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SRD5A3-CDG: Expanding the phenotype of a congenital disorder of glycosylation with emphasis on adult onset features

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Abstract

Increasing numbers of congenital disorders of glycosylation (CDG) have been reported recently resulting in an expansion of the phenotypes associated with this group of disorders. *SRD5A3* codes for polyprenol reductase which converts polyprenol to dolichol. This is a major pathway for dolichol biosynthesis for N-glycosylation, O-mannosylation, C-mannosylation, and GPI anchor synthesis. We present the features of five individuals (three children and two adults) with mutations in *SRD5A3* focusing on the variable eye and skin involvement. We compare that to 13 affected individuals from the literature including five adults allowing us to delineate the features that may develop over time with this disorder including kyphosis, retinitis pigmentosa, and cataracts.

INTRODUCTION

Steroid 5 alpha reductase type 3 (*SRD5A3*), also known as polyprenol-reductase, converts polyprenol to dolichol [Denecke and Kranz, 2009; Grundahl et al., 2012]. Dolichol is required as a carrier for mannose and glucose monosaccharides used as donors for N-

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glycosylation, O-mannosylation, C-mannosylation, and GPI anchor synthesis [Denecke and Kranz, 2009; Buczkowska et al., 2015]. The synthesis of dolichol is one of the first steps in glycosylation. Many proteins in the human genome are N-glycosylated and from 250 to 500 genes are involved in the process of glycosylation [Freeze et al., 2015]. N-linked glycans assist in protein folding, cell–cell interaction, and segregation of lysosomal enzymes. Over 100 human disorders have been associated with defects in glycosylation causing protein or lipid dysfunction [Freeze et al., 2015]. Abnormalities associated with CDG affect nearly every body system. There does not appear to be a single common phenotypic feature found in all CDG although neurological involvement has been reported in most. Current nomenclature for disorders of glycosylation is to list the gene name first, followed by a dash and then CDG. Thus, SRD5A3-CDG is the disorder caused by deleterious mutations in *SRD5A3*. It was previously known as CDG1q.

CLINICAL REPORTS

Patient 1

Patient 1 was born at 37 weeks gestation after an uneventful pregnancy with birth weight of 2.76 kg and length of 47 cm. She has had horizontal nystagmus since infancy. Ophthalmology evaluation at 4 months of age raised concern for optic nerve hypoplasia and recent evaluation confirmed that finding with only 80% normal nerve tissue in the right eye and <20% on the left. She has short stature and normal thyroid studies. She has a history of febrile seizures as a young child and a recent non-febrile seizure. Head MRI done at 9 years of age showed slight asymmetry of the lateral ventricles with mild left colpocephaly and a hypoplastic inferior cerebellar vermis. She was diagnosed with psoriasis as a child but recent dermatological evaluation is more consistent with diffuse ichthyosiform changes and palmoplantar keratoderma. She did not walk until 4 years of age, and her gait is still unstable. First words were at 6 years of age. At 12½ years old, she can put together four to five word sentences. She is reasonably social with other children.

Prior testing included BAC microarray, plasma carnitine, urine organic acids, plasma acylcarnitines, and cholesterol were normal. Karyotype was 46,XX. Echocardiography, renal ultrasound, and X-rays of the sacrum were normal. Testing during current evaluation included a SNP microarray that did not find deletions or duplications but did find three areas of homozygosity: arr[hg19] Xq11.1q12(61,932,503–67,123,772), 4q11q13.1(52,686,799–61,287,186), and 14q22.1q23.2(52,651,351–64,645,500). Very long chain fatty acids were normal. Carbohydrate deficient transferrin testing found: mono-oligo/di-oligo ratio of 0.44 (normal ≤0.06), a-oligo/di-oligo ratio of 0.026 (normal ≤0.011), tri-sialo/di-oligo ratio of 0.02 (normal ≤0.05), apo CIII-1/apo CIII-2 ratio of 2.39 (normal ≤2.910), and apo CIII-0/apo CIII-2 ratio of 0.18 (normal ≤0.48). Blood count, serum transaminases, and creatine kinase were normal. Prothrombin time (PT) was 10.2 sec (normal range 9–11.5 sec). Partial thromboplastin time (PTT) was 35 sec (normal range 22–34 sec). Protein C was 50% (normal range 70–180%), protein S was normal at 83%, antithrombin III was 53% (normal range being 80–129%).

