QRICH1 variants in Ververi-Brady syndrome—delineation of the genotypic and phenotypic spectrum

Melanie Föhrenbach | Rami Abou Jamra | Arndt Borkhardt | Triantafyllia Brozou | Petra Muschke | Bernt Popp | Linda K. Rey | Jörg Schaper | Harald Surowy | Martin Zenker | Christiane Zweier | Dagmar Wieczorek | Silke Redler

1Institute of Human Genetics, Heinrich-Heine-University, Düsseldorf, Germany
2Institute of Human Genetics, University Medical Center Leipzig, Leipzig, Germany
3Department of Pediatric Oncology, Hematology and Clinical Immunology, Heinrich-Heine-University, Düsseldorf, Germany
4Institute of Human Genetics, University Hospital of Magdeburg, Otto-von-Guericke-University, Magdeburg, Germany
5Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
6Department of Diagnostic and Interventional Radiology, Heinrich-Heine-University, Düsseldorf, Germany

Correspondence
Prof Silke Redler, MD, Institute of Human Genetics, HHU, Universitätsstr. 1, D-40225 Düsseldorf, Germany.
Email: silke.redler@med.uni-duesseldorf.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Numbers: PO 2366/2-1, RE 4149/1-1, WI 1440/8-1, ZW 184-6/1

Abstract
Ververi-Brady syndrome (VBS, # 617982) is a rare developmental disorder, and loss-of-function variants in QRICH1 were implicated in its etiology. Furthermore, a recognizable phenotype was proposed comprising delayed speech, learning difficulties and dysmorphic signs. Here, we present four unrelated individuals with one known nonsense variant (c.1954C > T; p.[Arg652*]) and three novel de novo QRICH1 variants, respectively. These included two frameshift mutations (c.832_833del; p.(Ser278Leufs*25), c.1812_1813delTG; p.(Glu605Glyfs*25)) and interestingly one missense mutation (c.2207G > A; p.[Ser736Asn]), expanding the mutational spectrum. Enlargement of the cohort by these four individuals contributes to the delineation of the VBS phenotype and suggests expressive speech delay, moderate motor delay, learning difficulties/mild ID, mild microcephaly, short stature and notable social behavior deficits as clinical hallmarks. In addition, one patient presented with nephroblastoma. The possible involvement of QRICH1 in pediatric cancer assumes careful surveillance a key priority for outcome of these patients. Further research and enlargement of cohorts are warranted to learn about the genetic architecture and the phenotypic spectrum in more detail.

Keywords
autism spectrum disorder, language development disorders, QRICH1, Ververi-Brady syndrome

1 | INTRODUCTION

Recent findings revealed de novo QRICH1 (glutamine rich 1) variants in five patients of which one derived from the DECIPHER database with the hallmarks delayed speech, learning difficulties and dysmorphic signs. Furthermore, a whole exome sequencing (WES) study provided encouraging evidence for involvement of QRICH1 in autism spectrum disorder (ASD). In the present study, we report four novel cases, expanding the phenotypic and genotypic spectrum of individuals with QRICH1 variants/Ververi-Brady syndrome (VBS).

2 | MATERIALS AND METHODS

2.1 | Patient 1

Patient 1 was the first child of healthy non-consanguineous parents of German origin. Family history was unremarkable.
Patient 1 was born at 37 weeks of gestation after a pregnancy complicated by preeclampsia and placental insufficiency. Birth measurements were normal (length: 50 cm (+0.21 SD), weight: 3060 g (+0.19 SD), OFC: 33 cm (−0.64 SD)). She displayed temperature dysregulation and feeding difficulties. Milestones of motor development were moderately delayed. She was able to sit at 7 months and to walk without support at age 17 months. Speech was limited to single words at the age of 32/12 years. She presented with congenital non-progressive melanocytic nevi and unilateral sensorineural hearing loss. Aged 1.5 years, normal CK level was observed. Aged 17/12 years, diagnosis of left side high-risk nephroblastoma was established. Despite nephrectomy and enrollment in the nephroblastoma trial SIOP 2001/GPOH, she deceased at age 32/12 years due to severe sepsis.

