Variable pulmonary manifestations in Chitayat syndrome

Six additional affected individuals

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Variable pulmonary manifestations in Chitayat syndrome: Six additional affected individuals

Aude-Annick Suter1 | Fernando Santos-Simarro2 | Pernille Mathiesen Toerring3 | Angela Abad Perez1 | Rosario Ramos-Mejia4 | Karen E. Heath2 | Victoria Huckstadt5 | Manuel Parrón-Pajares6 | Martin Atta Mensah1,7 | Wiebke Hülsemann8 | Manuel Holtgrewe9 | Stefan Mundlos1,10 | Uwe Kornak1,11 | Oliver Bartsch12 | Nadja Ehmke1,10

1Institute of Medical Genetics and Human Genetics, Charité – Universitätsmedizin Berlin, Berlin, Germany
2Institute of Medical and Molecular Genetics (INGEMM) and Skeletal dysplasia multidisciplinary Unit (UMDE), Hospital Universitario La Paz and CIBERER, ISCIII, Madrid, Spain
3Department of Clinical Genetics, Odense University Hospital, Odense, Denmark
4Department of Growth and Development, Garrahan Hospital, Buenos Aires, Argentina
5Department of Genetics, Garrahan Hospital, Buenos Aires, Argentina
6Department of Radiology and Skeletal dysplasia multidisciplinary Unit (UMDE), Hospital Universitario la Paz, Madrid, Spain
7Berlin Institute of Health (BIH), Berlin, Germany
8Handchirurgie Kinderkrankenhaus Wilhelmsstift, Hamburg, Germany
9Core Unit Bioinformatics – CUBI, Berlin Institute of Health (BIH), Berlin, Germany
10RG Development & Disease, Max Planck Institute for Molecular Genetics, Berlin, Germany
11Institute of Human Genetics, University Medical Center Göttingen, Göttingen, Germany
12Institute of Human Genetics, University Medical Centre of the Johannes Gutenberg University Mainz, Mainz, Germany

Correspondence
Nadja Ehmke, Institute of Medical Genetics and Human Genetics, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
Email: nadja.ehmke@charite.de

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Charité – Universitätsmedizin Berlin; Berlin Institute of Health

Abstract
Hand hyperphalangism leading to shortened index fingers with ulnar deviation, hallux valgus, mild facial dysmorphism and respiratory compromise requiring assisted ventilation are the key features of Chitayat syndrome. This condition results from the recurrent heterozygous missense variant NM_006494.2:c.266A>G; p.(Tyr89Cys) in ERF on chromosome 19q13.2, encoding the ETS2 repressor factor (ERF) protein. The pathomechanism of Chitayat syndrome is unknown. To date, seven individuals with Chitayat syndrome and the recurrent pathogenic ERF variant have been reported in the literature. Here, we describe six additional individuals, among them only one presenting with a history of assisted ventilation, and the remaining presenting with variable pulmonary phenotypes, including one individual without any obvious pulmonary manifestations. Our findings widen the phenotype spectrum caused by the recurrent pathogenic variant in ERF, underline Chitayat syndrome as a cause of isolated skeletal...
malformations and therefore contribute to the improvement of diagnostic strategies in individuals with hand hyperphalangism.

**KEYWORDS**
bronchomalacia, Chitayat syndrome, ERF, hyperphalangism, respiratory distress, ulnar deviation

## 1 | INTRODUCTION

Chitayat syndrome (MIM 617180) is characterized by bilateral hand hyperphalangism resulting in shortening and ulnar deviation of the index and sometimes third fingers, hallux valgus, mild facial dysmorphism and respiratory complications presenting from birth (Chitayat et al., 1993). It is caused by the recurrent missense variant NM_006494.2:c.266A>G; p.(Tyr89Cys) in ERF on chromosome 19q13.2 (MIM 611888) (Balasubramanian et al., 2017). ERF encodes the ETS2 repressor factor (ERF), which is ubiquitously expressed. It binds to the ETS-binding site (EBS) within the ETS2 promoter and belongs to the ETS family of transcription factors which regulate cellular proliferation and differentiation, embryological development, hematopoiesis, lymphocyte function and apoptosis (Bose et al., 2017; de Castro et al., 1997; Liu, Pavlopoulos, Modi, Moschonas, & Mavrothalassitis, 1997; Sevilla et al., 1999). ETS factors are also involved in bone and cartilage development (Kola et al., 1993). In osteoblasts, ETS2 was implicated in the regulation of osteopontin (Raouf & Seth, 2000; Vary et al., 2000). Overexpression of ETS2 in mice inhibits chondrogenesis and ossification with evidence for reduced proteoglycan content in the cartilaginous skeleton (Sumarsono et al., 1996). The recurrent ERF aminoacid substitution found in Chitayat syndrome is located in the DNA-binding domain. Pathogenic heterozygous variants in ERF leading to haploinsufficiency, including other missense variants in the DNA-binding domain, cause craniosynostosis 4 (MIM 600775) (Twigg et al., 2013). However, it still remains unclear why the p.(Tyr89Cys) variant is associated with a different phenotype (Balasubramanian et al., 2017).