Physical examination at 12½ years of age found a height of 134.5 cm (4 SD below mean), weight of 28.2 kg (2 SD below mean), and head circumference of 52.1 cm (1 SD below

mean). Eyes were wide set with a shallow nasal bridge and synophrys. Pupils were equal and round, and she had frequent horizontal nystagmus. She had a short nose and rounded nasal tip. There was generalized skin peeling and areas of erythema. The skin of her elbows, backs of her hands, and lower legs was darkened. She had thickened soles of her feet and palms of her hands. There was a fleshy prominence in her upper left sacral area with an indentation in the middle. Patellar reflexes were brisk bilaterally, and she had mild hypotonia and ataxia (See Figs. 1–3).

Patient 2

Patient 2 is the brother of Patient 1 and was delivered at 37 weeks' gestation after a normal pregnancy with a birth weight of 3.15 kg and length of 43.5 cm. He has a history of a functional murmur, but normal echocardiogram. He had a normal renal ultrasound. He was diagnosed with psoriasis, although a more recent dermatological evaluation is more consistent with diffuse palmoplantar keratoderma. He has bilateral iris and optic nerve colobomas with horizontal nystagmus. There is a history of febrile seizures. Head MRI found a hypoplastic inferior cerebellar vermis. He was diagnosed with hypothyroidism at 6 years of age and is on levothyroxine. Psychomotor development is significantly impaired. He started walking at 4 years of age and now can run but he is very awkward and falls easily. He tends to tire easily. He can say two to three word sentences. He likes to sing and can keep a tune.

Testing at 11 years old included—Chromosome microarray analysis with SNP array (arr[hg19]) that was initially reported to be normal. When his sister was found to have several areas of homozygosity, the lab was queried and they found that he had the same area of homozygosity on 4q, but it was not reported initially because his total amount of homozygosity did not exceed 10 MB. Blood count, serum transaminases, and creatine kinase were normal. PT was 10.8 sec (normal range 9–11.5 sec), PTT was 37 sec (normal range 22–34 sec), protein C was 43% (normal range 70–180%), protein S was normal at 84%, and antithrombin III was 35% (normal range being 80–129% activity).

Physical exam at 11 years of age noted a height of 141 cm (0 SD), weight of 31.2 kg (1 SD below mean), and head circumference of 52.5 cm (0.5 SD below mean). He had slightly close-set eyes with a short nasal bridge. There was a coloboma of the right iris at 6 o'clock and an ovoid shape of the left pupil. He had horizontal nystagmus and tended to roll his eyes up frequently. He had a thickened area of erythematous skin in his left upper coccygeal area. There was thickening of the skin of the soles and palms with darkening of his elbows and his knees. Patellar reflexes were brisk bilaterally, and he had mild hypotonia and ataxia. (See Figs. 4 and 5).

Family history—The siblings have a healthy brother and healthy parents except that father has vitiligo. Both parents come from Puerto Rico. Consanguinity was denied.

As a result of the abnormal CDG testing and the presence in both affected siblings of the same region of homozygosity on chromosome 4, which includes *SRD5A3*, Sanger sequencing of *SRD5A3* was performed and confirmed a novel homozygous nonsense mutation (c.603G>A, p.Trp201X) in both siblings.

Patient 3

Patient 3 is an 11-year-old male, born at term after an uncomplicated pregnancy. He started non-febrile seizures at 3 months old controlled with medication. Evaluation at that time included normal metabolic testing and a head MRI that showed increased extraneuronal space for age but no structural abnormalities. He had difficulty taking sufficient calories orally and a G-tube was placed providing all nutrition. Ophthalmological evaluation at 11 years of age documented horizontal nystagmus, bilateral optic nerve atrophy, and blunt foveal reflex. He has severe cognitive impairment. He does not speak, use signs, crawl, or stand.

On physical examination at 11 year of age, his head circumference was 47.1 cm (2.5 SD below mean). His eyes were mildly wide set with horizontal nystagmus. There was no scoliosis, kyphosis, or skin abnormalities. Muscle tone was low.

