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CLINICAL REPORT

Two novel presentations of KCNMA1-related pathology–– Expanding the clinical phenotype of a rare channelopathy

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Abstract

Background: *KCNMA1* mutations have recently been associated with a wide range of dysmorphological, gastro-intestinal, cardiovascular, and neurological manifestations.

Methods: Whole exome sequencing was performed in order to identify the underlying pathogenic mutation in two cases presenting with diverse phenotypical manifestations that did not fit into well-known clinical entities.

Results: In an 8-year-old boy presenting with severe aortic dilatation, facial dysmorphism, and overgrowth at birth a de novo p.Gly375Arg *KCNMA1* mutation was identified which has been reported previously in association with gingival hypertrophy, aortic dilatation, and developmental delay. Additionally, in a 30-week-old fetus with severe growth retardation and duodenal atresia a de novo p.Pro805Leu *KCNMA1* mutation was identified. The latter has also been reported before in a boy with severe neurological manifestations, including speech delay, developmental delay, and cerebellar dysfunction.

Conclusion: The current report presents the first antenatal presentation of a pathogenic *KCNMA1* mutation and confirms the specific association of the

p.Gly375Arg variant with early onset aortic root dilatation, gingival hypertrophy, and neonatal overgrowth.

KEYWORDS

channelopathy, *KCNMA1* loss-of-function, Liang-Wang syndrome, thoracic aortic aneurysm

1 | INTRODUCTION

Clinical phenotypes associated with loss-of-function variants in the *KCNMA1* gene (OMIM: 600150) have recently been described in two small patient cohorts (Bailey et al., 2019; Liang et al., 2019). The reported features in affected individuals include a broad spectrum of neurological and developmental impairment, as well as congenital malformations and dysmorphic features. A recurrent p.Gly375Arg loss-of-function variant has been detected previously in three patients. Here we describe a fourth patient, the first of African ancestry, with the same *KCNMA1* variant detected on whole exome sequencing, and expand the clinical spectrum of this rare channelopathy. Moreover, we present the first antenatal detection of a previously described pathogenic *KCNMA1* variant p.Pro805Leu.

2 | METHODS

2.1 | Whole exome sequencing

DNA of the probands (from peripheral blood in patient 1 and from amniocytes in patient 2) and the parents was subjected to whole exome sequencing (WES) according to the manufacturer's protocols including, (a) DNA fragmentation using Covaris M220 Focused-ultrasonicator; (b) sample preparation with the TruSeq DNA Sample Preparation kit (Illumina); and (c) enrichment using the SeqCap EZ Human Exome Library v3.0 kit (NimbleGen, Roche) and sequencing on a HiSeq 2000 (Illumina). Analysis of WES data was performed using VariantDB (Vandeweyer et al., 2014). Variants were filtered based on quality parameters (total depth ≥10, mapping quality ≥50, and quality by depth ≥4.8), either the absence or a frequency that is smaller than or equal to 0.001 in GnomAD (g2.1 AF (non topmed)), and absence in both healthy parents.

Sanger sequencing was performed on the region flanking the identified *KCNMA1* variants. Primers were designed with Primer3 (Untergasser et al., 2012). A PCR reaction was carried out on DNA from peripheral blood from the proband and clinically unaffected parents using GOTaq polymerase (Promega), followed by sequencing of the PCR products using the ABI BigDye Terminator V3.1 Cycle Sequencing kit (Applied Biosystems), respectively. Fragments were separated on an ABI 3130 Genetic Analyzer (Applied Biosystems) and the resulting sequences were analyzed using CLC DNA workbench (CLC Bio).

2.2 | Variant submission to ClinVar

The *KCNMA1* variants p.Gly375Arg (Clinvar accession: SCV001448194) and p.Pro805Leu (Clinvar accession: SCV001448195) were submitted to ClinVar.

