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**Child with a mild CHIME syndrome phenotype and carrying a novel p.(Asp52Asn) *PIGL* pathogenic variant in association with the previously reported p.(Leu167Pro) variant: a case report**

Marion Rolland<sup>1</sup>, MD; Christèle Dubourg<sup>2,3</sup>, MD, PhD; Auriane Cospain<sup>2,4</sup>, MD; Catherine Droitcourt<sup>\*1,5</sup>, MD, PhD; Laurent Pasquier<sup>\*4,6</sup>, MD, PhD

<sup>1</sup> Department of Dermatology, CHU Rennes, F-35000 Rennes, France

<sup>2</sup> Department of Molecular Genetics and Genomics, CHU Rennes, F-35000 Rennes, France

<sup>3</sup> University of Rennes, CNRS, IGDR, UMR 6290, F-35000 Rennes, France

<sup>4</sup> Department of Medical Genetics, Reference Center for Rare Diseases "Intellectual Deficiencies", Hôpital Sud - CHU Rennes, F-35203 Rennes, France

<sup>5</sup> University of Rennes, EA 7449 REPERES "Pharmacoepidemiology and Health Services Research", F-35000 Rennes, France

<sup>6</sup> <https://orcid.org/0000-0003-3985-1286>

\* Equal contributions

**Corresponding author:** Marion Rolland, Department of Dermatology, Pontchaillou Hospital, 2 rue Henri le Guilloux F-35000 Rennes, France, Tel.: + 33-299-284-349, Fax: + 33-299-284-100, E-mail: [marion.rolland@chu-rennes.fr](mailto:marion.rolland@chu-rennes.fr)

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## ABSTRACT

Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation and ear anomalies (CHIME) syndrome is a very rare, autosomal recessive, neuroectodermal disorder related to *PIGL* gene mutations. Here, we report a patient who showed an initial delay in psychomotor development and skin abnormalities consistent with CHIME syndrome but with atypical clinical features and laboratory findings. In line with our clinical suspicion, the c.500T>C, p.(Leu167Pro) variant (found in all the previously described cases of CHIME syndrome) was found on the paternal allele. A novel “likely pathogenic” *PIGL* missense variant (c.154G>A, p.(Asp52Asn)) was detected on the maternal allele. This case provides new insights into the clinical spectrum of CHIME syndrome and highlights the potential for phenotypic/genotypic variations.

## INTRODUCTION

Coloboma, congenital heart disease, ichthyosiform dermatosis, mental retardation and ear anomalies (CHIME) syndrome is a very rare autosomal recessive neuroectodermal disorder that was initially described by Zunich and Kaye in 1983<sup>1</sup>. This disease entity is related to pathogenic variants in the gene coding for the phosphatidylinositol glycan anchor biosynthesis class L (PIGL) protein (OMIM #280000), an enzyme located at the membrane of the endoplasmic reticulum. PIGL catalyzes the second step in glycosylphosphatidylinositol (GPI) biosynthesis, i.e. the de-N-acetylation of N-acetylglucosaminyl-phosphatidylinositol.<sup>2</sup> GPI has a critical role in the anchoring of many membrane proteins, some of which are involved in neurogenesis<sup>3</sup>.

To date, only eight cases of CHIME syndrome in people with confirmed *PIGL* variants have been reported<sup>4-6</sup>. Given the rarity of this syndrome, data on its clinical features and clinical spectrum are scarce. All six of the cases reported by Ng *et al.*<sup>4</sup> carried a compound heterozygous variant c.500T>C, p.(Leu167Pro). A second pathogenic variant was identified in 5 of the 6 patients<sup>4</sup>. In the seventh case of *PIGL*-related CHIME syndrome (reported by Knight Johnson *et al.*<sup>5</sup>), the c.500T>C, p.(Leu167Pro) variant was again detected on the first allele but the second allele carried an intragenic deletion of *PIGL*'s exons 4-6. In the eighth case (reported by Ceroni *et al.*<sup>6</sup>), the c.500T>C, p.(Leu167Pro) variant on the first allele was combined with a 802 base-pair deletion (involving the 5' untranslated region and the first 50 amino acids of *PIGL*) on the other allele.

Here, we report on a new case of genetically confirmed *PIGL*-related CHIME syndrome with an uncommonly mild phenotype and a novel *PIGL* variant.

