Figure S1. Patient 1

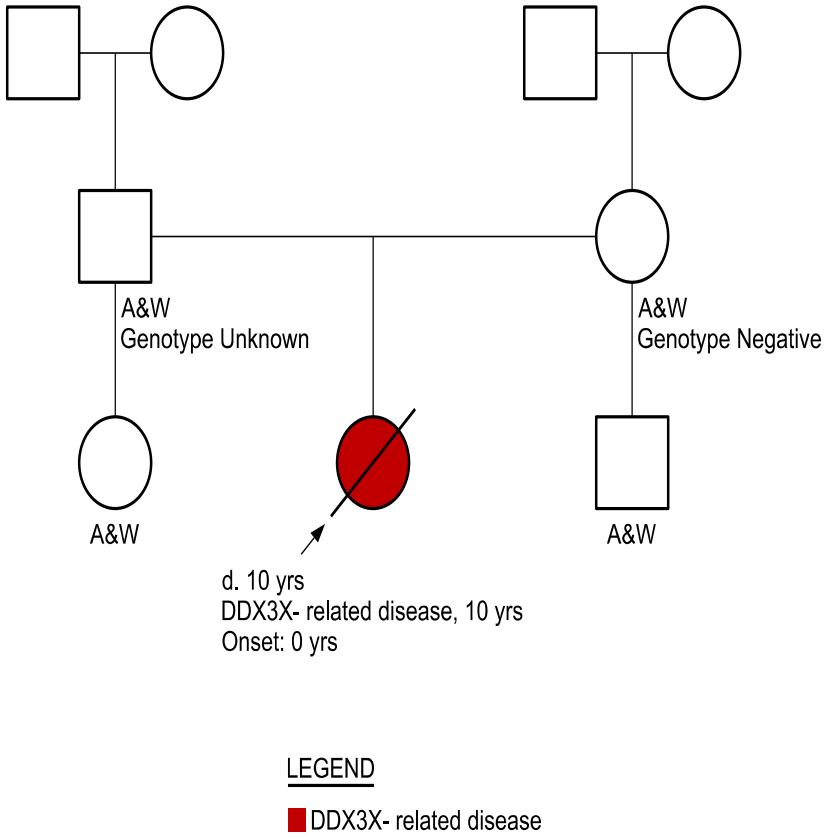
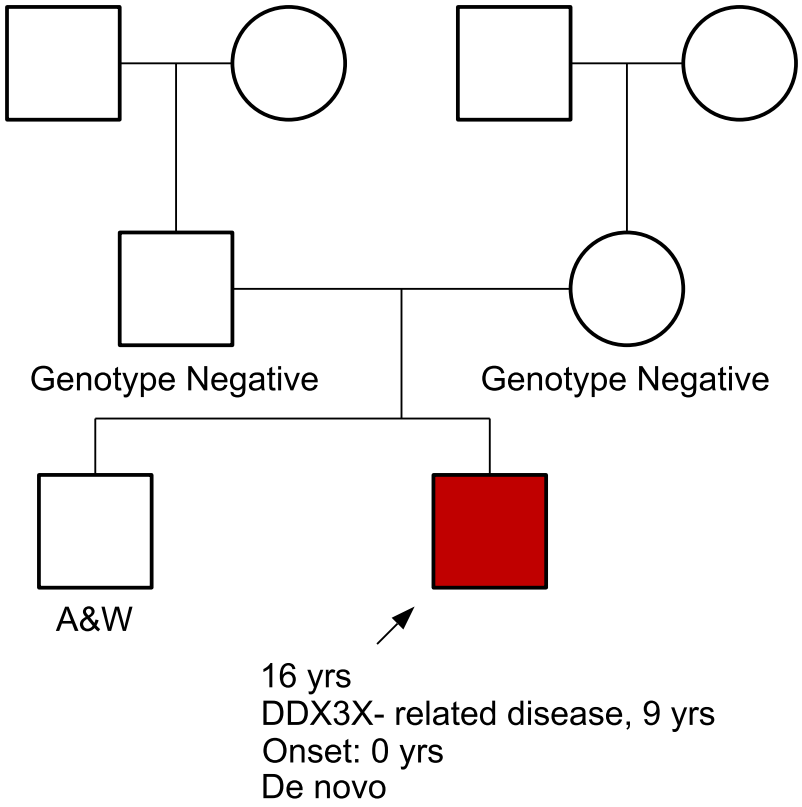


