

APPENDIX

Patients	Studies	Sex	Duration of pregnancy	CHIME criteria†	Other noteworthy clinical signs	Additional test results
<p>Patient A (referred to as 680-2-2 in Ng <i>et al.</i>'s report⁴, and patient 1 in Shashi <i>et al.</i>'s report⁸).</p> <p><i>NB: a sibling of patient B</i></p>	Zurich and Kaye, 1983 ¹ ; Shashi <i>et al.</i> , 1995 ⁸ ; Ng <i>et al.</i> , 2012 ⁸	Male	Term pregnancy	<ul style="list-style-type: none"> C: retinal colobomas. H: no features. I: a pruritic migratory ichthyosiform rash that developed at 1 week of life and persisted with remissions and relapses. M: at the age of 3.5 YA, the boy's neurodevelopmental level was that of a 12-month-old. Difficulties eating, and poor coordination of swallowing in the first decade of life. Worsening with age. E: conductive deafness due to skin exfoliation of in the auditory canal, persisting over time. 	<ul style="list-style-type: none"> Craniofacial dysmorphism: brachycephaly, cleft palate, epicanthic folds, broad, flat nasal root, overfolded helices of the ears, full lips, irregularly spaced teeth with bifid incisors. Abnormal growth: birth length and weight above the 90th percentile, followed by progressive growth deceleration. At 7 YA, weight and height were below the 5th percentile. Seizures: started at 9 months and worsened over time, despite treatment with antiepileptic medication. Genitourinary tract defects: none Dermatological symptoms: blond, sparse, thin hair. Infections: frequent sinus infections. 	<p>ALP level: unknown</p> <p>PIGL mutations found: c.274delC, p.(Leu92Phefs*15) and c.500T>C, p.(Leu167Pro)</p> <p>Techniques used: whole-exome sequencing and Sanger sequencing</p>
<p>Patient B (referred to as 680-2-3 in Ng <i>et al.</i>'s report⁴, and patient 3 in Shashi <i>et al.</i>'s report⁸).</p> <p><i>NB: a sibling of patient A</i></p>	Zurich and Kaye, 1983 ¹ ; Shashi <i>et al.</i> , 1995 ⁸ ; Ng <i>et al.</i> , 2012 ⁴	Male	Term pregnancy	<ul style="list-style-type: none"> C: retinal colobomas. H: transposition of the great vessels (underwent surgery at 3 weeks). I: xerosis. M: significant delay but revealed later than his brother: neurological development was normal at 4 months, profound mental retardation observed at 7 YA. The boy did not talk. E: conductive hearing loss, persisting over time. 	<ul style="list-style-type: none"> Craniofacial dysmorphism: flat, broad nasal root, small ears with overfolded helices, submucous cleft palate. Brachycephaly, hypertelorism, epicanthic folds, full lips, small, irregularly spaced teeth with bifid lower and upper incisors. Abnormal growth: height and weight above the 90th percentile. Seizures: started after cardiac surgery at 3 weeks, became less frequent with age, and only occurred with fever after the age of 7. Genitourinary tract defects: no features. Dermatological symptoms: Thickening of the palm and soles. Skin rash exacerbations were correlated with episodes of violent behaviour. Infections: not particularly frequent. 	<p>ALP level: unknown</p> <p>PIGL mutations found: c.274delC, p.(Leu92Phefs*15) and c.500T>C, p.(Leu167Pro)</p> <p>Techniques used: whole-exome sequencing and Sanger sequencing</p>
<p>Patient C (referred to as 680-2-1 in Ng <i>et al.</i>'s report⁴ and patient 5 in Shashi <i>et al.</i>'s report⁸).</p>	Shashi <i>et al.</i> , 1995 ⁸ ; Ng <i>et al.</i> , 2012 ⁴	Female	Term pregnancy	<ul style="list-style-type: none"> C: bilateral incomplete choroidal colobomas (examined at 8 months). H: Ventricular septal defect with severe PHT (surgery at 2.5 YA). I: congenital xerosis. Erythematous papular rash at birth which became migratory and was present at last follow-up (15 YA). M: Started to walk at 18 months, started to talk at 2 YA. 10-15 words acquired by the age of 15. E: Mild conductive hearing loss; skin exfoliation in the external auditory canal, requirement for ventilatory tubes. 	<ul style="list-style-type: none"> Craniofacial dysmorphism: hypertelorism and webbed neck at birth. Occipital flattening and prominent forehead at an older age. Abnormal growth: birth weight: 3.5 kg (75th percentile); birth length 52.5 cm (95th percentile). Growth deceleration in the 2nd year of life: 10th percentile for height and weight, 5th percentile for the head circumference. Seizures: myoclonic seizures (onset at 6 months) that responded poorly to treatment. Frequent, isolated, multifocal, bilateral epileptiform discharges on the EEG performed at 2 YA. Genitourinary tract defects: hydronephrosis due to an ureteropelvic junction obstruction (pyeloplasty performed at 15 months). Dermatological symptoms: lightly coloured, sparse, thin scalp hair, thick skin on palms and feet, and skin rash exacerbation correlated with episodes of violent behaviour. Infections: frequent ear infections. 	<p>ALP level: unknown</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and c.652C>T, p.(Gln218*)</p> <p>Techniques used: whole-exome sequencing and Sanger sequencing</p>