Family history—Maternal and paternal grandfathers are brothers and maternal and paternal grandmothers are sisters. He has a 1-year-old healthy sister.

CDG testing at 5 months of age found a type one pattern with elevated mono-oligo to di-oligo ratio of 0.557 (normal <0.074) and slightly elevated a-oligo to di-oligo ratio of 0.024. At 7 years of age, sequencing of 24 genes associated with CDG did not find potential candidate genes. Subsequently, exome sequencing found a homozygous nonsense mutation (c.57G>A, p.Trp19X) in *SRD5A3*, which was not part of the initial 24 CDG genes sequenced. Laboratory testing at 11 years of age found normal serum transaminases, PTT, and PT.

Patient 4

Patient 4 is a 34-year-old female who was noted to have nystagmus at 9 months of age reported to be due to optic atrophy. At 5 years of age, she was diagnosed with medulloblastoma treated with surgical resection, ventriculoperiotoneal shunt, and chemotherapy. Complications attributed to the medulloblastoma treatment included two brain hemorrhages, the development of meningiomas of the brain and spinal cord, and significant hearing loss. She always had poor balance and has used a wheelchair for the past 7 years. Other health issues included hypothyroidism and osteoporosis. Over the past several years, she has had episodes approximately 4–8 weeks apart of extreme lethargy and somnolence. She is legally blind and has developed marked kyphosis and scoliosis as an adult. She has a long history of cognitive impairment and when younger was in a class for the mentally handicapped. As an adult, she lives with her mother and works in a supported environment 2 days a week.

Physical examination is pertinent for a height of 143.2 cm (2.5 SD below mean), weight of 37.7 kg (3.5 SD below mean), and head circumference of 49.6 cm (4 SD below mean). Skull was asymmetric with sparse hair. Eyes were deep set without coloboma, cataract, or nystagmus. There were no skin abnormalities. Neurological examination showed hypotonia and ataxia.

Patient 5

Patient 5 is a full sister to patient 4. She was 33 years old at the time of last evaluation. Her history is pertinent for vision impairment with optic atrophy and nystagmus, cognitive impairment, tremor, ataxia, and muscle weakness. She had cataracts diagnosed in childhood, and in her 20's was found to have retinitis pigmentosa. Her muscle weakness and tremor have increased over the past 5–6 years. Head MRI at 22 years of age was normal. She has a history of cognitive impairment and as an adult lives with her mother and attends a day program. IQ is estimated to be in the mild disability range.

Physical examination found a height of 161.6 cm (1 SD below mean), weight of 99.8 kg (4 SD above mean), and head circumference of 55 cm (0 SD). Her eyes were deep set with an intermittent horizontal nystagmus. She had a recessed chin. She did not have kyphosis, scoliosis or skin abnormalities.

Family history—Patients 4 and 5 have a healthy sister. There is no history of individuals in the extended family with similar issues. Parents are of western European background. Consanguinity is denied.

CDG testing found an abnormal glycosylation type pattern in patient 5. Mono-oligo/di-oligo ratio was 0.544 (normal range <0.074) and a-oligo/di-oligo ratio was 0.027 (normal range <0.022). Testing was not done on patient 4. Whole exome sequencing showed compound heterozygous mutations of *SRD5A3* in patient 5: c.562+3delG and c.921C>G, p.Pro307Arg. Subsequently the same mutations were found in patient 4.

For the five patients detailed in the report only siblings four and five did not have nonsense mutations. Instead they carried two novel variants with c.562+3delG affecting a +3 donor splice site, while c.921C>G, p.Pro307Arg codes for a missense variant. In silico modeling tools were used to determine if the p.Pro307Arg change was likely pathogenic. Polyphen2 scored it to be "Probably Damaging" with a score of 1 (0 being least likely to be damaging, 1 being most likely). SIFT predicted it to be damaging with a score of 0.04 (0 being most likely to be damaging, 1 being least likely). More recently use of Combined Annotation Dependent Depletion (CADD) scoring has been shown to be an effective tool for scoring deleteriousness of variants. The p.Pro307Arg had a score of 26.7 which would rank it in the top 0.5% of deleterious variants.