## CASE REPORT

In November 2014, a 2-year-old boy was referred for the assessment of orange-colored skin lesions. He was the second son of healthy, non-consanguineous parents. Both parents were tall (height: 187 cm for the father and 176 cm for the mother) but had a normal body weight (73 and 58 kg, respectively) and a normal head circumference (56.5 and 54 cm, respectively). The family's medical history was otherwise unremarkable, and the boy's older brother was healthy, with normal growth parameters (height and weight).

The patient was being followed by the genetics department after the antenatal diagnosis of nephromegaly, hydramnios, and macrosomia. It is noteworthy that the antenatal karyotype was normal. The boy was born full-term, with a birth weight of 4550 g (99<sup>th</sup> percentile), length of 52 cm (97<sup>th</sup> percentile), and head circumference of 38 cm (99<sup>th</sup> percentile). A clinical examination soon after birth revealed hepatomegaly and macroglossia. The antenatal diagnosis of nephromegaly was confirmed postnatally using ultrasound. Delayed psychomotor development and febrile seizures were

diagnosed at the age of 3 months. Although language acquisition and communication skills were normal at 15 months of age, the delay in motor development was more persistent. He started to walk at the age of 22 months and was able to run at 3.5 years. Throughout his childhood, he suffered from frequent gastrointestinal, upper respiratory and pulmonary viral infections. Screening for primary immunodeficiency (a complete blood count and immunophenotyping of circulating lymphocytes) was normal. Beckwith-Wiedemann syndrome was initially suspected but was not confirmed by molecular analysis (i.e. no abnormal methylation patterns in the 11p15 region in blood and skin samples, and normal array CGH findings). Furthermore, the ocular, ear, nose and throat (ENT), and cardiac abnormalities usually observed in Beckwith-Wiedemann syndrome were not present. Liver function tests were normal and in particular, alkaline phosphatase (ALP) value was measured at 311 IU/L, within the normal range (142 to 335).

A dermatological examination revealed ichthyosiform changes, with xerosis and eczema on the cheeks and keratotic, follicular papules on the knees.

Examination of the skin at age 5 years revealed koilonychia, internal epicanthal folds, slowly growing, sparse, thin eyebrows and reduced hair density on the temporoparietal scalp (Figures 1.A to 1.C). Examination of the mouth showed gingival hypertrophy and conical, irregularly spaced teeth. These clinical features were strongly consistent with a diagnosis of ectodermal dysplasia.

The patient's neurological impairments became less severe with age, and the delay in psychomotor development eventually disappeared. Antiepileptic medication was discontinued at the age of 6, with no clinical relapse. Growth parameters exceeded normal values: at 6 years of age, the boy weighed 26.5 kg (+2 standard deviations [SD]), was 126 cm tall (+2 SD), and had a head circumference of 56 cm (+3 SD).

At age 7, exome sequencing revealed two heterozygous, missense variants in *PIGL* in a compound heterozygous state (NM\_004278.4). The paternal allele carried the missense variant c.500T>C, p.(Leu167Pro), already classified in the ClinVar database as “pathogenic”<sup>4-6</sup> (class 5 according to the American College of Medical Genetics (ACMG) classification<sup>7</sup>). The maternal allele carried the missense variant c.154G>A, p.(Asp52Asn), which had not previously been described in the GnomAD and ClinVar databases. This variant affects a residue that is highly conserved across species (from yeast up to man) and is predicted to have a deleterious effect on protein function by various *in silico* prediction tools (Align GVGD, SIFT, Mutation Taster, and PolyPhen, accessed through Alamut Visual). Hence, this variant was classified as “likely pathogenic” (ACMG class 4<sup>7</sup>). We submitted both variants to ClinVar; the accession numbers are respectively SCV001963616 for the variant c.154G>A, p.(Asp52Asn) and SCV001963617 for the variant c.500T>C, p.(Leu167Pro). The previously reported *PIGL* variants and the newly described variant are summarized in Figure 2.

On examination at the age of 9, the boy's growth had slowed down: his weight was 32.4 kg (+1 SD), height was 140 cm (+1.5 SD) and head circumference was 57 cm (+3 SD). The aforementioned skin abnormalities were stable, and in particular, hair growth remained very slow (Figure 4). Mild perifollicular hyperkeratosis was observed under dermoscopy of his scalp, and yellow crusts and mild erythema were noted. His neurodevelopmental status and social skills were normal.

