPS methods and analysis of more DSD patients and their relatives, the risks of a heterozygous DHH mutation may become clearer.

The DHH mutation detected in our patient was a homozygous, missense mutation (exon 2, c.491G > C) in codon 164 (p.R164P). This codon is only 2 amino acids away from a previously published mutation [12]. The mutation in our patient and that previously described both induce a proline mutation in an alpha helix in a highly conserved DHH residue and lead to disruption of the alpha helix [28]. In contrast to our case who had dysgenetic testes and absent Müllerian structures (partial gonadal dysgenesis), the previously published case had bilateral streak gonads with Müllerian structures (complete gonadal dysgenesis). This suggests that in addition to DHH mutation localization, other factors may influence phenotype expression. Bitgood et al., noted that in Dhh-null male mice bred on different genetic backgrounds spermiogenesis was arrested at different stages. They suggested that other unidentified factors are likely to participate with Dhh to express phenotype [31]. This is similar to the SRY and SF-1 genes, where mutations have been associated with a spectrum of 46, XY DSD phenotypes [1, 12].
our patient. Continued surveillance into adulthood for the potential development of neuropathy will be required.

The psychological distress experienced by our patient and her family as they grasped the nature and implications of her condition added to the complexity of clinical management. Our patient’s parents were initially reluctant to disclose investigation findings to her and upon learning her diagnosis our patient transiently questioned her gender identity. Gender dysphoria is reported in DSD patients, more commonly female patients with prenatal testosterone exposure [20] and conditions associated with virilisation at puberty [19] but recent reports suggest that overall it is uncommon [18, 36]. In contrast, one might expect acute psychological distress for an adolescent or adult receiving a diagnosis of a genotype incongruent to their gender of rearing to be common. Psychological support is advocated for patients with DSD and they are ideally managed in experienced multidisciplinary teams [2, 6].

Conclusions

In conclusion, our case describes a rare cause of 46, XY DSD presenting in adolescence as primary amenorrhoea and lack of secondary sex characteristic development. Of interest, we report a novel mutation in DHH and highlight the potential for psychological distress to develop in the diagnostic work-up of DSD patients. The use of a MPS DSD gene panel enabled the diagnosis of a homozygous mutation in DHH and will ensure that our patient continues to receive screening for the potential co-existent peripheral neuropathy associated with DHH. We also describe that similar homozygous DHH mutations can be associated with variable phenotypes.
Abbreviations

DHH: desert hedgehog; DHT: dihydrotestosterone; DSD: disorder of sex development; HCG: human chorionic gonadotrophin; MPS: massively parallel sequencing; SF-1: steroidogenic factor-1

Acknowledgements
We would like to thank Associate Professor Timo Lassman for his assistance with bioinformatics analysis.

Funding
KLA, JAvdB, GR and AHS are funded by a National Health and Medical Research Council (NHMRC) program grant (APP1074258). AHS is supported by an NHMRC research fellowship (APP1062854).

Availability of data and materials
Datasets utilised for this case report have been referenced.

Authors’ contributions
KMR was responsible for drafting the manuscript and literature review. KMR, KJ and CSC have been the physicians responsible for overseeing the care of this patient. KLA was responsible for co-ordinating the genetic analysis for this case supported by her colleagues JAvdB, GR and group head AHS. DT provided bioinformatics analysis and generated the three-dimensional protein model of DHH (Fig. 4). NS was involved in the surgical care of this patient and provided the intra-operative images. LN provided specialist neurological assessment. KF provided the surgical care of this patient and provided the intra-operative images (Fig. 2). LN provided specialist neurological assessment. KF provided histopathology images (Fig. 3) and interpretation for the case. CSC gave the three-dimensional protein model of DHH (Fig. 4). LN provided specialist neurological assessment. KF provided the surgical care of this patient and provided the intra-operative images.

Ethics approval and consent to participate
The Princess Margaret Hospital for Children Ethics Committee has given approval for this case report.

Consent for publication
Written informed consent was obtained from the patient and the patient’s legal guardian for publication of this case report and accompanying images.

Competing interests
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Received: 3 December 2017 Accepted: 22 February 2018 Published online: 02 March 2018

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Title:
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Date:
2018-03-02

Citation:
Rothacker, K. M., Ayers, K. L., Tang, D., Joshi, K., van den Bergen, J. A., Robevska, G., Samnakay, N., Nagarajan, L., Francis, K., Sinclair, A. H. & Choong, C. S. (2018). A novel, homozygous mutation in desert hedgehog (DHH) in a 46, XY patient with dysgenetic testes presenting with primary amenorrhoea: a case report. INTERNATIONAL JOURNAL OF PEDIATRIC ENDOCRINOLOGY, 2018 (1), https://doi.org/10.1186/s13633-018-0056-3.

Persistent Link:
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