DISCUSSION

Delineating common features associated with SRD5A3-CDG can be diagnostically challenging given the limited information available in some case reports. The Table I lists the common features found in the patients reported here and compares them to case reports from the literature that have detailed clinical information that was not limited to a table. The literature cases are separated into under and over 18 years of age to highlight the features that may develop with age.

The patients reported here have features that run the gamut of what has been reported with SRD5A3-CDG and detail within family and between family variability. Patients 1 and 2 are

on the severe end of the spectrum of this disorder and share optic nerve abnormalities, nystagmus, hypotonia, ataxia, cerebellar vermis hypoplasia, severe intellectual disability, abnormal skin, and unusual sacral lesion. Patient 1 has more severe skin findings and marked short stature while her brother has an average stature and more severe structural eye abnormalities with retinal and iris colobomas. Patient 3 who has a homozygous nonsense mutation, as do patients 1 and 2, has significant intellectual disability, epilepsy, and optic atrophy but no structural eye abnormalities or skin abnormalities. Patients 4 and 5 are not as severely intellectually delayed and lack skin changes but as adults have developed kyphosis and retinitis pigmentosa. These two are of interest because they are among the first individuals reported with SRD5A3-CDG due to compound heterozygous mutations with one of the mutations being a missense mutation. The majority of individuals with SRD5A3-CDG reported in the literature have homozygote or compound heterozygote nonsense or frame shift mutations, most with documented consanguinity [Assam et al., 2001; Prietsch et al., 2002; Al-Gazali et al., 2008; Kahrizi et al., 2009; Cantagrel et al., 2010; Grundahl et al., 2012; Kasapkara et al., 2012; Kara et al., 2014].

Patients 1 and 2 were not from a consanguineous relationship, but they did have a few small areas of homozygosity detected on microarray, which from our experience is relatively common in individuals of Puerto Rican descent. The initial microarray report in patient 2 highlights that each lab has its own policy for reporting areas of homozygosity. The lab that did the testing on patient 1 and 2 only reports areas of homozygosity if they exceed 10 Mb. The sister did with her three small areas of homozygosity but the brother did not and so he was not reported to have an area of homozygosity on chromosome four initially. If that result had not been questioned it could have led us away from the correct diagnosis.

As highlighted by patients 4 and 5, individuals with SRD5A3-CDG have issues that can develop over time. There are two families reported in the literature with a total of five adults with SRD5A3-CDG. Three siblings are in their 40’s and all have severe intellectual disability, cataracts beginning at 17 years and kyphosis at 8 years old. One of the trio has iris colobomas [Kahrizi et al., 2009]. The other family consists of two brothers (38 and 40 years old) with ataxia, nystagmus, optic atrophy, cataracts, and a form of retinitis pigmentosa. It is not clear at what age the cataracts became apparent. The older brother has mild intellectual disability while the younger brother does not have significant delays, and neither brother has a history of skin abnormalities [Kara et al., 2014]. All individuals diagnosed with SRD5A3-CDG as children will need close monitoring for the development of cataracts, retinitis pigmentosa, and kyphosis as they age.

Even within SRD5A3-CDG there is variability, but nearly every affected individual reported to date has cognitive delays, nystagmus/optic atrophy/optic hypoplasia, and ataxia (some with documented vermis hypoplasia) (see table). The cerebellum and optic tract seem especially vulnerable to deficiency of *SRD5A3*. In addition to optic nerve hypoplasia/atrophy, multiple individuals have been reported with colobomas of the optic nerve and iris and later in life development of retinal abnormalities including retinitis pigmentosa as well as glaucoma and cataracts. This does not appear to be a solely structural defect due to damage to the developing optic tract, but also impacts on long term optic nerve maintenance. Liver dysfunction and elevated creatinine kinase were not common findings in the SRD5A3-

CDG cases presented here. There were a few abnormalities found only once namely polymicrogyria and transposition of the great vessels in patients 2 and 4, respectively, of the family reported by Al-Gazli family, and in the patient reported by Kasapkara et al., cardiomyopathy. It is possible that a feature found only in a single individual may be due to confounding genetic conditions given the consanguinity of the families.