## DISCUSSION

In our case, the genotype/phenotype correlation partially matched a diagnosis of CHIME syndrome. Along with the core features of this syndrome, other clinical signs have been described: epileptic seizures, facial dysmorphism (including a prominent forehead, hypertelorism, and epicanthal folds), widely spaced teeth, and skin, hair and nail anomalies (such as sparse, thin hair, thick palms and soles, and migratory ichthyosis)<sup>5,6,8-10</sup>. Our patient's clinical features, including early-onset epilepsy, hair, tooth and nail abnormalities, and ichthyosiform dermatitis were consistent with a diagnosis of CHIME. Persistent, excessive growth has also been reported in two cases of CHIME syndrome<sup>6</sup>. The clinical and molecular features of the eight previously reported *PIGL*-related CHIME syndrome are summarized in the supplementary data (Table S1).

Our patient exhibited a mild phenotype. In particular, no ophthalmological, echocardiographic, or significant ENT anomalies were found. Furthermore, the boy's psychomotor and neurological impairments receded with age. It is noteworthy that in a cell-based functional assay, the c.500T>C, p.(Leu167Pro) variant was associated with a moderately but significantly lower level of GPI anchor markers, relative to other GPI deficiencies<sup>4</sup>. Interestingly, this variant is the common denominator of the eight previously reported cases and has never been reported in a homozygous state. Given that the c.500T>C, p.(Leu167Pro) variant appears to have a small effect *per se*, the severity of the phenotype might be determined by the variant on the other allele. This might explain the phenotype in the present case: assuming that the effect of the p.(Asp52Asn) variant has a small impact, the combined effect of the two variants might result in a moderate clinical expression of the CHIME syndrome.

Consequently, our patient's phenotype provides new data on the clinical spectrum of CHIME syndrome. It is noteworthy that *PIGL* gene variations are also associated with Mabry syndrome (characterized by hypotonia, seizures, intellectual disability and increased blood levels of tissue nonspecific alkaline phosphatase), which is phenotypically distinct from CHIME syndrome<sup>3,11-13</sup>.

Our case illustrates phenotypic/genotypic variations in CHIME syndrome. Exome sequencing was particularly useful for diagnosis, widening the clinical spectrum of CHIME syndrome and enabling accurate genetic counseling<sup>3,11</sup>.

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## FIGURE LEGENDS

Figure 1: Cutaneous features characteristic of CHIME syndrome:

1.A: Thin eyebrows and internal epicanthal folds at age 9 years

1.B: Slowly growing, sparse, thin hair, with reduced density on the temporoparietal scalp with an area of hypotrichosis at the junction of the vertex and the upper parietal scalp at age 9 years

1.C: Conical, irregularly spaced teeth at age 5 years

Figure 2: Reported *PIGL* gene variants. The green boxes correspond to the seven exons. The figure was created with Proteinpaint (<https://pecan.stjude.cloud/proteinpaint>)

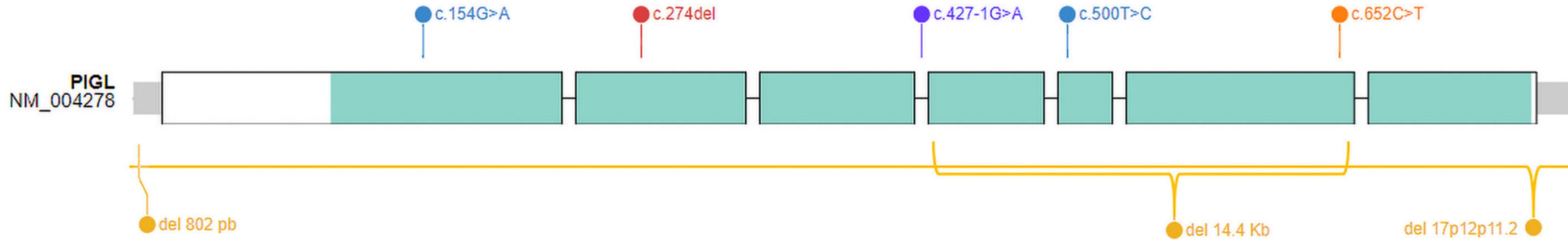
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Supplementary data - Table S1: Clinical and molecular features of patients with *PIGL*-related CHIME syndrome









LEGEND

2 MISSENSE   
 1 FRAMESHIFT   
 1 NONSENSE   
 1 SPLICE   
 3 deletion