On physical examination at age 29/12 years, weight (11.4 kg, −1.45 SD) and OFC (47 cm, −1.97 SD) were in the normal range, whereas height (85 cm, −2.29 SD) was decreased. She presented with mild craniofacial dysmorphisms (Figure 1).

2.2 | Patient 2

Patient 2 was the third child of healthy unrelated parents originating from Germany. Family history was unremarkable.

Patient 2 was born after an uneventful pregnancy at week 38 of gestation. Birth measurements were normal (length: 50 cm (−0.48 SD), weight: 3020 g (−0.67 SD), OFC: 35.5 cm (+0.43 SD)). She displayed prolonged neonatal jaundice, hypotonia and recurrent upper respiratory tract infections. Motor milestones were reached with a moderate delay. She was able to sit at age 13 months, and to walk at age 21 months. She showed basic motor impairments in balance, gait, and coordination. Speech was moderately delayed with a major focus on speech articulation difficulties. Cognitive skills were in a normal range (IQ: 100). She presented with deficits in social communication and interactions with the hallmarks: (a) anxiety-related behavior; (b) low levels of frustration tolerance; (c) distress at small changes; (d) tendency to social withdrawal; and (e) childlike behavior patterns. She attended an integrative school for language therapy. EEG showed unspecific changes with theta-rhythmization without seizures. She had mild scoliosis, slightly accelerated skeletal age. She displayed normal CK levels aged 12 and 19 months.

MRI of the brain at age 11 years revealed a small pineal cyst (ø 7.2 mm). On physical examination at age 157/12 years, weight (53 kg, −0.40 SD), OFC (55.5 cm, +0.52 SD) and height (158 cm, +0.52 SD) were in the normal range. She presented with mild craniofacial dysmorphisms (Figure 1).

2.3 | Patient 3

Patient 3 was the third child born to unrelated healthy non-consanguineous parents originating from Vietnam. Family history was unremarkable. Pregnancy was complicated by decreased fetal movements. He was born at term naturally with normal growth parameters (length: 53 cm (+0.22 SD), weight: 3710 g (+0.2 SD), OFC: 35 cm (−0.46 SD)). At age 8 months, he had achieved only partial head control and was unable to roll over. He was able to sit at age 12 months, and to walk at age 30 months. Age of first words was normal, but during course of infancy, he presented with severe expressive language delay (few simple sentences) and communication delay. The patient’s development was measured at age 58 months using ‘Münchener Funktionelle Entwicklungsdiagnostik’. Testing pointed to developmental age of 20 to 28 months. The patient presented with hyporeflexia of lower limbs during early childhood. Babinski sign was not present. Gait appeared abnormal due to muscular hypotonia of the trunk and lumbar hyperlordosis. CK levels were normal at age of 2.3 years, 2.9 years.

FIGURE 1 Clinical photographs of the patients with QRICH1 variants. (A–B). Patient 1 at the age of 29/12 years with hypertelorism, short flat philtrum with thin upper lip, broad nasal bridge and bulbous tip. Alopecia universalis due to chemotherapy (A). Patient 2 at the age of 157/12 years with long face, hypertelorism, deep-set eyes, prominent nasal bridge (B). Written consent for publishing images of the patients 3 & 4 was not obtained from the parents. [Colour figure can be viewed at wileyonlinelibrary.com]
and 4.1 years, respectively. He had undescended testes, camptodactyly of the right third finger, carious teeth and atopic dermatitis. EEG at age 4.10/12 years showed unspecific changes with theta-rhythmization without seizures. MRI of the brain performed at age 5.12/12 years revealed a small pineal cyst (ø 6 mm) and no further anomalies.

On physical examination at age 5.12/12 years, weight (22.3 kg, +0.59 SD), and height (113 cm, −0.32 SD) were in the normal range, whereas OFC (49 cm, −2.23 SD) was decreased. This boy was described with a friendly behavior and mildly dysmorphic features including prominent upper lip and wide mouth.

2.4 | Patient 4

This boy was born at gestational week 40 by cesarean section with normal growth parameters (weight: 3090 g, −1.21 SD, length: 51 cm, −0.65 SD, OFC: 35 cm, −0.46 SD). Family history was remarkable as the patient had an older brother with developmental delay.