Congenital disorders of glycosylation (CDG) can present in many ways including intellectual disability, hypotonia, seizures, hepatic involvement, protein losing enteropathy, coagulopathy, skeletal abnormalities, and retinitis pigmentosa. SRD5A3-CDG is a defect early in the CDG pathway affecting the critical step of converting polyprenol to dolichol. *SRD5A3* is not the sole producer of dolichol since evaluation of fibroblasts from a child with a homozygous stop codon in exon one at p.Trp19X in *SRD5A3* found normal levels of dolichol but elevated polyprenol levels [Grundahl et al., 2012]. Despite the normal levels of dolichol, there was hypoglycosylation with only 70% of transferrin in serum correctly glycosylated. Grundahl et al. [2012] hypothesized that one explanation may be not the absence of dolichol (which would be lethal) but the increased ratio of polyprenol to dolichol leading to the phenotype associated with SRD5A3-CDG. Different cell lines may also variably rely on the de novo pathway versus potential alternate pathways or salvage from turnover. Interestingly the next step in the pathway, the conversion of dolichol to dolichol phosphate by *DOLK* leads to cardiomyopathy, seizures, hypotonia, and ichthyosiform skin changes, but significant eye abnormalities have not been reported [Denecke and Kranz, 2009]. Synthesis of dolichol phosphate is the step just prior to the start of N-glycosylation and O-, and C-mannosylation. The optic nerve may be more sensitive to accumulation of polyprenol and this could explain why optic nerve atrophy/hypoplasia are ubiquitous in SRD5A3-CDG but not as frequent in other N-linked CDG.

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References

Al-Gazali L, Hertecant J, Algawi K, El Teraifi H, Dattani M. A new autosomal recessive syndrome of ocular colobomas, ichthyosis, brain malformations and endocrine abnormalities in an inbred Emirati family. Am J Med Genet Part A. 2008; 146A:813–819. [PubMed: 18271001]

Assam B, Hackler R, Peters V, Schaefer JR, Arndt T, Mayatepek E, Jaeken J, Hoffmann GF. A new subtype of a congenital disorder of glycosylation (CDG) with mild clinical manifestations. Neuroped. 2001; 32:313–318.

Buczkowska A, Swiezewska E, Lefeber DJ. Genetic defects in dolichol metabolism. J Inherit Metab. 2015; 38:157–169.

Cantagrel V, Lefeber DJ, Ng BG, Guan Z, Silhavy JL, Bielas SL, Lehle L, Hombauer H, Adamowicz M, Swiezewska E, De Brouwer AP, Blumel P, Skyut-Cegielska J, Houliston S, Swistun D, Ali BR, Dobyns WB, Babovic-Vuksanovic D, van Bokhoven H, Wevers RA, Raetz CRH, Freeze HH, Morava E, Al-Gazali L, Gleeson JG. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. Cell. 2010; 142:203–217. [PubMed: 20637498]

Denecke J, Kranz C. Hypoglycosylation due to dolichol metabolism defects. Biochim Biophys Acta. 2009; 1792:888–895. [PubMed: 19419701]

Freeze HH, Eklund EA, Ng BG, Patterson MC. Neurological aspects of human glycosylation disorders. Annu Rev Neurosci. 2015; 38:105–125. [PubMed: 25840006]

Grundahl JEH, Guan Z, Rust S, Reunert J, Muller B, Du Chesne I, Zerres K, Rudnik-Schoneborn SA, Ortiz-Bruchle N, Hausler MG, Siedlecka J, Swiezewska E, Raetz CRH, Marquardt T. Life with too much polyprenol: Polyprenol reductase deficiency. Mol Genet Metab. 2012; 105:642–651. [PubMed: 22304929]

Kahrizi K, Najmabadi H, Kariminejad R, Jamali P, Malekpour M, Garshasbi M, Ropers HH, Kuss AW, Tzschach. An autosomal recessive syndrome of severe mental retardation, cataract, coloboma and kyphosis maps to the pericentromeric region of chromosome 4. Eur J Hum Genet. 2009; 17:125–128. [PubMed: 18781183]

Kara B, Ayhan O, Gokcay G, Basbogaoglu N, Tolun A. Adult phenotype and further phenotypic variability in SRD5A-CDG. BMC Med Genet. 2014; 15:10. [PubMed: 24433453]