Figure S2. Patient 2



LEGEND

DDX3X- related disease

Figure S3. Patient 3

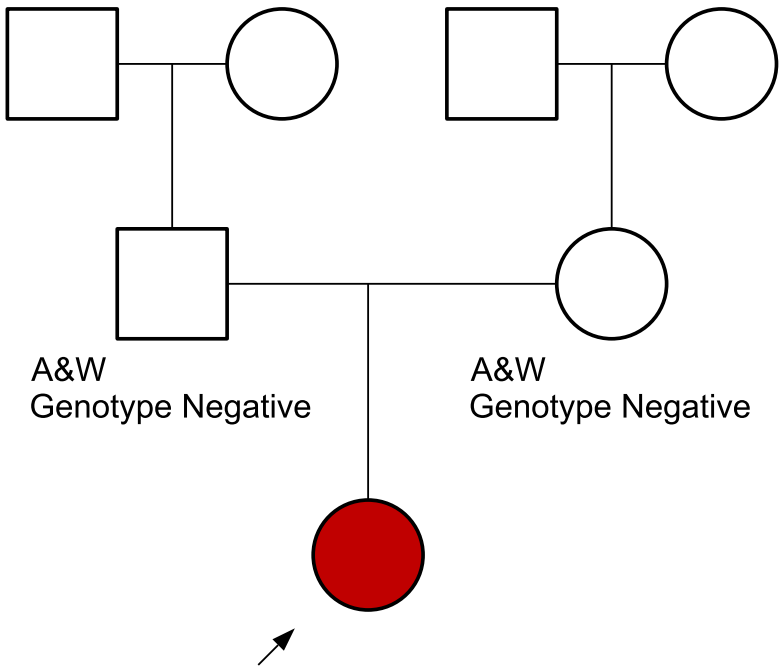


Figure S4. Patient 4

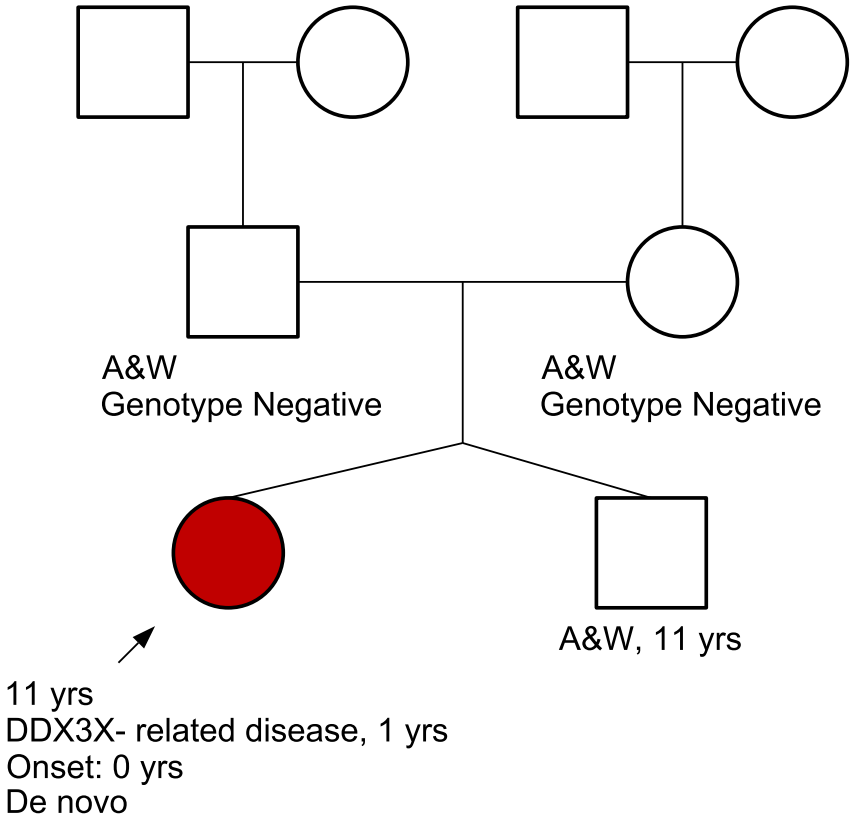


Figure S5. Patient 5

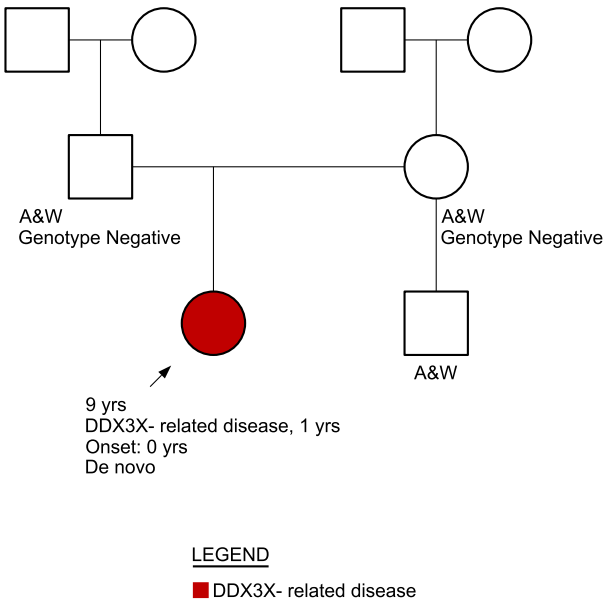


Figure S6. Patient 6

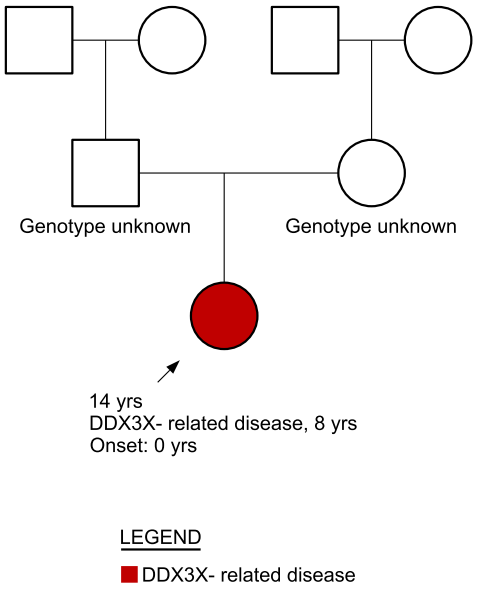


Figure S7. Patient 7

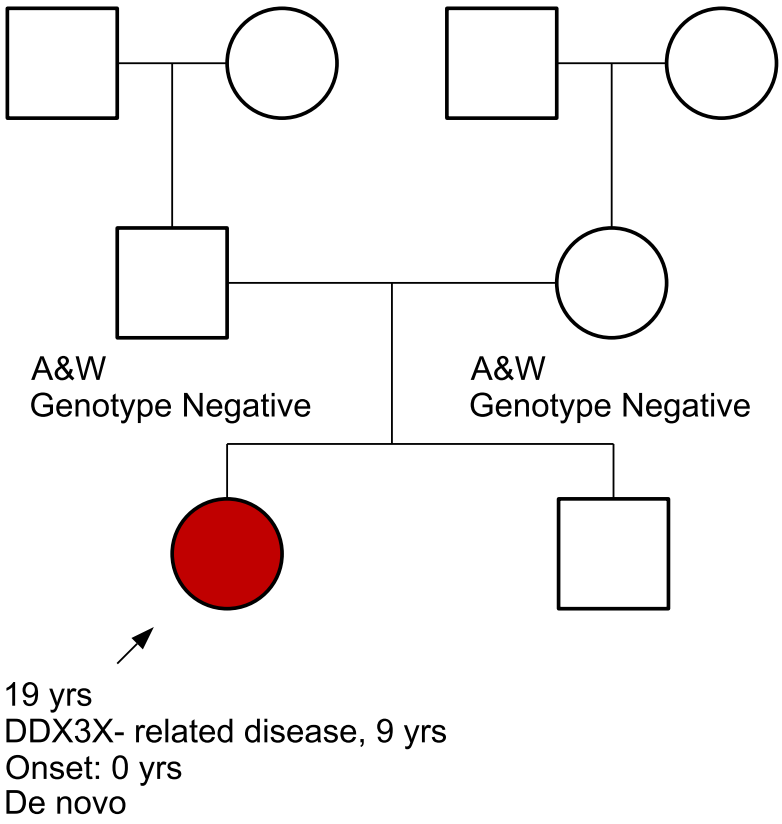


Figure S8. Patient 8

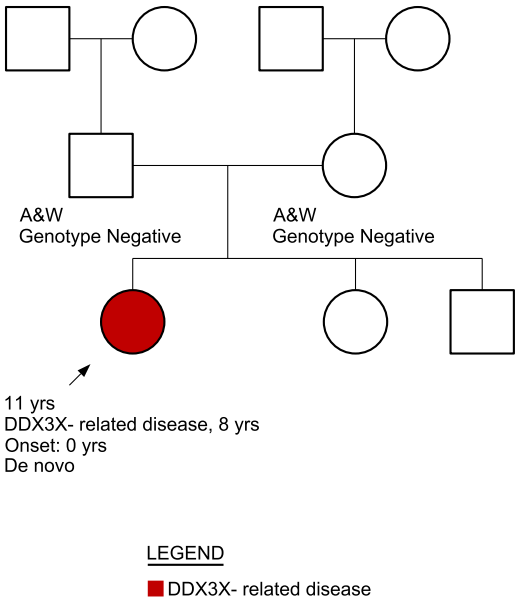


Figure S9. Patient 9

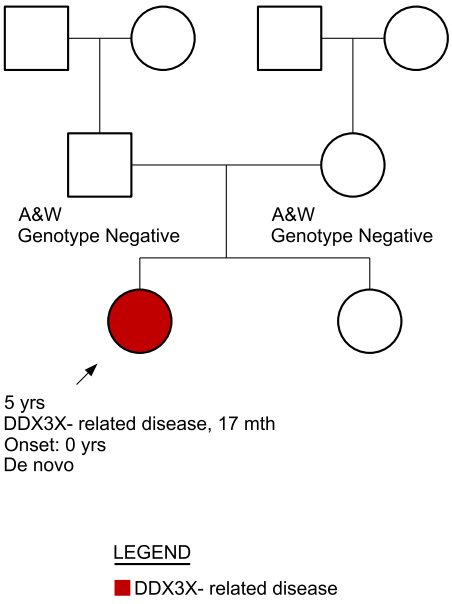


Figure S10. Patient 10

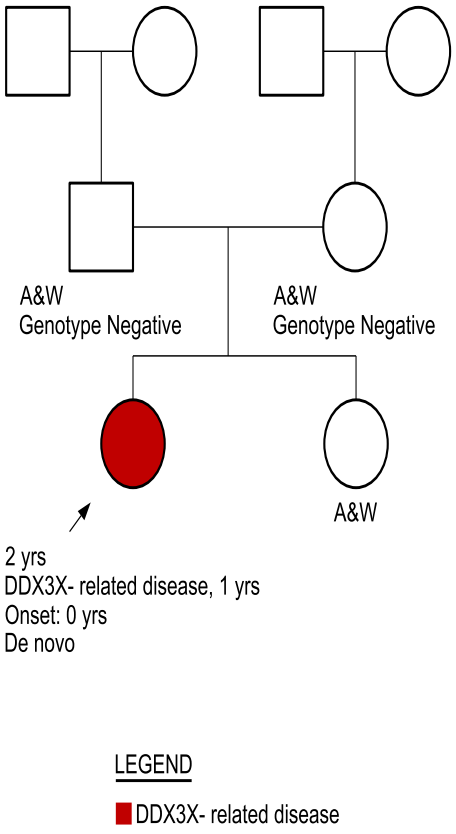


Figure S11. Patient 11

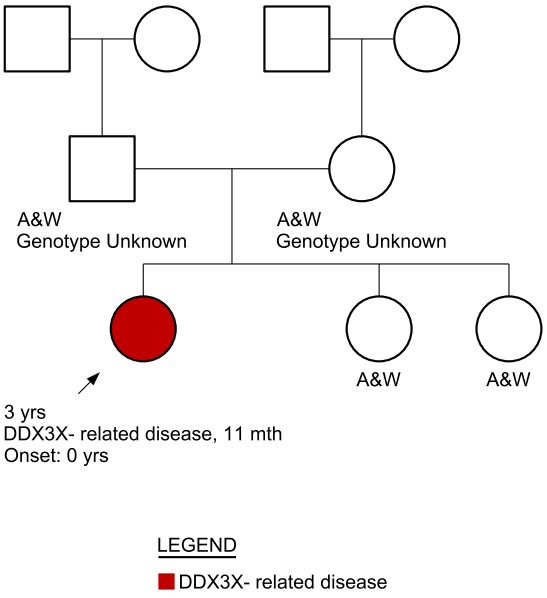


Figure S12. Patient 12

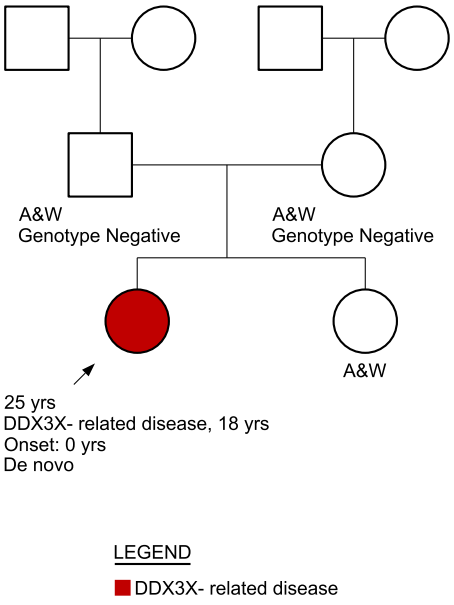


Figure S13. Patients 13 and 14

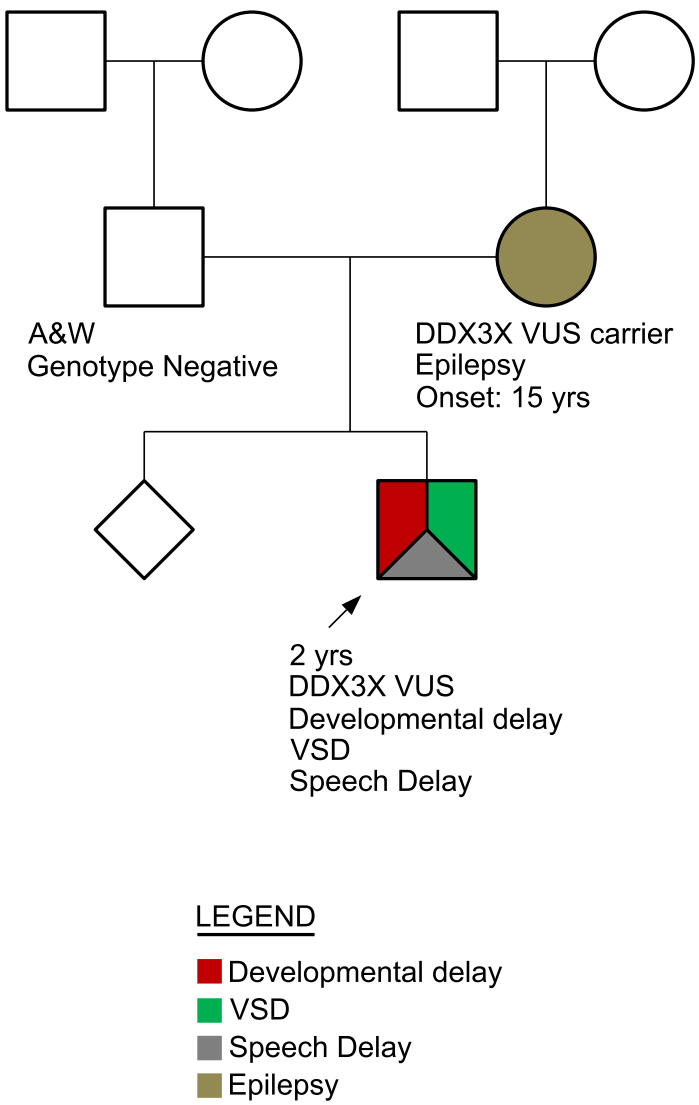


Table S1: Expanded Extra cardiovascular manifestations

