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CASE REPORTS IN DIVERSE POPULATIONS

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PERCHING syndrome: Clinical presentation in the first African patient confirmed by clinical whole genome sequencing

Prince Makay[1,2,3] | Gerrye Mubungu[1,2,3] | Aimée Mupuala[2] | Krista Bluske[4] | Carolyn Brown[4] | Sarah A. Schmidt[4] | Mamy Ngole[1] | Patrick Fuanani[1,2] | Denise L. Perry[4] | Prosper Lukusa[1,2,3] | Koenraad Devriendt[3] | Ryan J. Taft[4] | Aimé Lumaka[1,2,5]

[1]Centre for Human Genetics, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

[2]Department of Pediatrics, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

[3]Centre for Human Genetics, University Hospital, University of Leuven, Leuven, Belgium

[4]Illumina Inc, San Diego, California, USA

[5]Laboratoire de Génétique Humaine, GIGA-Research Institute, University of Liège, Liège, Belgium

Correspondence
Aimé Lumaka, Laboratoire de Génétique Humaine, GIGA-R, University of Liège, Liège, Belgium, Bât. B34 +2, Sart Tilman, Avenue de l'Hôpital 13, 4000 Liège 1 - Belgium.
Email: aime.lumaka@gmail.com

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Abstract

PERCHING syndrome is a rare multisystem developmental disorder caused by autosomal recessive (AR) variants (truncating and missense) in *the Kelch-like family member 7* gene *(KLHL7)*. We report the first phenotypic and molecular description of PERCHING syndrome in a patient from Central Africa. The patient presented multiple dysmorphic features in addition to neurological, respiratory, gastroenteric, and dysautonomic disorders. Clinical Whole Genome Sequencing in the proband and his mother identified two novel heterozygous variants in the *KLHL7 gene*, including a maternally inherited intronic variant (NM_001031710.2:c.793 + 5G > C) classified as Variant of Uncertain Significance and a frameshift stop gain variant (NM_001031710.2:c.944delG; p.Ser315ThrfsTer23) of unknown inheritance classified as likely pathogenic. Although the diagnosis was only evoked after genomic testing, the review of published patients suggests that this disease could be clinically recognizable and maybe considered as an encephalopathy. Our report will allow expanding the phenotypic and molecular spectrum of Perching syndrome.

KEYWORDS
Central Africa, Dysmorphism, KLHL7, PERCHING syndrome, WGS

1 | INTRODUCTION

Perching syndrome is an autosomal recessive multisystem disorder (OMIM #617055) caused by homozygous or compound heterozygous variants (truncating and missense) in *Kelch Like Family Member 7 gene* (*KLHL7*), located on chromosome 7p15. The acronym PERCHING has been proposed to include the most characteristic features and each letter represents two important phenotypic elements: **P** for Postural and Palatal abnormalities, **E** for Exophthalmos and Enteral-tube dependency/feeding issues, **R** for Respiratory distress and Retinitis pigmentosa, **C** for Contractures and Camptodactyly, **H** for Hypertelorism and Hirsutism, **I** for IUGR/growth failure and Intellectual disability/developmental delay, **N** for Nevus flammeus and Neurological malformations, and **G** for facial Gestalt/Grimacing and Genitourinary abnormalities (Jeffries et al., 2018). This disorder is also referred to as KLHL7-related Bohring-Opitz-like phenotype due to overlapping phenotype. Although the phenotypic spectrum of Perching syndrome is broad and multisystemic (Table 1), there seems to be a dysmorphic presentation that may allow the clinical recognition of this syndrome.

Since the first report of this syndrome in 2016 (Angius et al., 2016), 18 patients have been reported. We report on the first African patient with Perching syndrome and compare the phenotype to reported non-African, Asian, and European patients.