Kasapkara CS, Tumer L, Ezgu FS, Hasanoglu A, Race V, Matthijs G, Jaeken J. SRD5A3-CDG: A patient with a novel mutation. Eur J Paediatr Neurol. 2012; 16:554–556. [PubMed: 22240719]

Prietsch V, Peters V, Hackler R, Jakobi R, Assmann B, Fang J, Korner C, Helwig-Rolig A, Schaeffer JR, Hoffmann GF. A new case of CDG-x with stereotype dystonic hand movements and optic atrophy. J Inherit Metab Dis. 2002; 25:126–130. [PubMed: 12118527]

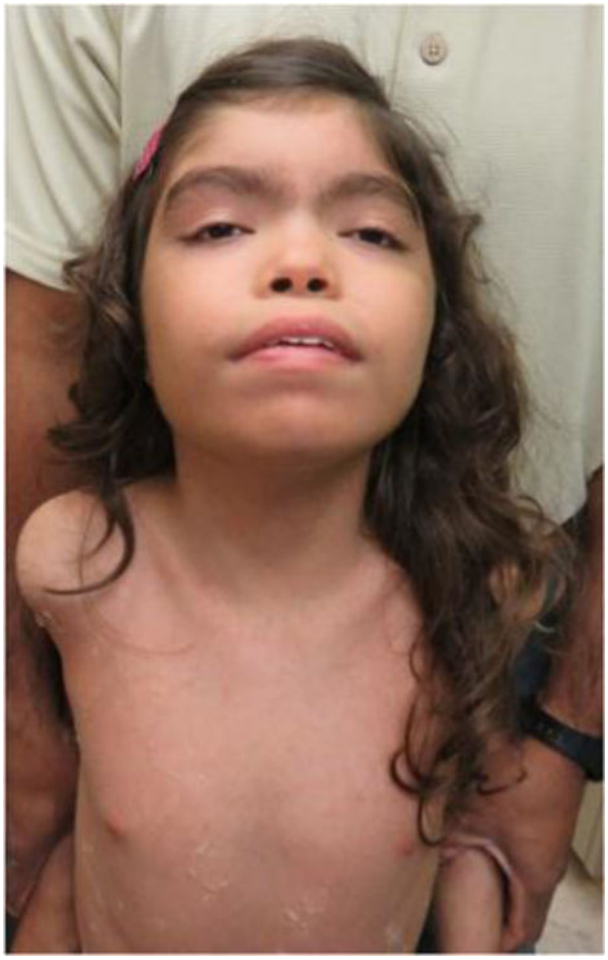

Figure 1.
Facial view of Patient 1. Note wide set eyes and tendency to look upward.

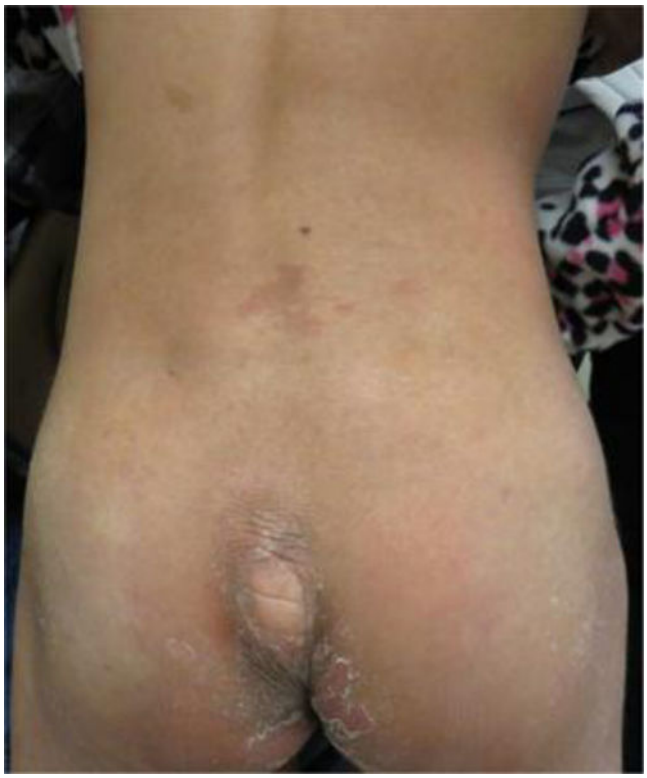

Figure 2.
Sacral tag in Patient 1.