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Gender / Race	F / W	M / W	F / W	F / W	F / Other	F / A	F / W	F / W	F / W	F / W	F / W	F / W	F / W	M / W
ID/DD	Severe	Moderate/ Severe	Mild DD	Global DD	Severe	Global DD	Severe	Mild	Global DD	Global DD	Mild	Global DD	Mild	Global DD
Hypotonia/ Hypertonia	Mild truncal/ central hypotonia Peripheral hypertonia	Hypertonia	Hypotonia of the upper body with poor head control	Fluctuating tone (increased tone with hyperexcitability when excited or upset)	Mild hypotonia	-	Hypotonia	Mild hypotonia	Mild diffuse hypotonia with preserved power and reflexes	Central hypotonia (8 months) Generalized hypotonia	Central hypotonia	Mild hypotonia	-	Mild hypotonia
Micro/Brachycephaly and head features	Microbrachycephaly	Brachycephaly	-	-	Microcephaly	-	Bitemporal narrowing.	-	Microcephaly Bitemporal	Brachycephaly	-	-	-	-

	Low forehead and anterior hairline				Prominent forehead				narrowing. Double hair whorls	Prominent forehead				
Movement disorder	-	Periodic limb movement disorder	-	-	-	-	-	-	Motor stereotypy	-	Mild progressive dystonia of the upper extremities with involuntary arm movements	-	-	-
Seizures/Epilepsy	Generalized seizures (secondary to structural abnor	Generalized tonic-clonic seizures	-	-	Myoclonus epileptic versus nonepileptic	-	Nonintractable epilepsy (unspecified epilepsy type)	-	-	-	-	-	Generalized seizures (idiopathic)	-

	malities)													
Behavioral	-	Short emotional and behavioral outbursts (infancy) ADHD	-	Stranger anxiety	History of anxiety and hair-pulling	-	-	-	-	-	-	ADHD	-	Headbanging when upset
Structural brain/spinal MRI abnormality	Cerebellar vermis hypoplasia with enlargement of the posterior fossa (Dandy-Walker variant)	Dandy-Walker variant with abnormal cerebellar development Complete absence of the vermis Extensive bilateral frontal	Spinal MRI: Low-lying conus