In the first months, muscular hypotonia was noted. The boy could sit at age 10 months and walk at age 16 to 17 months. Age of first words was reported normal, but then delayed speech development was noted. Testing with the Snijders Oomen Nonverbal Intelligence Test for elderly children and adults (SON-R51/2-17) at age 9 years 7 months revealed an IQ of 78, and he attended a school for children with special needs. As a young adult, he lived and worked in a sheltered environment. Behavioral abnormalities included hyperactivity and problems in social interaction. Treatment with methylphenidate was performed for several years and could alleviate attention deficit hyperactivity disorder symptoms. CK level was reported to be normal in early childhood but no more medical reports are existing. At last physical examination at age 12.5 years, weight (30.1 kg, −2.04 SD), height (143 cm, −1.48 SD) and OFC (52 cm, −1.91 SD) were in the normal range.

He had a slender habitus, and minor facial aspects included a long face, large ears, wide palpebral fissures, periorbital fullness, a long philtrum, a high palate and thin lips.

All four patients had normal chromosomal and normal microarray analysis results and normal testing for Fragile-X. In addition, targeted testing for Coffin-Lowry syndrome in patient 4 as well as testing for spinal muscular atrophy (SMA) and congenital muscular dystrophy 1 (CMD) in patient 3 revealed normal results, respectively.

2.5 | Methods

The four individuals were clinically assessed by experienced clinical geneticists (Table 1). Ethics approval was obtained from the respective ethics committees (Ethics vote 253_15B (University of Erlangen), 224/16-ek and 402/16-ek (University of Leipzig) and 4886 (University of Düsseldorf)), and the legal guardians of all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki Principles. Trio-based WES, respectively Exome Pool-Seq was performed as described in Horn et al.,5 Brozou et al.,6 and Popp et al.,7 and Sanger sequencing was performed to verify the variants and to perform segregation analysis (Supplemental Table 1, Supplemental Table 2). All variants were deposited at https://www.ncbi.nlm.nih.gov/clinvar/ (patients ID SUB7543611, SUB7557151, SUB7557126, SUB7551181).

3 | MOLECULAR RESULTS

In the first patient, trio-based WES identified a de novo heterozygosity for the variant at position QRICH1 NM_017730.3:c.2207G > A; p.(Ser736Asn). This variant has not been reported before in the dbSNP8 and gnomAD variant databases (Supplemental Table 2, Supplemental Figure 1), and it is to our knowledge the first reported missense mutation related to VBS. The mutation is located in the YcfA/nrd intein domain of QRICH110 and bioinformatic prediction tools uniformly point toward a potential damaging effect on the protein structure (Supplemental Table 3), indicating a likely impact on the functionality of the domain (Supplemental Figure 1). The QRICH1 amino acid sequence is generally evolutionary conserved, including the affected serine residue and the surrounding amino acid sequence (Supplemental Figure 2).

The other three patients harbor truncating mutations (Supplemental Table 1, Supplemental Table 2, Supplemental Figure 1). The de novo heterozygous frameshift deletion in patient 2 at QRICH1 NM_017730.3:c.832_833del; p.(Ser278Leufs*25)) is not listed in the dbSNP and gnomAD variant databases. In Patient 3 a de novo heterozygous stop gain was also identified via trio-based WES (QRICH1 NM_017730.3:c.1954C > T; p.[Arg652*]), which has previously been reported in the literature and in dbSNP and ClinVar (rs1236702036). This variant had been identified for the first time in a patient reported in Vereri et al.,2 According to GnomAD this variant has not been observed in 124352 individuals. The de novo heterozygous frameshift deletion in patient 4 QRICH1 NM_017730.3:c.1812_1813delTG; p.(Glu605Glyfs*25) had been revealed with exome sequencing in an Exome Pool-Seq screening approach, and is not reported in dbSNP.