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Patient D (referred to as 33300 in Ng <i>et al.</i> 's report ⁴)	Tinschert <i>et al.</i> , 1996 ⁶ ; Ng <i>et al.</i> , 2012 ⁴	Female	37 WG	<ul style="list-style-type: none"> C: bilateral retina and choroid colobomas. H: ventricular septal defect (underwent surgery at 10 months). I: pruritic ichthyotic erythema developed in the first month of life. At the age of 21 months: plaque-like, erythematous, scaly skin lesions on the head, face and neck, with extension to the arms and trunk; erythematous and hyperkeratotic palms and soles. M: severe retardation. At 21 months of age, the boy's mental development level was that of a 12-month-old. E: 40 dB conductive hearing loss 	<ul style="list-style-type: none"> Craniofacial dysmorphism: flat occiput, left parietal lipoma (2 cm), up-slanting palpebral fissures, hypertelorism, epicanthal folds, right ptosis, broad nasal tip with anteverted nares, short philtrum, macrostoma with full lips, dysplastic ears. Abnormal growth: normal height and weight but head circumference below the 3rd percentile at 21 months. Seizures: seizures after cardiac surgery, EEG normal at 11 months. Genitourinary tract defects: nephromegaly and partially ectopic renal pelvis (right side); impaired renal function (chromium EDTA and iodine hippurate assessment). Dermatological symptoms: sparse, thin, blond scalp hair. Infections: not particularly frequent. Other features: Pregnancy complicated by maternal hypertension; forceps delivery. Fever up to 39°C, hypoglycaemia and hypocalcaemia in the neonatal period. 	<p>ALP level: normal</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and del 17p12p11</p> <p>Techniques used: CGH microarray and Sanger sequencing</p>
Patient E (referred to as 665-3-1 in Ng <i>et al.</i> 's report ⁴)	Schnur <i>et al.</i> , 1997 ¹⁰ ; Ng <i>et al.</i> , 2012 ⁴	Female	42 WG	<ul style="list-style-type: none"> C: bilateral retinal colobomas. H: no features. I: congenital severe xerosis; the skin started to become patchy, red and scaly at 2 weeks; widespread, confluent change; the rash was more severe on the trunk and limbs and involved the scalp but the face was relatively spared. M: at 28 months: speech was that of a 14-month-old, and motor skills were those of a 15- to 19-month-old. The impairment persisted over time. E: Conductive hear loss, due to keratinaceous debris in the external auditory canal. 	<ul style="list-style-type: none"> Craniofacial dysmorphism: brachycephaly, mild up-slanting of the palpebral fissures, pale blue irises, hypertelorism, flat midface, thin upper lip, flat, long philtrum, low-set ears, overfolded helices, underdeveloped nasal tips, upturned nares, widely spaced, square-shaped teeth. Abnormal growth: macrosomia (birth weight: 4.15 kg; birth length: 57 cm) persisting over time. Weight and height at the 95th percentile at 3 YA. Seizures: Beginning at 14 months and associated with fever until chemotherapy. Genitourinary tract defects: recurrent urinary tract infections due to a duplicated collecting system with grade 5 reflux; one ureter entering the vagina (surgical reimplantation performed). Dermatological symptoms: initially slow hair growth; prone to secondary skin infections (impetiginization, scabies). Other features: <ul style="list-style-type: none"> - two maternal uncles dead of "birth defects" in infancy. - neonatal transient tachycardia and hypoglycaemia. - hypotonia noticed at the age of 4 months. - hepatomegaly. - recurrent pneumonia (probably due to aspiration). - acute lymphoblastic leukaemia diagnosed at 4 YA, leading to premature death. 	<p>ALP level: mildly elevated</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and a second unidentified mutation (parents' DNA unavailable)</p> <p>Techniques used: whole-exome sequencing and Sanger sequencing</p>
Patient F (referred to as 3988 in Ng <i>et al.</i> 's report ⁴)	Sidbury and Puller, 2001 ¹⁴ ; Ng <i>et al.</i> , 2012 ⁴	Male	Term pregnancy	<ul style="list-style-type: none"> C: bilateral retinal colobomas. H: subaortic stenosis. I: neonatal erythroderma that turned into mild erythema with ichthyotic changes, particularly on the neck, axillae, and popliteal fossa. The face was relatively spared. M: delayed psychomotor development. E: conductive hear loss. 	<ul style="list-style-type: none"> Craniofacial dysmorphism: frontal bossing, flat midface with elongated philtrum, low-set, posteriorly angulated ears, and square teeth. Abnormal growth: not assessed. Seizures: present, requiring treatment with sodium valproate. Genitourinary tract defects: hydronephrosis. 	<p>ALP level: unknown</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and c.427-1G>A, p.?</p> <p>Techniques used: whole-exome sequencing and Sanger sequencing</p>