3 | RESULTS

3.1 | Case 1

A male patient was first assessed at a Genetic Clinic in Johannesburg, South Africa, at the age of 3 months. His parents are a healthy, non-consanguineous couple of African ancestry. His mother reported an uneventful pregnancy with no illnesses, antepartum complications, or teratogenic exposures. Fetal ultrasound scans during the pregnancy were reported as normal. The baby was delivered by cesarean section at 41 weeks due to prolonged rupture of membranes. His birth length was on the 98th centile with weight and head circumference >98th centile. He was investigated after delivery for respiratory distress and was diagnosed with laryngomalacia. An initial echocardiogram at 5 weeks of age revealed dilatation of the aortic root (15 mm; z-score +4,3), in addition to a small 2 mm patent ductus arteriosus, that later spontaneously closed. Upon initial genetic consultation, the child was noted to be macrocephalic with a number of unusual features (Table 1), including facial dysmorphism (hypertelorism, a broad nasal root, a wide mouth with downturned corners, high arched palate, and gingival hypertrophy) and a large umbilical hernia. He was sequentially assessed at the Genetic and Cardiology Clinics over several years and was last seen at 8 years of age. His facial features coarsened over time, with the development of significant gingival hypertrophy and upper airway obstruction. Additional clinical problems included

TABLE 1 Clinical description of two novel patients compared with previously described patients with the same mutation as well as with all other known KCNMA1 loss-of-function mutations

	p.Gly375Arg				p.Pro805Leu		All *KCNMA1* LOF mutations
Patient	**1**	**Patients 1, 2, and 3 (Liang et al., 2019)**			**2**	**Patient 8 (Liang et al., 2019)**	**Total (Du et al., 2020; Liang et al., 2019; Tabarki et al., 2016; Yesil et al., 2018; Zhang et al., 2015)**
De novo	+	+	+	+	+	+	12/15 (80%)
Gender (male)	M	M	F	F	M	M	9/15 (60%)
Age at last evaluation	8y	3y 4m	21y	12y	Prenatal	4y	NA
Birth parameters							
Gestational age	41w	36w	37w	40w	30w (TOP)	40w	39w (36–41)
weight	4.65 (>98%)	3.80 kg (98%)	2.95 kg (50%)	3.97 kg (93%)	720 g (1%)	5.58 kg (99.9%)	2.13–5.58 kg
Length	54cm (98%)	48 cm (55%)	50 cm (85%)	48.5 cm (36%)	31 cm (0%)	55 cm (99%)	48–55 cm
Occipitofrontal diameter	39 (>98%)	35 cm (85%)	33.5 cm (50%)	35 cm (83%)	24,1 cm (0%)	35.5 cm (55%)	33.5–39 cm
Cardiovascular anomalies							
Aortic root dilatation	+	+	+	+	NA	–	4/14 (29%)
Circle of Willis dilatation	+	–	–	–	NA	–	1/14 (7%)
Patent ductus arteriosus	+	–	+	–	NA	–	2/14 (14%)
Visceral anomalies							
Megabladder	–	+	–	–	NA	–	1/14 (7%)
Abnormal bowel motility	–	–	+	+	NA	–	2/14 (14%)
Duodenal atresia	–	–	+	–	+	–	2/15 (13%)
Neurological features							
ID/DD	–	+	+	+	NA	+	13/14 (93%)
Ataxia	–	–	–	–	NA	–	5/14 (36%)
Epilepsy	–	–	+	+	NA	–	8/14 (57%)
Cerebral/cerebellar atrophy	–	–	+	–	–	–	6/15 (40%)
Other							
Laryngeal anomalies	+	–	–	+	NA	–	2/14 (14%)
Gyngival hypertrophy	+	+	+	+	–	–	
Umbilical hernia	+	–	+	–	NA	–	2/14 (14%)
Facial dysmorphism	+	+	+	+	NA	–	6/14 (43%)
Eye anomalies	+	+	+	–	NA	–	7/14 (50%)

Abbreviations: ID/DD, intellectual disability/developmental delay; LOF, loss-of-function; m, months; TOP, termination of pregnancy; w, weeks; y, years.

the development of bilateral strabismus and a fall-off in both weight and height with short stature by the age of 4 years. Subsequent echocardiography and CT angiogram noted alarming aortic aneurysm affecting predominantly the aortic root, and the development of mild to moderate aortic regurgitation (Figure 1). The aortic root at last review measured 59 mm (Z-score +15,4). In addition to the aortic involvement, a CT scan of the brain documented dilatation of the circle of Willis (Figure 2). The child has age-appropriate neurodevelopment and currently attends a mainstream school. Electrocardiograms and Holter registrations revealed no abnormalities and QTc values were within the normal range.