4 | DISCUSSION

QRICH1-related neurodevelopmental disorder/VBS is a rare entity. The mutations identified in QRICH1 so far included de novo nonsense and frameshift mutations and have been suggested to exert their effect through loss-of-function (LoF).1,2,4 In the four patients of the present study, we identified one known nonsense mutation and three novel mutations, two frameshift and interestingly one missense mutation, expanding the mutational spectrum.

The patient carrying the missense variant is similarly affected regarding speech and motor delay as well as cognitive impairment. This missense mutation likely affects the functionality of QRICH1. The described missense mutation resides in a conserved region of the YcfA/nrd intein protein domain and various bioinformatics prediction
| Gene with pathogenic variant | Cohort from Föhrenbach et al. | Patients reported in Ververi et al., Clin Genet. 2018 Feb;93(2):286-292 | Patients reported in Lui et al., Clin Genet. 2019 Jan;95(1):160-164 | Patient 5 |
|-----------------------------|-----------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| QRICH1 c.2207G > A; p. (Ser736Asn) | Patient 1 | Patient 1 | Patient 1 | Patient 5 |
| QRICH1 c.1954C > T; p.(Arg652*) | Patient 2 | Patient 2 | Patient 2 | Patient 5 |
| QRICH1 c.1812_1813delTG;p.(Glu605fs) | Patient 3 | Patient 3 | Patient 3 | Patient 5 |
| QRICH1 c.1953dup;p.(Arg652Alafs) | Patient 4 | Patient 4 | Patient 4 | Patient 5 |
| QRICH1 c.138_139delinsTT;p.(Gln46_Gln47delinsHis*) | Patient 1 | Patient 1 | Patient 5 | Patient 5 |
| QRICH1 c.1606C > T; p.(Arg536*) | Patient 2 | Patient 2 | Patient 5 | Patient 5 |
| QRICH1 c.1531C > T; p.(Arg511*) | Patient 3 | Patient 3 | Patient 5 | Patient 5 |

| Gender | Female | Female | Male | Male | Male | Female | Female | Male |
|--------|--------|--------|------|------|------|--------|--------|------|
| Consanguinity in parents | —— | —— | ——— | ——— | ——— | —— | —— | —— |
| Ethnicity | German/Caucasian | German/Caucasian | Vietnamese | German/Caucasian | Caucasian | Traveling families | Chinese | —— |
| Pregnancy | Preeclampsia, | Decreased fetal | Uneventful | Uneventful | IUGR | Uneventful | Single umbilical artery |
| — | movements, | movements, | | | | |
| placental | increased fetal | increased fetal | | | | |
| insufficiency | nuchal skin | nuchal skin | | | | |
| thickness | fold thickness | fold thickness | | | | |
| Birth [weeks] | 37 | 38 | 40 | 40 | 40 | 40 | 38 | 38 |
| Weight [g] | 3060 | 3020 | 3710 | 3090 | 3830 | 2800 | 2400 | Normal, not further specified |
| Length [cm] | 50 | 50 | 53 | 51 | Not reported | Not reported | Not reported | Normal, not further specified |
| OFC [cm] | 33 | 35.5 | 35 | 35 | Not reported | Not reported | Not reported | Normal, not further specified |
| Feeding difficulties | + | — | — | — | — | — | + | + |
| Temperature dysregulation | + | — | — | — | — | — | — | — |
| Muscular hypotonia | — | ++ | ++ | ++ | — | + | — | + |
| Neonatal jaundice | — | + | — | — | — | — | — | — |
| Recurrent infections | — | + | + | — | — | — | — | — |
| ID | + | — | + | (+) | — | — | — | — |
| Sat/walked independently [mo] | 7/17 | 13/21 | 12/30 | 10/16-17 | Normal, not further specified | /-24 | 9/22 | Mildly delayed, not further specified |
| Language delay | + | + | + | + | + | + | + | + |
| Single words at age | 3.2 years | Dyslalia | Severe expressive language delay | Moderate expressive language delay | First words at age 2 to 2.5 years, severe delay in language | First words at age 2 years, severe delay in language | First words at age 2 to 2.5 years, delay in language, poor expressive speech | First words aged 18 months, moderate expressive language delay | Mild delayed |