medullaris terminating at L3 without findings for spinal dysraphism or other	Normal	Normal	-	Prominent lateral ventricles	Normal	Absent posterior pituitary Delayed myelination (mild)	-	Normal Cerebral palsy (7 months) Left hemiplegia	Periventricular leukomalacia Infantile Cerebral palsy and left hemiplegia	Normal	Normal

	Prominence of the atria of the lateral ventricles (mild)	polymicrogyria Heterotopic gray matter within the right cerebellar hemisphere Stable soft tissue nodule along the left tentorial leaflet	imaging stigmata for tethered cord. 3. Possible small left thymic cyst.											
CCH/CCA	CCA and septum pellucid	-	-	-	-	-	CCA (partial) with an absence of the posterior body and splenium	-	-	-	-	-	-	-

Dysmorphic features	Wide face and midfacial hypoplasia Hypertelorism, epicanthic folds, and downslanted palpebral fissures Synophrys Posteriorly rotated and	Full and long eyebrows Deep-set eyes with full lashes Small nose and mouth with thin lips and downturned corners. Large and anteverted ear lobules	-	-	Down slanting palpebral fissures Right strabismus Prominent and posteroinferiorly rotated ears Small nose and mouth Malar and maxillary hypoplasia with prominent chin	-	Long and myopathic face Ocular hypertelorism Bilateral epicanthus High-arched palate, crowded teeth	Slightly depressed nasal bridge	Small nose and upturned nares Thin upper lip Bifid uvula, Mild retrognathia Short neck	Down slanting palpebral fissures Bulbous and tubular nose. Hypoplastic alae nasi. Prominent columella Long philtrum	Long and myopathic face Long philtrum	Long and myopathic face	-	-

	low-set ears. Short and bulbous nose with a broad nasal bridge Small mouth with thin lips Retrognathia.									Retrognathia				
CL/CP	Bilateral CL/CP (posterior)	-	-	-	-	-	-	-	CL/CP (posterior)	-	-	-	-	-

