Clinical characteristics of PBD Patients harboring *PEX6* mutations

| Ref. | Population | G | Mutation1 | Mutation2 | AAO | DD | Family history | Clinical manifestation | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Neurology | Sensory | Others |
| (12) | Mixed European | M | p.Val92Gly | p.Arg601Gln | At birth | >12 y | U | Dystonia | Pigmentary retinopathy and macular dystrophy; sensorineural hearing loss | Pigmentation along blashko lines; beau's line on nails; amelogenesis imperfect; canines and premolars; positional posterior plagiocephaly |
| | European + Cuban | F | p.Arg99Leu | p.Arg601Gln | 3 yo | >4 y | U | Normal | Pigmentary retinopathy and macular dystrophy; sensorineural hearing loss | Hemangioma; amelogenesis imperfect; normal nails |
| (13) | Dutch | M | p.Arg860Trp | N | 4 yo | NA | U | Hypotonia; gait abnormalities; developmental delay; intellectual disability; neuropathy; white matter abnormalities | Normal vision; sensorineural hearing loss | No hepatomegaly/liver dysfunction or adrenal insufficiency |
| | American | M | p.Arg860Trp | N | At birth | 8 y | Y[$] | Hypotonia; gait abnormalities; developmental delay; neuropathy | Vision disability | Hepatomegaly/liver dysfunction |
| | American | M | p.Arg860Trp | N | 4 yo | 7 y | Half brother of [$] | Hypotonia; gait abnormalities; developmental delay; intellectual disability; neuropathy; white matter abnormalities | Vision disability | Hepatomegaly/liver dysfunction |
| | Spanish | M | p.Arg860Trp | N | 1 yo | NA | U | Hypotonia; gait abnormalities; intellectual disability; neuropathy; white matter abnormalities | Vision disability; hearing loss | Hepatomegaly/liver dysfunction; dysfunction or adrenal insufficiency |
| | Swedish | M | p.Arg860Trp | N | 6 yo | 4 y | The father of the patient confirmed the asymptomatic heterozygous mutation carrier | Normal muscle tone; gait abnormalities; developmental delay; intellectual disability; neuropathy; white matter abnormalities | NA | NA |
| | Australian | M | p.Arg860Trp | N | 3 yo | NA | U | Hypotonia; normal intelligence; gait abnormalities; developmental delay; white matter abnormalities | Normal vision; hearing loss | Hepatomegaly/liver dysfunction; Normal adrenal function |
| | American | F | p.Arg860Trp | N | 2 yo | 18 y | U | Hypotonia; gait abnormalities; developmental delay; intellectual disability | Vision disability | Hepatomegaly/liver dysfunction |
| | Dutch | M | p.Arg860Trp | N | 1 yo | NA | The mother of the patient confirmed the asymptomatic heterozygous mutation carrier | Hypotonia; white matter abnormalities; normal gait; normal intelligence; normal development; no neuropathy | Normal hearing | Hepatomegaly/liver dysfunction; normal adrenal function |
| (14) | Polish | M | p.Ala94Pro | p.Ala94Pro | At birth | 6 y | The mother of the patient confirmed the asymptomatic heterozygous mutation carrier | Psychomotor development delay; refractory seizures; white matter abnormalities brain atrophy; a small intraparenchymal cyst in right frontal lobe | Hypoplastic optic disks; nystagmus; strabismus; hypoacusis | Hepatomegaly/liver dysfunction; dysfunction or adrenal insufficiency; dysmorphic features: high forehead, broad nasal bridge, hypoplastic supraorbital ridges and microcephaly |
| (15) | American | NA | p.Phe218Leu | p.Arg601Gln | NA | NA | Y | N | Sensorineural hearing loss; retinal dystrophy | Enamel defects |
| | American | NA | p.Val92Gly | p.Arg601Gln | NA | NA | Y | N | Sensorineural hearing loss; retinal dystrophy | Enamel defects |
| | American | NA | p.Arg99Leu | p.Arg601Gln | NA | NA | Y | N | Sensorineural hearing loss; retinal dystrophy | Enamel defects |
| | British | NA | p.Glu439Gfs*3 | p.Cys905Phe | NA | NA | Y | N | Sensorineural hearing loss; retinal dystrophy | Enamel defects |