Based on the proband's aortic dilatation, circle of Willis anomaly, umbilical hernia, and strabismus, a connective tissue disorder was initially suspected. A thoracic aortic aneurysm/dissection (TAAD) multi-gene panel was performed by the Centre for Medical Genetics at the University of Antwerp, and was reported as negative for causative pathogenic variants. More extensive genetic testing was undertaken to determine a possible etiology for the unusual phenotype. A de novo WES analysis at

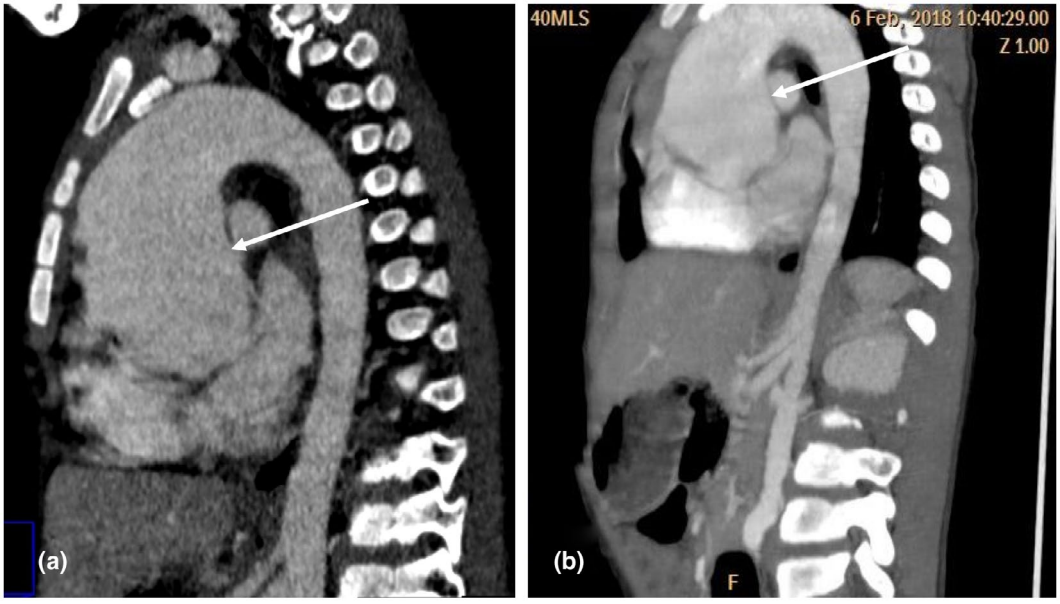

FIGURE 1 Computed tomography scan of chest showing substantial aortic root dilatation (white arrows), (a) pre-contrast administration; (b) post-contrast administration