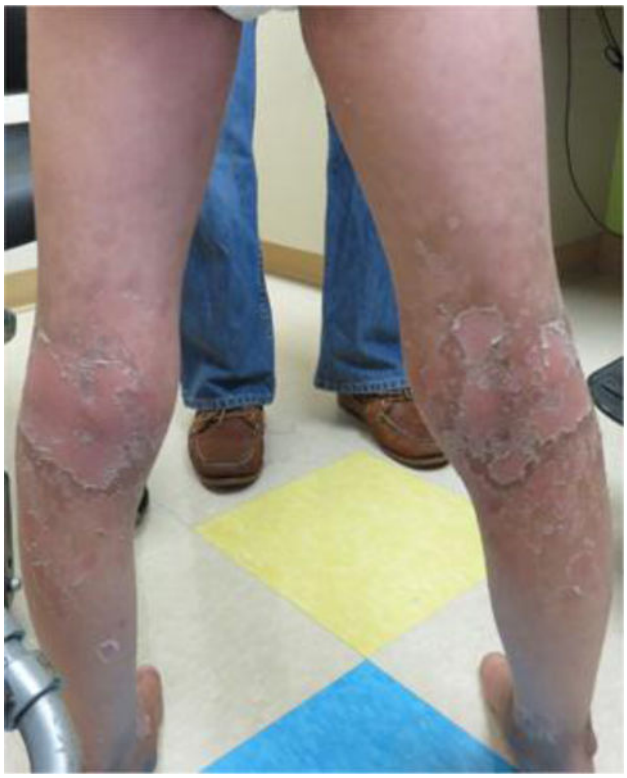

Figure 3.
Legs in Patient 1 showing ichthyosis and hyperpigmentation.

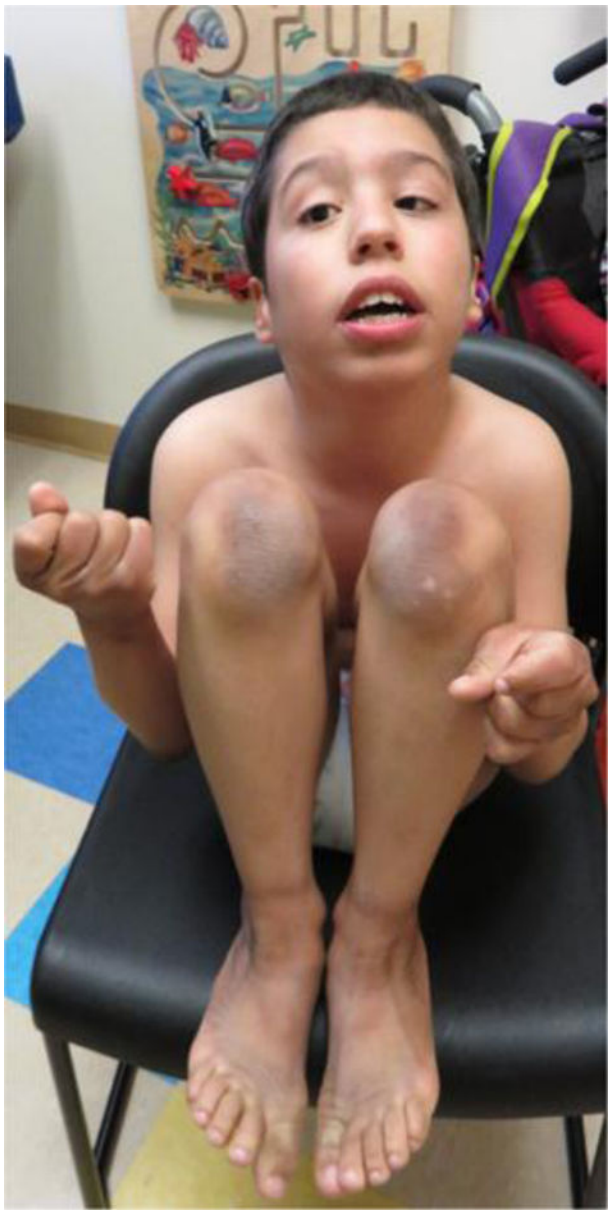

Figure 4.
Full body view of Patient 2–note hyperpigmentation of knees and feet and tendency to look upward and inward.