| | Israelitish | NA | p.Cys905Phe | p.Cys905Phe | NA | NA | Y | N | Sensorineural hearing loss; retinal dystrophy | Enamel defects |
| (16) | Japanese | M | p.Cys484Tyr | p.Arg517Pro | At birth | >3.6 y | The mother of the patient confirmed the asymptomatic heterozygous mutation carrier | Psychomotor retardation; hypotonia; poor visual contact; nystagmus | Apparent hypoacusia; poor visual contact; nystagmus | Splenomegaly; hepatomegaly/liver dysfunction; facial dysmorphism |
| (17) | Germany | F | p.Arg601Trp | p.Val788Met | At birth | 2.7 y | U | Hypotonia; lack of reflexes; west syndrome with hypsarrhythmia; severe psychomotor delay | Bilateral sensorineural hearing loss | Dysmorphic features: a high forehead, hypertelorism, epicanthus and an arched palate; hepatomegaly/liver dysfunction |
| (18) | Egyptian | M | p.Gly413Val | p.Gly413Val | 0.7 yo | >19 y | Y[$$] | Developmental delay; deep white matter changes; behavioral abnormalities | Bilateral sensorineural hearing loss; pigmentary retinopathy; nystagmus | Enamel dysplasia; facial dysmorphism; microcephaly; hepatomegaly/liver dysfunction |
| | Egyptian | F | p.Gly413Val | p.Gly413Val | 0.9 yo | >8 y | Sibling of [$$] | Developmental delay; deep white matter changes | Bilateral sensorineural hearing loss; pigmentary retinopathy; nystagmus | Enamel dysplasia; facial dysmorphism; microcephaly; hepatomegaly/liver dysfunction |
| (11) | British | F | p.Pro274Leu | p.Arg644Trp | <1 yo | >20 y | Y[#] | Normal intelligence | Bilateral sensorineural hearing loss; retinal pigmentation | Amelogenesis imperfect; beau's lines, onychoschizia |
| | British | F | p.Pro274Leu | p.Arg644Trp | At birth | >16 y | Sibling of [#] | Normal intelligence | Bilateral sensorineural hearing loss; retinal pigmentation | Amelogenesis imperfect; beau's lines, onychoschizia |
| | British | F | p.Arg601Gln | p.Leu614Argfs*5 | <3 yo | >18 y | Y[##] | Normal intelligence | Bilateral sensorineural hearing loss; retinal pigmentation | Amelogenesis imperfect; beau's lines, leukonychia |
| | British | F | p.Arg601Gln | p.Leu614Argfs*5 | <3 yo | >18 y | Sibling of [##] | Normal intelligence | Bilateral sensorineural hearing loss; retinal pigmentation | Amelogenesis imperfect; beau's lines, leukonychia |
| (19) | Canadian | M | p.Arg601Gln | p.Arg786Trp | 6.5 yo | 2 y | U | Cognitive decline; attention deficits; increased deep tendon reflexes in lower extremities; dysmetria; ataxia gait; decreased vibration sense; symmetrical leukodystrophy | Bilateral sensorineural hearing loss; bilateral vocal cord nodules; exotropia OS | Macrocephaly; normal adrenal function; hepatomegaly/liver dysfunction |
| (20) | French Canadian | NA | c.802_815del | c.802_815del | At birth | 0.5 m | U | Hypotonia, seizures; brain malformations; large fontanelle | Clouded cornea | Atrial septal defect; bilateral microcystic kidneys; hepatomegaly/liver dysfunction |
| | French Canadian | NA | c.802_815del | c.802_815del | NA | <1y | U | Hypotonia; brain malformations | Na | Kidney disease; cryptorchidism; ectopic patellar calcifications; bilateral club feet; hepatomegaly/liver dysfunction |
| | French Canadian | NA | c.802_815del | c.802_815del | NA | <0.4 y | U | Prematurity and intrauterine growth retardation; hypotonia; polymicrogyria | Na | Renal cysts; ectopic patellar; cervical calcifications; agenesis of cervical vertebrae; hepatomegaly/liver dysfunction; large fontanelle; increased nuchal fold |
| | French Canadian | NA | c.802_815del | c.802_815del | NA | <0.5 y | Y[#$] | Hypotonia; seizures; ventriculomegaly | Nystagmus; deafness | Large fontanelle; increased nuchal fold; hepatomegaly/liver dysfunction; equinovarus deformity; cryptorchidism; ectopic patellar calcifications; low platelets; respiratory insufficiency |