**TABLE 1** Clinical features of the reported patients. Clinical features of the patients with heterozygous QRICH1 variants.
| TABLE 1 (Continued) |
|----------------------|------------------|------------------------|------------------|------------------|------------------|-----------------|
| Behavioral abnormalities | -                              | +                        | +                        | +                        | -                        | -                        |
|                      | Deficits in social communication and interaction; childlike behavior, low levels of frustration tolerance, anxiety-related behavior, tendency to social withdrawal | Friendly but shy behavior, few communication | Hyperactivity, problems in social interactions | Severe delay in social interaction, autism spectrum disorder |
| Seizures             | -                        | -                        | -                        | -                        | -                        | -                        |
| EEG changes          | -                        | +                        | +                        | -                        | -                        | -                        |
|                      | Theta-rhythmization      | Theta-rhythmization      | -                        | -                        | Not available            |
| Gait ataxia          | -                        | -                        | +                        | -                        | +                        | -                        |
| Brain abnormalities  | -                        | Pineal cyst              | Pineal cyst              | -                        | -                        | -                        |
|                      | Unilateral conductive hearing loss | +                        | -                        | -                        | -                        | -                        |
| Increased CK         | -                        | -                        | -                        | +                        | +                        | -                        |
| Congenital defects   | -                        | -                        | -                        | -                        | -                        | -                        |
|                      | Transposition of the great vessels |
| Undescended testes   | -                        | -                        | +                        | -                        | -                        | -                        |
| Nephroblastoma       | +                        | -                        | -                        | -                        | -                        | -                        |
| Congenital melanocytic nevi | +                        | -                        | -                        | -                        | -                        | -                        |
| Café-au-lait spot    | -                        | -                        | -                        | -                        | +                        | -                        |
| Atopic dermatitis    | -                        | -                        | +                        | -                        | -                        | -                        |
| Skeletal abnormalities | -                        | -                        | -                        | -                        | -                        | -                        |
|                      | Retarded bone age, irregular metaphyseal boundaries of proximal phalangeal growth plates, chondrodysplasia |
|                      | Irregular metaphyseal boundaries of the proximal phalangeal growth plates |
| Retarded bone age    | -                        | -                        | -                        | -                        | +                        | +                        |

(Continues)
TABLE 1 (Continued)

| Campodactyly finger | — | — | + | — | — | — | — | — |
|---------------------|---|---|---|---|---|---|---|---|
| Hyperlordosis | — | — | + | — | — | — | — | — |
| Accelerated skeletal age | — | + | — | — | — | — | — | — |
| Scoliosis | — | + | — | — | — | — | — | + |
| Clinodactyly | — | — | — | — | — | — | — | + |

| Bilateral fifth clinodactyly |
|-----------------------------|
| Carious teeth | — | — | + | — | — | — | — | — |
| Hyperandrogenaemia | — | + | — | — | — | — | — | — |
| Ankyloglossia | — | — | — | — | — | — | — | — |

| Involuntary tongue movements, decreased muscle tone, decreased reflexes, intention tremor, calf pain on walking long distances, tendency to fall |
|-----------------------------|

| Age at examination (years) | 2.9 | 15.3 | 5.5 | 12.5 | 8 | 12 | 9 | ? | 11 |
|---------------------------|-----|------|-----|------|---|----|---|---|----|
| Weight (kg) | 11.4 | 53 | 22.3 | 30.1 | 23.3 | 40.3 | 17.65 | −2.02 SD |
| Height (cm) | 85 | 158 | 113 | 143 | 122.7 | 157 | 144 | −2.5 SD | −1.3 SD |
| OFC (cm) | 47 | 55.5 | 49 | 52 | 51 | 55.5 | 46 | ? |
| Cranofacial anomalies | + | + | + | + | + | + | + | + |