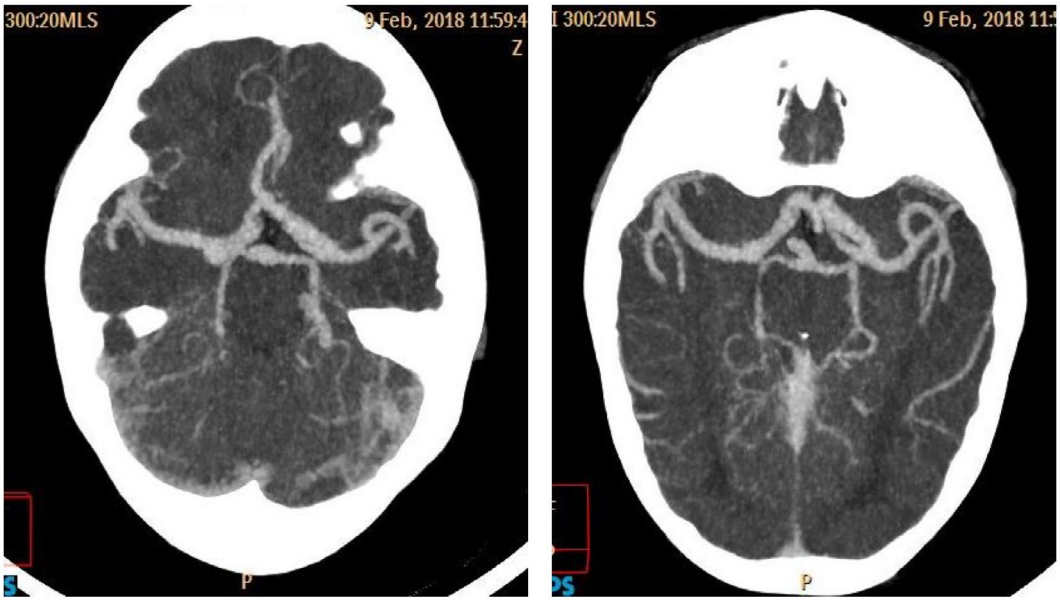

FIGURE 2 Computed tomography scan of brain showing giant circle of Willis

Radboud University Medical Center, Nijmegen revealed a variant that was detected in a highly conserved region of the *KCNMA1* gene (NM_001161352.2: c.1123G>A; p.Gly375Arg; Chr10: 78869939 (GRCh37)).

3.2 | Case 2

A male fetus was born after termination of pregnancy at 30 weeks and 5 days (G1P1A1). During pregnancy, ultrasound evaluation revealed severe intra-uterine growth restriction (at 29 weeks and 2 days: head circumference 241,3 mm (P0), abdominal circumference 189,4 mm (P 0,3), and estimated fetal weight 623 g (P0)) with echogenic bowels and later a double bubble sign (Figure 3). No cerebral abnormalities were noted. There was a reversed end diastolic flow in the umbilical artery, brain sparing in the midcerebral artery, and a reversed a-wave in the venous duct. During pregnancy, SNP array did not reveal any pathogenic chromosomal deletion/duplication. Birth weight was 720 g (P1) and birth length was 31 cm (P0). Physical exam did not reveal dysmorphic features. Obduction revealed a proximal duodenal atresia, with hypoplastic colon and absent gall bladder. Placental weight was 98 g (<P3).

WES analysis (Radboud) revealed a de novo *KCNMA1* variant (NM_001322832.2: c.2414C>T; p.Pro805Leu; Chr10:78709021 (GRCh37)), which has been previously reported (Liang et al., 2019). Moreover, an incidental finding of a pathogenic variant in the *COL3A1* gene (c.3496T>C; p.Arg1166* was identified in the fetus and the mother. The 31-year-old mother was healthy. Her family history is uneventful for vascular EDS-associated health problems.

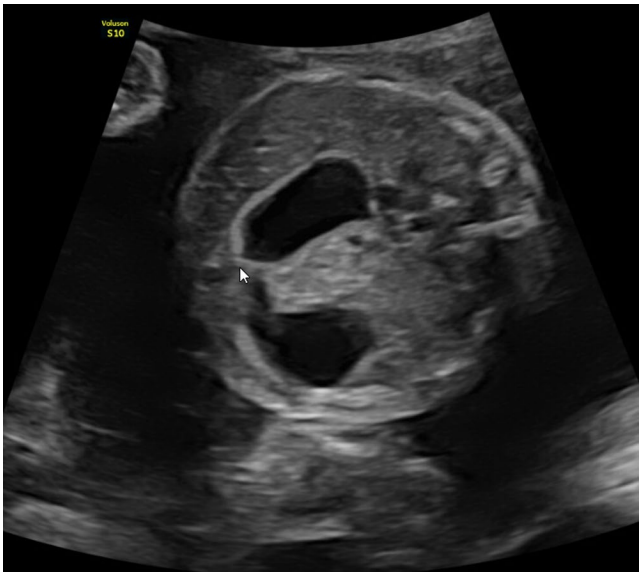

FIGURE 3 Ultrasound image of the duodenal atresia (double bubble) observed in case 2