TABLE 1 Detailed clinical features of patients with recessive variants in the *KLHL7* gene, compared with our patient

	Angius et al., 2016					Bruel et al., 2017						Kanthi et al., 2018	Jeffries et al., 2018		Heng et al., 2019		Cheraghi et al., 2020		Our patient
Patients ID	**CS_144**	**CS_258**	**CS_259**	**CS_260**	**CS_169**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**1**	**2**	**1**	**2**	**1**	**2**	**1**
Age, sex at diagnosis	F, 7mo	F, 4y	F, 6mo	M,11mo	M, 5mo	F	M	M	M	F	M	M, 3y	F, 3y	M, 3mo	M, 21y	F, 19y	F, 9y	F, 3y	M, 13mo
Age of death if deceased	21mo		24mo		5.5mo	2y	1y												2y
Origin	Turkey	Turkey	Turkey	Turkey	Turkey	Syria	Syria	Italy	UK	UK	UK	India	Gua	Gua	UK	UK	Iran	Iran	DR Congo
Consanguinity	yes	yes	Yes	yes	yes	?	?	no	no	no	yes	yes	no	no	no	no	no	no	no
Variant	p.C421S	p.L341fs	p.L341fs	p.R420C	p.R372Q	c.618 +1G > A	c.474 +1G > A	p.K383X	p.R351X	p.R351X	c.935_936 + 19del	p.V61del	p.R326X	p.R326X	p.R351X	p.R351X	p.F83fs	p.F83fs	c.793 +5G > C; p.S315fs
Craniofacial																			
Microcephaly	NA	NA	NA	NA	NA	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trigonocephaly						−	−	−	+	−	−		−	−			−	−	−
Facial grimacing						−	−	−	−	−	−		+						
Long face																			+
Triangular face												+							−
Prominent forehead												+							−
Highly arched eyebrows												+	−	−					−
Full cheeks	−	+	+	+	+								−	−					−
Retro/micrognathia						+	+	+	+	−	+		+	+			+	+	−
Midface retrusion													+	+					−
Smooth philtrum																			+
Low-set, posteriorly rotated ears						−	−	−	+	−	+		+	+	−	−	−	−	−
Broad inferior crus of antihelix																			+
Underdeveloped inferior crus of antihelix																			+
Everted antitragus																			+
Macrotia																	−	−	+
Dysplastic ears												+			+	+			
Widely spaced eyes						+	+	+	+	+	+		+	−	+	+	+	+	−
Downslanted palpebral fissures													+	+			−	−	+/−
Proptosis						+	+	+	+	+	+		−	−			+	+	−
Strabismus						−	−	−	+	+	+		+	+			−	−	−
Nystagmus													+						
Ptosis													+						
Retinitis pigmentosa	−	+	NA	+	NA	−	−	−	−	−	NA	+	−		+	+	+	−	NA
						−	−	−	NA	NA	+		+		+	+			NA

TABLE 1 (Continued)

	Angius et al., 2016					Bruel et al., 2017						Kanthi et al., 2018	Jeffries et al., 2018		Heng et al., 2019		Cheraghi et al., 2020		Our patient
Patients ID	**CS_144**	**CS_258**	**CS_259**	**CS_260**	**CS_169**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**1**	**2**	**1**	**2**	**1**	**2**	**1**
Other ophthalmic exam abnormalities																			
Depressed nasal bridge	+	+	+	+	+	−	−	−	NA	NA	NA		+	+			−	−	−
Broad nasal tip																			+
Anteverted nares						+	+	+	+	+	+		−	−			−	−	−
Wide nose													+	+					−
contraction of oropharyngeal muscles/ Jaw contracture	+	+	+	+	+	−	−	−	−	−	−	+							+
Abnormal palatal structure	+	+	+		+	−	+	−	+	+	+	+	+	+	+	+	−	−	
Tented upper lip																			+
Narrow mouth													+	−					+
Cardiovascular																			
Cardiac anomalies	NA	NA	NA	NA	NA	−	+	−	−	+	+	NA	+	+			+	+	−
Respiratory																			
Respiratory distress	−	−	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+
Recurrent infections						+	+	+	+	+	+		+	+			+		+
Trunk: Wide internipple distance																			+
Abdomen/Gastroenteric																			
Swallowing difficulties	+	+	+	+	+							+	+	+					
Feeding difficulties	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+
Enteral-tube dependency												+	+	+	+	+			
Poor growth/FTT												+	+	+			+	+	+
Genitourinary																			
Genitourinary anomalies	NA	NA	NA	NA	NA	−	−	−	+	−	+	NA	−	+			−	−	NA
Neurological and musculoskeletal																			
Global developmental delay	NA	−	−	NA	+	+	+	+	+	+	+	+	+	+			+	+	+
Typical resting posture						−	+	+	+	+	+	+	+	+			−	−	+
Global abnormal tonus						+	+	+	+	−	+	+	+	+			+	+	+
Minimal expressive speech													+						−
Seizures						+	+	+	−	+	−		−	−			+	+	+
Brain abnormalities	NA	NA	NA	NA	NA	+	+	+	+	+	+	+	+	+			NA	NA	NA
joint contracture	+	+	+	NA	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Hyperreflexia												−	+	+					+