Hypertelorism, short flat philtrum with thin upper lip and broad nasal bridge and bulbous tip. Alopecia universalis due to chemotherapy
Hypertelorism, deep-set eyes, prominent nasal bridge, preauricular fistulae
Prominent upper lip, big mouth
Long face, relative large ears, wide palpebral fissures, periorbital fullness, long philtrum, high palate, thin lips
Flat malar region, prominent long nose with a slightly long columella, smooth philtrum, wide mouth with thin upper lip, protruberant lower lip, slightly deformed second to fifth toes bilaterally
Bilateral ptosis, mild hypertelorism, prominent nose, thin upper lip, wide mouth
Brachcephaly, upslanting palpebral fissures, broad nose with broad nasal tip, wide mouth, thin upper lip, low-set cup-shaped ears with tethered earlobes, transverse palmar creases
Large ears, mildly high-arched palate
Wide mouth, thin upper lip, mildly bulbous nose, large ears, bilateral clinodactyly
tools unanimously supports a damaging effect. The amino acid sequence of QRICH1 is generally conserved, suggesting that a mutation in this gene could have a high impact on the functionality of this protein. No further putative pathogenic was identified in the patient that could explain the observed phenotype. Nevertheless, since only few variants are reported yet, increased data sets are warranted to corroborate this finding.

Regarding the two patients carrying the variant c.1954C > T; p.(Arg652*)) both exhibited severe delay in language and social interaction deficits. However, the patient described in Ververi et al.,2 was found to have a normal motor development, whereas patient 3 displayed profound motor delay. Furthermore, our patient had additional features comprising minor congenital malformations.

In individual 2, WES identified the truncating variant c.832_833del; p.(Ser278Leufs*25). Interestingly, the girl presented at the milder end of the VBS spectrum, with normal mental development but solely remarkable social behavior deficits.

Overall, the observed phenotypes do not seem to correlate with type of mutations or location in the gene (Supplemental Figure 1). However, the so far small cohort of QRICH1 variant carriers, which include only one missense variant, prevents the study of detailed genotype-phenotype correlation.

This study not only expands the genetic, but also the clinical spectrum for QRICH1-related disorders (Table 1). In accordance with previous observations, our report underlines findings of speech delay, in particular expressive speech delay, and learning difficulties or mild ID, respectively. Regarding all nine reported individuals with QRICH1 variants so far, an even more specific phenotype emerges with the hallmarks: (a) expressive speech delay; (b) learning difficulties/mild ID; (c) moderate motor delay; (d) tendency to microcephaly and short stature; and (e) profound social behavior deficits. The collection of additional patients will show if a common facial phenotype really exists as only few facial photographs have been published yet. So far, there is no easily recognizable facial phenotype in the patients. The only overlapping facial features are prominent nose and thin upper lip.

The phenotypic spectrum of our reported patients comprised additional unexpected new findings, which raise the question if they are in need of early detection screening or treatment strategies.

Notably, in patient 1 nephroblastoma/Wilms tumor was diagnosed. To our knowledge, QRICH1 has not been reported in association with nephroblastoma or distinct tumor entities. None of the other reported patients with QRICH1 variants had nephroblastoma or pediatric cancer.1,2 It seems possible that occurrence of nephroblastoma was an additional finding. However, since WES revealed no other variants in either of the Wilms tumor candidate genes in the young girl,13 the hypothesis that QRICH1 might confer risk to develop nephroblastoma cannot be completely excluded. Enlarged cohorts and careful clinical examination are mandatory to learn about the cancer risk in QRICH1, and thus improve future patient care.

![Series of X-ray examinations of the left hand of patient 2 between the ages of 7 up to 12 years. The metaphyses of the proximal phalanges are normal between the first examinations at age 7 years and 9 months up to 8 years and 9 months (A-C). On the following examinations there is minimal irregularity of the metaphyseal contour, which is interpreted as normal variation (D-I). The most striking finding in this girl is the acceleration of skeletal development, please note that all the growth plates of the phalanges are already closed at age 12 years and 4 months, but the skeletal age corresponds to an age of 15 years (H-I).](#)
Interestingly, two of the herewith reported four individuals presented with identical epileptiform variants in the EEG without seizures. Follow-up of these findings will contribute to better define the potential risk of epilepsy and the necessity for treatment intervention. Additionally, MRI in both of these patients revealed asymptomatic pineal cysts. Even though pineal cysts are a quite common entity, the observation of pineal cysts in two of our four patients is striking. Cysts of the pineal region are mostly clinically benign, usually asymptomatic and often an incidental radiologic finding. However, some can become symptomatic with various and serious symptomatic presentations comprising mass effects on surrounding structures and the rare complication of pineal apoplexy.12,13 We, therefore, suggest that a larger number of patients with QRICH1 variants shall be evaluated by screening in order to determine prevalence and to see if natural history may be any different than in the general population.