4 | DISCUSSION

Here, we report the first African patient with a de novo p.Gly375Arg substitution in the *KCNMA1* gene – a mutation that has been described previously in three other cases presenting a severe form of the Liang-Wang syndrome, a rare syndrome that was only recently described (Liang et al., 2019). Moreover, we report on the first antenatal presentation of the syndrome. The de novo *KCNMA1* p.Pro805Leu mutation in the male fetus has also been reported previously in a 4-year-old male (Liang et al., 2019).

KCNMA1 encodes the alpha subunit of a large conductance calcium-sensitive potassium channel (BK-channel) which is expressed in the cell membrane. The BK-channel is formed by tetramerization of four pore forming alpha subunits, which are in their turn modulated by calcium and voltage sensitivity-regulating beta and gamma subunits (Latorre et al., 2017). By controlling the excitability of cells in a wide variety of tissues and organs, the channel is involved in the regulation of neurotransmitter release, smooth muscle cell contraction, and the tuning of cochlear hair cells (among others). Additionally, it appears to regulate mesenchymal stromal cell migration and differentiation. The subunit has an N-terminal part with seven helical transmembrane domains (S0–S6) and a C-terminal part with multiple binding sites for regulatory ligands such as calcium (by which the channel is activated) and magnesium (Li et al., 2018; Liang et al., 2019).

KCNMA1 was first discovered as a disease-causing gene in a large family, where gain-of-function resulted in epilepsy and paroxysmal dyskinesia (Du et al., 2020). Currently, two mutations have been shown to confer gain-of-function to the BK-channel (p.Asp434Gly and p.Asn995Ser) (Du et al., 2005; Zhang et al., 2015). Later on, autosomal dominant (Carvalho-de-Souza et al., 2016; Liang et al., 2019) and recessive (Tabarki et al., 2016; Yesil et al., 2018) loss-of-function or putative loss-of-function *KCNMA1* variants have been associated with a wide range of brain and muscle disorders (Bailey et al., 2019; Liang et al., 2019). These patients exhibit heterogeneous phenotypes with neurological and developmental features including ataxia, intellectual disability, developmental delay, hypotonia, and cerebral or cerebellar atrophy. Eye abnormalities have also been reported frequently.

Our patient 1 and three other patients (Liang et al., 2019) with the p.Gly375Arg substitution share a severe form of the Liang-wang syndrome, characterized by highly overlapping features with marked involvement of visceral, cardiovascular, and connective tissue abnormalities (Table 1). Visceral abnormalities include intestinal malrotation, atresia, and dilatation and bladder enlargement, findings that were not observed hitherto in patients with other *KCNMA1* loss-of-function

mutations. Umbilical hernia, a high arched palate, laryngomalacia, and gingival hyperplasia are all recurrent features previously described uniquely in *KCNMA1* patients with a p.Gly375Arg *KCNMA1* variant and present in our patient 1. Overlapping facial dysmorphic features include hypertelorism, a broad nasal root, and a wide mouth with downturned corners. Interestingly, the male patients (patient 1 from Liang et al., 2019 and our patient) reveal a severely dilated aortic root, whereas female patients (patient 2 and 3 from Liang et al., 2019) show a milder enlargement, reflecting the typical gender discrepancies of (syndromic) aortopathies (Kuivaniemi et al., 2014; Roman et al., 2017; Steckmeier, 2001). The involvement of the aortic root in these four patients and the relatively high expression of *KCNMA1* in the aorta suggests a vital function of KCNMA1 transmembrane segments in vascular smooth muscle cell contractility. Additionally, a patent ductus arteriosus was noted as a cardiac feature, which is also seen in patient 2 of Liang et al (Liang et al., 2019).