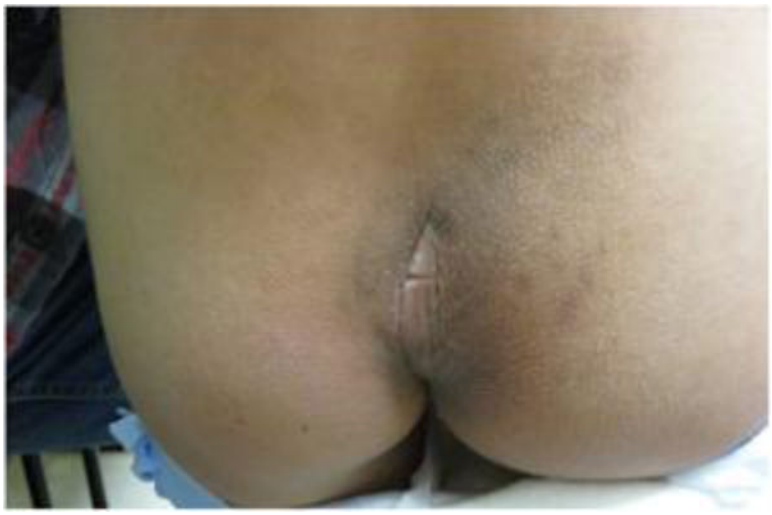

Figure 5.
Sacral tag in Patient 2.

Table I

Summary of Phenotypic Features in Cases Reported and From Literature

Patients	Sex	Patient 1 Female	Patient 2 Male	Patient 3 Male	Patient 4 Female	Patient 5 Female	Review <18 y/o[a] M:F-5/3	Review >18 y/o[b] M:F-4/1
Ophthalmic	Colobomas	−	+	−	−	−	6 of 8	1 of 5
	Optic nerve hypoplasia/atrophy	+	+	+	+	+	7 of 8	2 of 2
	Nystagmus	+	+	+	+	+	4 of 8	2 of 2
	Cataracts	−	−	−	−	+	0 of 8	5 of 5
	Retinitis pigmentosa	−	−	−	−	+	0 of 8	2 of 5
Neurologic	Hypotonia	+	+	+	+	+	5 of 8	NR
	Cognitive delays	+	+	+	+	+	8 of 8	4 of 5
	Seizures	+	Febrile	+	−	−	1 of 8	0 of 5
	Ataxia	+	+	−	+	+	2 of 4	2 of 5
	Cerebellar abnormalities	+	+	−	−	−	4 of 8	NR
Dermatologic	Icthyosiform changes	+	+	−	−	−	4 of 8	NR
	Hyperpigmentation-patchy	+	+	−	−	−	2 of 8	NR
	Palmoplantar keratoderma	+	+	−	−	−	3 of 8	NR
	Sacral lesion	+	+	−	−	−	1 of 8	NR
Endocrine	Hypothyroidism	−	+	?	+	−	0 of 7	NR
	Growth hormone def	−	−	?	−	−	1 of 8	NR
Skeletal	Kyphosis	−	−	−	+	−	0 of 8	3 of 5
Lab studies	Increased serum transaminases	−	−	?	?	−	0 of 4	NR
	Type I serum transferrin IEF	+	−	+	?	+	5 of 5	1 of 1
	Decreased anticlotting factors	−	−	?	?	−	2 of 8	0 of 1
	SRD5A3 mutations	c.603G>A (hom)	c.603G>A (hom)	c.57G>A (hom)	c.562+3delG/c.921C>G	c.562+3delG/c.921C>G		

NR, not reported; ?, not evaluated; hom, homozygous.

[a] Assam et al. [2001], Al-Gazali et al. [2008], Grundahl et al. [2012], Kasapkara et al. [2012], Prietsch et al. [2002].

[b] Kahrizi et al. [2009], Kara et al. [2014].