| | French Canadian | NA | c.802_815del | c.802_815del | At birth | <0.5 m | Belong to the same family with [#$] | Seizures; ventriculomegaly | Congenital cataracts | Respiratory distress; large fontanelle; ectopic patellar calcifications; hepatomegaly/liver dysfunction |
| (21) | NA | NA | p.Asp305fs | c.1962-1G > A[$] | NA | NA | NA | NA | NA | NA |
| | NA | NA | p.Arg601Gln | p.N849T | NA | NA | NA | NA | NA | NA |
| | NA | NA | p.Arg601Gln | p.R860Q[$$] | NA | NA | NA | NA | NA | NA |
| | NA | NA | p.Arg601Gln | p.R860Q | NA | NA | NA | NA | NA | NA |
| | NA | NA | c.882+1G > A | p.Pro274Leu | NA | NA | NA | NA | NA | NA |
| | NA | NA | p.Arg860Trp | N | NA | NA | NA | NA | NA | NA |
| (22) | German | F | p.Ser232HisfsX15 | p.Ser232HisfsX15 | At birth | 0.25 y | | Severe psychomotor retardation; hypotonia | Nystagmus | Hepatomegaly/liver dysfunction |
| | Romanian | M | p.Ser232HisfsX15 | p.Ser232HisfsX15 | At birth | 0.5 m | | Hypotonia; poor sucking, gavage feeding | N | Hepatomegaly/liver dysfunction; renal cyst; calcific stipling |
| | Turkish | F | p.Gly473ArgfsX13 | p.Gly473ArgfsX13 | NA | 3.5 m | | Hypotonia; seizure; poor sucking, gavage feeding | Cataract | Hepatomegaly/liver dysfunction |
| (23) | Jewish | M | p.Thr572Ile | IVS10+2T > C | At birth | 1.4 y | Y[#*] | Recurrent seizures; psychomotor delay; marked axial hypotonicity with dystonic limb hypertonicity; later stage: a vegetative state with opisthotonus, dystonia, myoclonic seizures | Nystagmus; grade I subcapsular cataracts; retinal pigmentation; bilateral sensorineural hearing loss | Narrow external auditory canals; antimongoloid slanting of the eyes; large anterior and posterior fontanels; widely open sutures; webbed neck; widely spaced nipples; bilateral palmar; simian lines; right undescended testis; extreme laxity of the hips; bilateral forefoot adduction; hepatomegaly/liver dysfunction |
| | Jewish | F | IVS10+2T > C | Arg809Val, Ile845Thr | At 0.25 yo | >20 y | Mother of [#*] | A fine tremor in both hands; borderline normal IQ | Strabismus; nystagmus; night blindness; restrictional peripheral visual fields to 100; retinal pigmentation; bilateral sensorineural hearing loss | Liver dysfunction |
| | Jewish | M | p.Thr572Ile | Thr572Ile | NA | >20 y | Father of [#*] and his parents were first cousins and had a family history of USH | NA | Bilateral sensorineural hearing loss; mild retinal pigmentation | Liver dysfunction |
| (24) | Japanese | NA | Leu57Pro | Leu57Pro | NA | NA | NA | NA | NA | NA |
| (25) | Japanese | NA | IVS7+1G > A | IVS7+1G > A | NA | 0.25 y | NA | NA | NA | NA |
| | Japanese | NA | IVS7+1G > A | IVS7+1G > A | NA | 0.33 y | NA | NA | NA | NA |
| | Japanese | NA | IVS15+2T > C | Arg812Gln | NA | NA | NA | NA | NA | NA |
| | Japanese | NA | Gln243X | N | At birth | 2d | NA | NA | NA | NA |
| | Japanese | NA | IVS1-2A > G | IVS1-2A > G | NA | NA | NA | NA | NA | NA |
| | Japanese | NA | S434fs > 449X | S434fs > 449X | NA | 0.71 y | NA | NA | NA | NA |
| | Japanese | NA | G135fs > 157X | G135fs > 157X | NA | 0.08 y | NA | NA | NA | NA |
| | Japanese | NA | P177fs > 205X | VR92-93del | NA | NA | NA | NA | NA | NA |
| | Japanese | NA | Arg812Trp | N | NA | 3.5 y | NA | NA | NA | NA |
| | Japanese | NA | V273fs > 281X | V273fs > 281X | NA | 0.42 y | NA | NA | NA | NA |

[#] [##] [$] [$$] [#$] [#*], proband of the family; [$], additional mutation p.A549V in PEX6; [$$], additional mutation c.681-2A > C in PEX12. AAO, age at onset; D, diagnosis; DD, disease duration; G, gender; IRD, infantile Refsum disease; NA, not assessed; NALD, neonatal adrenoleukodystrophy; PBD, peroxisome biogenesis disorder; U, unmarkable; Y, yes; ZS, Zellweger syndrome; ZSD, Zellweger spectrum disease.