Our first patient also presents with two other unique findings which were never reported before in *KCNMA1* patients: an upper airway obstruction and importantly, an enormously enlarged circle of Willis. The latter finding is an important expansion of the previously noted arteriopathy that characterizes this syndromic channelopathy.

For the first time, we also report on antenatal presentation of Liang-Wang syndrome with duodenal atresia presenting as the classic "double bubble" image on prenatal ultrasound. This is the first patient with a *KCNMA1* loss-of-function variant other than p.Gly375Arg that presents visceral abnormalities. Moreover, our second patient did present with severe intra-uterine growth retardation. The identical *KCNMA1* variant p.Pro805Leu was found de novo in another male patient (Patient 8 from Liang et al., 2019) presenting with severe speech delay, development delay, intellectual disability, apraxia, and abnormal cerebral MRI (see Table 1). Remarkably, patient 8 did not present with intestinal problems and his birth parameters were large with birth length and weight above the 99th percentile. We, therefore, speculate that our patient's uterine growth retardation might be due to an absent end diastolic flow in the umbilical artery, which points to placental insufficiency, rather than to the p.Pro805Leu *KCNMA1* variant (Battaglia et al., 1993; Wang et al., 2009). Since the identified *COL3A1* variant is a haplo-insufficient mutation and the latter have been associated with milder and late onset vascular disease but no gastrointestinal complications so far (Frank et al., 2015; Pepin et al., 2014), we believe it is unlikely to have caused the phenotype in the fetus by itself. However, since both *COL3A1* and *KCNMA1* have essential functions in the gastrointestinal system, we cannot exclude the possibility that both variants can act as genetic modifiers of the observed gastrointestinal phenotype and may have contributed to the overall disease severity (Rahit & Tarailo-Graovac, 2020).

p.Gly375Arg is located in the sixth transmembrane domain (S6), which spans the BK-channel pore and thereby regulates the opening of the channel; p.Pro805Leu resides in the second regulator of conductance of K domains RCK2, responsible for intracellular calcium censing. Both variants have been associated with absent or reduced current of the BK-channel, respectively (Liang et al., 2019), but the exact molecular mechanisms underlying the marked clinical variability have not yet been unraveled. The BK-channel is encoded by only one gene, but diversity in function and regulation across tissues is achieved by tightly regulated tissue-specific alternative splicing: more than 65 different protein coding transcripts have been discovered already for *KCNMA1* (Bell et al., 2010; Consortium, 2013). Interestingly, multiple splicing prediction programs predict that both variants create cryptic splice acceptor sites that are equally (p.Gly375Arg) or almost equally (p.Pro805Leu) as strong as the native sites. If the cryptic splice sites are used instead of the native ones, this would in both cases result in a frameshift mutation. Additionally, several potassium channels are post-transcriptionally edited by RNA-editing proteins, which influences electrophysiological and tetramerization properties, and in *KCNMA1* already one such domain has been identified recently (Pullirsch & Jantsch, 2010). In conclusion, we hypothesize that the different reported LOF variants might influence tissue-specific regulatory mechanisms, consequently creating tissue-specific phenotypes.

The actual contribution of the proposed modifier effects, splice variants, RNA-editing, and additional molecular machinery will need to be unveiled to explain the clinical variability and to better understand *KCNMA1*-related pathology.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Ethical clearance for this case report was granted by the human research ethics committee (medical) from the University of the Witwatersrand (Johannesburg) and the Radboud University Medical Center Nijmegen. The parents of both cases consented to publication of this case report and to the use of clinical images.

AUTHOR CONTRIBUTIONS

J.R.B, C.F., and B.L.: writing—original draft preparation; J.R.B., M.A., J.M., and A.V.: molecular data analysis; C.F., M.K., M.V.R., M.W., K.D., L.C.D., and M.B.: patient clinical follow-up; J.R.B., C.F., M.K., M.V.R., M.W, K.D., L.D.C., M.B., M.A., J.M., A.V., W.H., and B.L.: writing—review and editing.

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