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Patient G	Knight Johnson <i>et al.</i> , 2017 ⁵	Male	Term pregnancy	<ul style="list-style-type: none"> C: bilateral chorioretinal colobomas. H: double outlet of the right ventricle and pulmonary stenosis. I: loose, thickened skin, progressing to fine-scale ichthyosis. M: mental retardation but the patient was alert and interactive and had a happy demeanour and no behavioural abnormalities. E: conductive hear loss. 	<ul style="list-style-type: none"> Craniofacial dysmorphia: bilateral cleft lip and cleft palate, micrognathia, broad, depressed nasal bridge, prominent forehead, shortened philtrum, epicanthal folds, and hypertelorism. Abnormal growth: macrosomia: birth weight at the 98th percentile. Seizures: idiopathic generalized epilepsy (proven by EEG). Genitourinary tract defects: none. Dermatological symptoms: thickened skin on the palms and soles, sparse hair. Other features: Family history (father) of eczema and dry skin. 	<p>ALP level: unknown</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and a heterozygous intragenic 14.4 kbp deletion encompassing <i>PIGL</i> exons 4-6</p> <p>Techniques used: CGH microarray and Sanger sequencing</p>
Patient H	Ceroni <i>et al.</i> , 2018 ⁶	Male	35 WG	<ul style="list-style-type: none"> C: bilateral retinal colobomas. H: no features. I: neonatal xerosis, hyperpigmented and ichthyosiform lesions developed at 1 YA on the neck, axillae, and knees. Round, well-delimited lesions with hyperpigmented borders in the thorax and abdominal areas, palmar hyperkeratosis. M: delayed; started to walk at 22 months and was not talking at 4 YA. E: not evaluated. 	<ul style="list-style-type: none"> Craniofacial dysmorphia: prominent forehead, hypertelorism, up-slanting palpebral fissures, everted lower lip, small widely-spaced teeth with fusion of the central and lateral right incisors, uplifted ear lobes, short neck. Abnormal growth: birth weight of 3150 g and birth length of 48 cm; macrosomia persisted at 1.9 YA. Seizures: began at 8 months during a febrile episode, partial control with combination therapy. Genitourinary tract defects: hydronephrosis and bilateral pyelocaliceal ectasia. Dermatological symptoms: fine hair, which was sparse in the temporal region. Other features: neonatal respiratory distress. 	<p>ALP level: 456 and 319 UI/L (N 150-380)</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and intragenic deletion of 802 base pairs ([hg19]chr17:16119889-16120690)</p> <p>Techniques used: whole-exome sequencing and Sanger sequencing</p>
Patient I	The present report	Male	Term pregnancy	<ul style="list-style-type: none"> C: no features. H: no features. I: xerosis predominantly on the hands and feet, with desquamation; eczema on the cheeks; orange-coloured palms and soles; keratotic, follicular papules on knees noticed at the age of 2 months M: initially present but decreased with time; normalized at 6 YA. E: no features. 	<ul style="list-style-type: none"> Craniofacial dysmorphia: macroglossia, prominent forehead, internal epicanthus, and conical, irregularly spaced teeth. Abnormal growth: persistent macrosomia. Seizures: hyperthermal seizures resolving with age (antiepileptic medication discontinued at 6 YA, with no relapses). Genitourinary tract defects: nephromegaly. Dermatological symptoms: koilonychia, slow-growing, sparse, thin eyebrows and hair (with a lower density in the temporoparietal area), and hypertrophic gingivitis. Infections: in the gastrointestinal tract, ear (requirement for ventilatory tubes), nose, throat, and lungs. Other features: gastroesophageal reflux. 	<p>ALP level: normal</p> <p>PIGL mutations found: c.500T>C, p.(Leu167Pro) and c.154G>A, p.(Asp52Asn)</p> <p>Techniques used: clinical exome sequencing</p>

Table S1: Clinical and molecular features of patients with *PIGL*-related CHIME syndrome

Abbreviations: PHT: pulmonary hypertension, YA: years of age, WG: weeks of gestation, CGH: comparative genomic hybridization.

† CHIME criteria, according to the acronym “coloboma, heart defect, ichthyosis, mental retardation, abnormal ears”).