Evaluation of Three Patients with 46,XY Gonadal Dysgenesis Due to Desert Hedgehog Gene Mutations

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Background: Desert Hedgehog (*DHH*) gene acts on early testicular development, testis cord formation and differentiation of fetal Leydig cells. It also has a role in nerve sheath formation. *DHH* gene mutations are very rare causes of 46,XY gonadal dysgenesis (GD). Gonadal tumors and peripheral neuropathy have been associated with *DHH* mutations.

Aims and Objectives: To present three patients with 46,XY GD due to novel homozygous *DHH* mutations.

Methods: Targeted next-generation sequencing of three patients by in-house designed DSD gene-panel.

RESULTS: Three patients (two siblings- patient 1 and 2- and a 3rd patient) with *DHH* mutations were reviwed (Table 1).

Table 1. Clinical and laboratory findings in 3 patients who have mutations in *DHH* gene

	Patient 1	Patient 2	Patient 3
Age (year)	14.5	12.8	1.8
Presentation	Ambigious genitalia	Sibling has ambigious genitalia	Ambigious genitalia
Age at presentation	1 year	14 days	19 days
External genitalia	Phallus 1.2 cm, penoscrotal hypospadias, bilateral inguinal testis	bilateral inguinal testes, phallus 0.5 cm, normal female	Phallus 2 cm, penoscrotal hypospadias, bilateral inguinal testes
Karyotype	46,XY	46,XY	46,XY
Assigned sex	Female at birth converted to male at 5 years of age	Female	Female at birth converted to male at 6 months of age
Consanguinity	Yes	Yes	Yes
Family history	-	-	Elder brother has hypospadias
Mullerian structure	Remnant of Mullerian structure evident on biopsy	No	No
LH (IU/mL)	1.33	1	4.68
FSH (IU/mL)	1.97	15.6	3.13
Basal testosterone (ng/ml)	0.05	0.33	1.48
Testosterone response following HCG test (ng/ml)	0.3	3.8	-
AMH (ng/ml)	5.34 (N:1.12-143.64)	-	27.7 ng/ml (N:37.7-262.69)
Inhibin B (pg/ml)	552 (N:<480)	20 (N:<480)	-
Cortisol (mcg/dl)	31.2	35.5	34.9
Gonadectomy	-	Bilateral gonadectomy (5.2 years old)	-
Testicular histology	-	Gonadal dysgenesis with loss of Leydig cell, Sertoli only cell, with intratubuler germ cell neoplasia , atypic Germ cell positive for PLAP, OCT3/4 , C-KI	-
Nucleotide	Homozigous, Exon 3 c.1146G>A	Homozigous, Exon 3 c.1146G>A	Compound Heterozygous [Exon 1];[Exon3] c.[71G>C];[1063C>T]
Protein	p.Trp382*	p.Trp382*	p.[Gly24Ala];[Arg355Cys]
Mutation type	Nonsense	Nonsense	[Missense];[Missense]
Mutation taster	Disease causing	Disease causing	[Disease causing];[Disease causing]
Polyphen 2 score	-	-	[Probably damaging];[Probably damaging]
SIFT	-	-	Damaging tolerated
Reference	Novel	Novel	[Novel];[Novel]
Neurological examination	Decreased vibratory sensation in the lower limbs	Decreased vibratory sensation in the lower limbs, bilateral pes cavus	Normal
Neuropathy	Yes	Yes	No
Electromyography	Sensory-motor neuropathy in distal of lower extremities	Sensory-motor neuropathy in distal of lower extremities	-

Conclusions:

- *DHH* gene mutation should be analyzed in patients with 46,XY GD for diagnosis and the presence of potential neuropathy and gonadal tumors.
- *In vivo* studies are needed to further delineate the phenotype-genotype relation.