Musculo-skeletal	Pectus carinatum Coxa valga bilaterally (mild) Hypoplastic nails (all) Single palmar crease	-	Left pes planovalgus. Metatarsus adductus of the left foot	-	Long fingers Hyperextensible and proximally placed thumbs	-	Wheelchair-bound with muscle weakness and osteopenia. Kyphosis Clinodactyly Congenital dislocation of the left elbow	Clinodactyly (5^{th} toe and 5^{th} finger bilaterally)	Wide chest with wide-set nipples	Syndactyly of the 2^{nd} and 3^{rd} toe (right)	Right-sided torticollis Flat arches Mild ankle pronation with externally rotated feet (while walking)	Low muscle mass Mild osteopenia	-	-
Scoliosis	-	-	-	-	-	-	-	-	Progressive juvenile neuromuscular	-	-	Mild levoscoliosis	-	-

									scoliosis					
Hyperlaxity		-	-	-	Joint hypermobility	-	-	-	-	-	-	Recurrent knee subluxation	-	-
Short stature	12% ile	7% ile	SFGA	-	SFGA and FTT	-	<1% ile Severe growth retardation	6% ile	-	-	-	-	-	3% ile
Precocious puberty	Premature thelarche	-	-	-	-	-	-	-	-	-	-	-	-	-
Visual/Refractory defects. Ophthalmopathies	Bilateral nasolacrimal dysgenesis Dacryostenosis (left)	Bilateral lamellar cataracts Bilateral hyperopia Pseudophakia (right)	-	-	Alternating exotropia CVI with bilateral strabismus	Refractive problem	Alternating exotropia Optic atrophy (right) Bilateral hyperopic	-	Accommodative esotropia with bilateral hyperopia (mild)	Alternating exotropia Myopia	-	Strabismus	-	-

	Amblyopia (left) Anisometropia Exotropia Optic dysmorphology	Pseudopapilledema (right) Aphakia (left) Retinal detachment (left) Band keratopathy (left) Optic nerve hypoplasia					astigmatism CVI		Mild CVI					
Hearing	Mixed hearing loss	Conductive left hearing loss	-	-	-	-	-	-	-	-	-	-	-	Congenital left-sided deafness

Recurrent ENT infections	Recurrent otitis media with chronic eustachian tube dysfunction History of sinus infection	Chronic serous otitis media, left-sided with bilateral chronic eustachian tube dysfunction	-	-	Bilateral acute suppurative otitis media	-	Recurrent otitis media with chronic eustachian tube dysfunction	-	Bilateral serous otitis media with effusion and a structurally narrow right external auditory canal	Recurrent bilateral otitis media with effusion and eustachian tube dysfunction	Recurrent bilateral otitis media with effusion and eustachian tube dysfunction	-	-	Recurrent otitis media with chronic eustachian tube dysfunction
Laryngeal/tracheal or other ENT problems	-	-	Fusiform enlargement of the right sternocleidomastoid muscle, consistent	-	Adenotonsillar hypertrophy	-	-	-	Laryngomalacia with initial swallowing difficulties at birth	Mild tracheomalacia	Preauricular accessory tragus (bilateral)	-	-	Complete tracheal rings with tracheal stenosis Precarinal

			with fibromatosis colli.											blind deep pouch
Others	Intestinal malrotation Midgut volvulus and small intestinal rupture	Patulous anus Pelviectasis (moderate) and caliectasis of the left renal collecting system	Anorectal malformation: Anterior anus and rectoperineal fistula Mild bilateral pelvicaliectasis		HbC Sickle cell trait OSA and sleep-related hypoventilation syndrome	History of nosebleeds. Concerns for hereditary hemorrhagic telangiectasia BRBPR (x2)	Mitochondrial complex I deficiency		PKU (carrier) Xanthinuria type 1 (carrier)	GERD and Oropharyngeal dysphagia		Carnitine deficiency (mild) PCOS		
Status	Death	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive

ADHD, Attention deficit hyperactivity deficit; BRBPR, Bright red blood per rectum; CCA, Corpus callosum agenesis; CCH, Corpus callosum hypoplasia; CVI, Cortical visual impairment; DD, Developmental delay; ENT, Ear, nose and throat; FPIES, Food protein-induced enterocolitis syndrome; FTT, Failure to thrive; GERD, Gastroesophageal reflux disease; ID, Intellectual disability; IOP, Intraocular pressure; OSA, Obstructive sleep apnea; PCOS, Polycystic ovarian syndrome; PKU, Phenylketonuria; SFGA, Small for gestational age; URTI, Upper respiratory tract infection