Current literature suggested creatin kinase (CK) elevation in patients with QRICH1 variants in early childhood. Ververi et al. reported mildly raised CK in two of the three patients, which was no more present at later stages. In our patients, we could not observe elevated CK levels, independent of patient’s age, gender and ethnicity. Patient 3 displayed a phenotype in early childhood suggesting SMA and/or CMD. However, targeted genetic testing revealed normal results and CK levels were in a normal range during a period of nearly 2 years. During the course of development, apparent clinically signs of a neuromuscular disorder were no more present and CK levels were no more studied. Clinical presentation of the other patients did not raise concern for an underlying disorder, which demanded CK values at later stages. In summary, we could not confirm literature findings of CK elevation in VBS. A continuous follow-up of CK levels in patients with VBS starting from young age would be valuable to further delineate the role of CK levels in this rare syndrome.

There is some evidence that in individuals with QRICH1 variants, the skin and the skeletal system might be affected. Two patients presented with congenital nevi, respectively with one large-sized café-au-lait spot.

Delayed/accelerated bone age, irregular metaphyseal boundaries of proximal phalangeal growth plates, scoliosis and/or hyperlordosis were found in five of the nine patients.1,2 Lui et al. reported one patient with irregular growth plates of the proximal phalanges and chondrodysplasia characterized by diminished linear growth and abnormal growth plate morphology.1 The radiographic findings in our patients with variants of QRICH1 did not point to irregular growth plates of the proximal phalanges. In patient 2, we could gather a comprehensive series of X-ray examinations of the left hand between the ages of 7 up to 12 years. The metaphyses of the proximal phalanges are normal between the first examinations at age 7 years and 9 months up to 8 years and 9 months. On the following examinations, there is minimal irregularity of the metaphyseal contour, which is interpreted as normal variation (Figure 2). The most striking finding in this girl was the acceleration of skeletal development, the growth plates of the phalanges were already closed at age 12 years and 4 months, but the skeletal age corresponded to an age of 15 years (Figure 2). In patient 1, chest X-ray at age 2 years and 7 months showed that the metaphyses of the proximal humerus and the costochondral junction of the ribs were normal. Patient 3 had an X-ray of the chest at the age of 3 months and an examination of the pelvis at the age of 4 years. Both examinations show normal metaphyses. Unfortunately, patient 4 could not provide X-ray examinations. In summary, we could not confirm findings of Lui et al. in our reported patients.

In conclusion, the present study generated novel insights into the mutational and phenotypical landscape of VBS. This study contributes to the delineation of the phenotype, which comprises key symptoms, such as, expressive speech delay and notable social behavior deficits. At the same time, it demonstrates the broad phenotypic spectrum associated with QRICH1-associated disorders. Enlargement of QRICH1 cohorts is prerequisite to learn in more detail about the range of clinical manifestations and genotype-phenotype correlations in this developmental disorder.

ACKNOWLEDGEMENTS

DW and SR are members of ERNITHACA. SR and DW acknowledge financial support from the German Research Foundation (DFG) (RE 4149/1-1, WI 1440/8-1). SR and DW are both involved in the Center of Rare Diseases Düsseldorf (ZSED). CZ and BP were supported by grants from the DFG (ZW 184-6/1, PO 2366/2-1). Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.13853.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Christiane Zweier https://orcid.org/0000-0001-8002-2020
Silke Redler https://orcid.org/0000-0002-0991-252X

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Additional supporting information may be found online in the Supporting Information section at the end of this article.

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**How to cite this article:** Föhrenbach M, Jamra RA, Borkhardt A, et al. QRICH1 variants in Ververi-Brady syndrome—delineation of the genotypic and phenotypic spectrum. *Clinical Genetics*. 2021;99:199-207. [https://doi.org/10.1111/cge.13853](https://doi.org/10.1111/cge.13853)