(Continues)

TABLE 1 (Continued)

	Angius et al., 2016					Bruel et al., 2017						Kanthi et al., 2018	Jeffries et al., 2018		Heng et al., 2019		Cheraghi et al., 2020		Our patient
Patients ID	**CS_144**	**CS_258**	**CS_259**	**CS_260**	**CS_169**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**1**	**2**	**1**	**2**	**1**	**2**	**1**
Camptodactyly	+	+	+	+	+	−	−	+	+	NA	+	+	+	−	+	+	+	+	+
Clinodactyly													+	−					−
Cutaneous syndactyly of toes																			+
Abnormal palmar crease													+	+					+
Clenched hands													+	+			+	+	−
Overlapping toes													+	−			+	+	+
Foot anomalies	?	+	−	NA	+								+	+			+	+	−
Short stature												+	+	+			+	+	+
Skin, nail and hair																			
Facial Nevus flammeus						+	+	+	+	+	−	+	+	−	+	+	−	−	−
Sparse scalp hair												+							+
Hirsutism						+	+	+	−	+	+	+	−	−			+	+	−
Dysautonomic features																			
Hyperthermia	+	+	?	+	−	−	−	−	−	−	−	+	−	−					+
Cold-induced sweating	−	+	−	−	−							+							−
Hematology																			
Anemia								−				−							+
thrombocytopenia								−		+		−	−	−					
Prenatal																			
Polyhydramnios													−	−					NA
IUGR	NA	NA	NA	NA	NA	+	+	+	+/−	−	+	NA	+	+			−	−	NA

Abbreviations: −, Absent; +, Present; F, Female; FTT, Failure to thrive; Gua, Guatemala; IUGR, Intrauterine growth retardation; M, Male; mo, month; NA, Not available; UK, United Kingdom; y, year.

2 | CASE REPORT

The index patient was referred to the genetic clinic at the age of 13 months for global developmental delay and abnormal morphologic appearance. This boy was born preterm (36 weeks) from healthy and non-consanguineous parents. Mother presented pre-eclampsia and genital bleeding during pregnancy, but no further details were provided. He was born by caesarian section for hemorrhagic placenta previa. The APGAR score was 1 at the first minute necessitating resuscitation for over 10 minutes. The patient was treated in the Neonatology Intensive Care Unit (NICU) for respiratory distress, then readmitted multiple times in the postnatal period for recurrent pulmonary infections. Birth weight was 2450 g (−1.75 SD). He was the third of four children. There was a pair of dizygotic twins, including a girl who presented similar phenotype and course of disease as this proband, reportedly. She died at the age of 4 years in the context of respiratory distress.

His development was globally delayed, with severe hypotonia noticed from 4 months. At 13 months of age he was still unable to hold his head, sit without support, or develop speech. Seizures were observed for the first time at 9 month of age and increased in frequency with multiple episodes a day despite valproate acid and phenobarbital treatment and omega-3 supplementation. In addition to recurrent respiratory infections, he also exhibited recurrent febrile episodes of unknown causes and feeding difficulties. He received a blood transfusion at age 6 and 8 months, respectively. Chest X-ray, performed at 9 months, was compatible with bronchitis while cardiac ultrasound did not reveal any anomaly. MRI was not performed due to financial limitations.

The patient had significant global growth delay (according to the CDC growth charts (Kuczmarski et al., 2002) for 13 months) with low weight (4.900 kg = −7.10 SD), marked short stature (62 cm = −5.74 SD) and severe microcephaly (OFC 38 cm = −8.27 SD). Dysmorphic evaluation (Figure 1) showed microcephaly, long face, sparse scalp hair, downslanted palpebral fissures, broad nasal tip, smooth philtrum, tented upper lip, narrow mouth, jaw contracture, macrotia, broad inferior crus of antihelix at left, underdeveloped inferior crus of antihelix of the right ear, everted antitragus, wide internipple distance, absence of medial transverse palmar crease on the right, partial bilateral cutaneous syndactyly of toes 2–4. There were joint contractures (elbows, knees, phalanges), with overlapping toes, camptodactyly of fingers and a typical resting posture (internal rotation of shoulders, elbow flexion and forearm pronation with clenched hands). He presented hyperreflexia.

The mother provided approval for clinical Whole Genome Sequencing (cWGS), which was donated by the Illumina iHope program, and for the inclusion of clinical photographs in scientific publication. Duo-based cWGS (proband and unaffected mother), performed using TrueGemome™ Sequencing at 28×, identified two heterozygous variants in the *KLHL7*. There was an intronic variant NM_001031710.3: c.793 + 5G > C (GRCh37 Chr7:23183649G > C), maternally inherited. This is a known very rare variant (gnomAD v3.1.2 allele count 4, Allele frequency: 0.00003286) with no homozygous individuals in population databases. It is predicted to disrupt the splice donor site according to Human Splice Finder (https://hsf.genomnis.com/home). The second variant was a novel frameshift stop gain variant NM_001031710.3: c.944delG (p.Ser315ThrfsTer23) (GRCh37 Chr7:23205324delG), predicted to cause a premature termination 23 codons downstream. This variant was absent in the mother, the father was unavailable. The frameshift variant is absent from population databases and affects a highly conserved residue. There is no benign prediction for this variant. The frameshift variant is classified as likely pathogenic (LP) according to the ACMG-AMP guidelines, whereas the intronic variant was classified as a variant of uncertain significance (VUS) (Richards et al., 2015). Although the father did not consent for testing and neither parent consented for testing the unaffected siblings, compound heterozygosity was assumed based on the strong phenotypic match with the deceased sister, which was suggestive for the familial recurrence of KLHL7-related Perching syndrome."

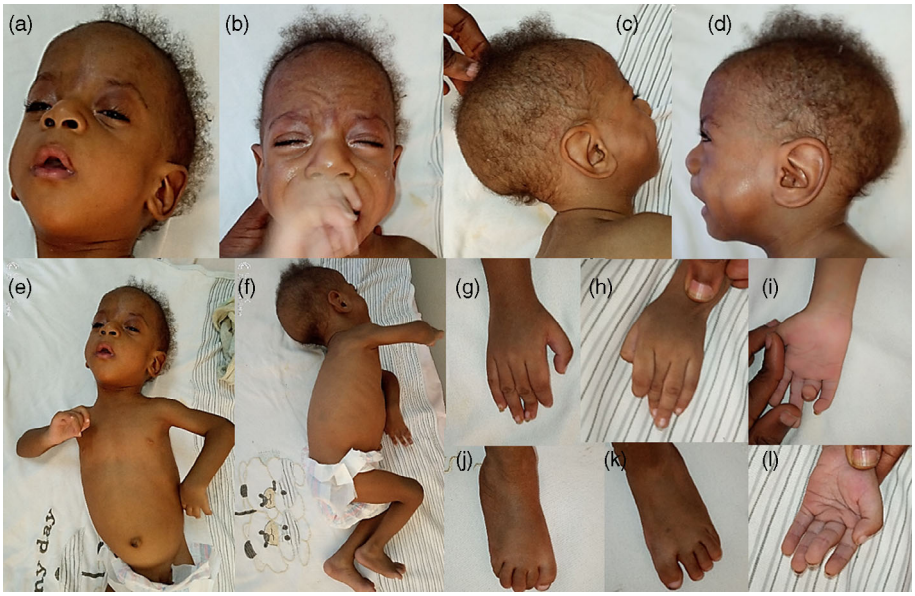

FIGURE 1 Clinical photographs of the patient. Photographs at the age of 13 months showing long face (a, b), downslanted palpebral fissures (b), broad nasal tip (a, b), smooth philtrum (a), tented upper lip vermilion (a), narrow mouth (a), sparse scalp hair, macrotia (c, d), jaw contracture (c, d), broad inferior crus of antihelix (d), underdeveloped inferior crus of antihelix (c), everted antitragus (c, d), typical resting posture (internal rotation of shoulders, elbow flexion and forearm pronation) (e, f), wide internipple distance (e), knee contracture (f), camptodactyly of fingers (g, h), absence of medial transverse palmar crease (i), partial cutaneous syndactyly of toes 2–4 (j, k), overlapping toes (j, k).

3 | DISCUSSION

This report provides the first clinical description of Perching syndrome in a patient from Africa. This is a very rare autosomal recessive disorder with only 18 other patients reported, most of them from Turkish origin (Angius et al., 2016; Bruel et al., 2017; Cheraghi et al., 2020; Heng et al., 2019; Jeffries et al., 2018; Kanthi et al., 2018).

The first patients with homozygous *KLHL7* mutations were reported as Crisponi syndrome/cold-induced sweating syndrome (CS/CISS)-like or Bohring Opitz syndrome (BOS)-like due to the overlap clinical presentation although those syndromes are distinct and have different disease-causing genes (Angius et al., 2016; Bruel et al., 2017; Jeffries et al., 2018).

The phenotype in our patient matches reported presentations in Perching patients for P (typical resting posture), for E (feeding difficulties), for R (respiratory distress and recurrent infections), for C (jaw contracture, joint contracture, camptodactyly), for I (failure to thrive, global developmental delay, seizures), for G (microcephaly, long face, downslanted palpebral fissures, broad nasal tip, smooth philtrum, tented upper lip, narrow mouth, macrotia, broad inferior crus of antihelix at left, underdeveloped inferior crus of antihelix of the right ear) and additional phenotypic manifestations (abnormal palmar crease, overlapping toes, sparse scalp hair and hyperthermia). Due to financial limitations, ophthalmologic and imaging evaluations were not conducted to assess eye and brain abnormalities in our patient.

Interestingly, this patient was previously considered to have encephalopathy of acquired origin due to the history of asphyxia, long resuscitation and subsequent seizures, resulting in microcephaly, failure to thrive and abnormal posture. Although an environmental contribution cannot be excluded, the neurologic trajectory in this patient is reminiscent of previously reported patients (Angius et al., 2016; Bruel et al., 2017; Cheraghi et al., 2020; Heng et al., 2019; Jeffries et al., 2018; Kanthi et al., 2018) and suggests that encephalopathy is a component of the *KLHL7*-related neurodevelopmental disorder. This case also demonstrates that neonatal distress, very frequent in low- and middle-income countries, may overshadow the phenotype of congenital disorders and these patients should not be excluded from genetic investigations. Also, due to a lack of training in the dysmorphology field, likely some cases continue to escape to clinical diagnosis (Lumaka et al., 2016).

Our patient died at the age of 2 years and 1 month. At the time of his death, he was receiving multidisciplinary care.

AUTHOR CONTRIBUTIONS

P.M., P.F., M.N., G.M., A.M., and A.L. were actively involved in clinical evaluation, counseling and follow-up of the patient. P.L., K.D., and A.L. reviewed the patients. K.B., C.B., S.A.S., D.L.P. and R.J.T. were involved in Sequencing and data interpretation. All authors were actively involved in the redaction of this manuscript, its revisions and approved the final version.

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CONFLICT OF INTERESTS

K.B, C.M.B., S.S., D.P., and R.J.T. are Employee and Shareholder in Illumina, Inc. R.T. serves as Scientific Advisor for Creyon Bio, Inc. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Genomic results supporting the diagnostic have been submitted to Clinvar with accession numbers SCV002097242 and SCV002097243. Those data and related information are also available from the corresponding author upon reasonable request. A list of novel variants in Developmental disorders genes (DDG2P) is provided in Table S1. These were excluded based on either the insufficient phenotype overlap or zygosity-inheritance discordance or both.

ORCID

Prince Makay https://orcid.org/0000-0002-2910-9590
Gerrye Mubungu https://orcid.org/0000-0002-8870-0575
Aimé Lumaka https://orcid.org/0000-0002-5468-8678

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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