To date, seven individuals with molecularly confirmed Chitayat syndrome have been described in the literature (Balasubramanian et al., 2017; Caro-Contreras, Alcantara-Ortigoza, Ahumada-Perez, & Gonzalez-Del, 2019; Chitayat et al., 1993; Shin, StJoseph, Mannan, & Khan, 2019). Furthermore, two individuals with high clinical suspicion of Chitayat syndrome and one individual with suspected Chitayat syndrome but without hand hyperphalangism have been reported (Tanaka, Matsuo, Nishimura, & Nagai, 1994). It is of interest that all individuals reported so far showed respiratory distress requiring assisted ventilation in the first 8 weeks of life, mostly due to bronchomallacia or interstitial lung disease. Here, we report six additional individuals from four unrelated families with molecularly confirmed Chitayat syndrome. Only one of the individuals reported here had a history of respiratory distress requiring assisted ventilation, and the remaining individuals showed variable pulmonary manifestations, also including one individual lacking obvious pulmonary disease.

## 2 | MATERIALS AND METHODS

### 2.1 | Editorial policies and ethical considerations

The study was approved by the ethics committee of the Charité—Universitatsmedizin Berlin (Individuals 1 and 2). Individuals 3, 4, 5 and 6 were included in a research project with IRB approval (MINECO SAF2017-84646-R) in Madrid, Spain. All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individuals included in the study. Additional informed consent was obtained from all individuals for which identifying information is included in this article.

### 2.2 | Human material and diagnostic testing

Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. Illumina’s All Exon Kit V6 was used for targeted enrichment of DNA of Individuals 1, 2 and their parents. Data processing and variant filtration were applied as previously published (patient 2 in Ehmke et al., 2020). The remaining variants were filtered according to a dominant and recessive mode of inheritance. The de novo ERF variants were confirmed with Sanger sequencing in Individuals 1 and 2.

In Individuals 3, 5 and 6, a custom designed skeletal dysplasia panel (Roche Nimblegen, SkeletalSeqV4 or V6) including 327/419 genes was applied in the Hospital Universitario La Paz, Madrid, Spain. Validation in these three individuals and segregation analysis of the ERF variant in Individual 4 was performed using Sanger sequencing. The sequencing and variant filtering have been published (Sumentchordi-Montane et al., 2018).

## 3 | RESULTS

### 3.1 | Clinical description of the cohort

This study included three unrelated affected individuals (Individuals 1–3) as well as a mother (Individual 4) and her two daughters (Individuals 5 and 6, half-siblings) with Chitayat syndrome. The clinical data of the six individuals are shown in Table 1 and Figures 1 and 2.
### Table 1: Clinical features of Individuals 1–6 and summary of 7 individuals with molecularly confirmed Chitayat syndrome described in literature

<table>
<thead>
<tr>
<th>Individual</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Summary of this cohort</th>
<th>Summary from seven individuals described in literaturea</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>f</td>
<td>f</td>
<td>f</td>
<td>f</td>
<td>f</td>
<td>f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>16 years</td>
<td>3 years</td>
<td>8 years</td>
<td>31 years</td>
<td>11 years</td>
<td>7 years</td>
<td></td>
<td></td>
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<tr>
<td>Recurrent ERF variant</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6/6</td>
<td>7/7</td>
</tr>
<tr>
<td>Inheritance</td>
<td>de novo</td>
<td>de novo</td>
<td>de novo</td>
<td>u</td>
<td>Affected mother (I4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skeletal abnormalities</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>6/6</td>
<td>7/7</td>
</tr>
<tr>
<td>Finger hyperphalangy (finger)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6/6</td>
<td>4/7</td>
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<td>HP:000924</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ulnar deviation of fingers (finger)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6/6</td>
<td>7/7</td>
</tr>
<tr>
<td>HP:0030367</td>
<td>(second)</td>
<td>(second)</td>
<td>(second−third)</td>
<td>(second)</td>
<td>(second−fourth)</td>
<td>(second−third)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HP:0009465</td>
<td>(second−fifth)</td>
<td>(second−fifth)</td>
<td>(second−fifth)</td>
<td>(second−third)</td>
<td>(second−fifth)</td>
<td>(second−fifth)</td>
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<td></td>
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<tr>
<td>Small phalanges and/or shortening of</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>second finger</td>
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<td>Shortening of other fingers</td>
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<td>6/6</td>
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<td></td>
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<td>Hallux valgus</td>
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<td>+</td>
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<td>+</td>
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<td>6/6</td>
<td>7/7</td>
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<td></td>
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<tr>
<td>Pectus excavatum</td>
<td>+</td>
<td>−</td>
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<td>+</td>
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<td>+</td>
<td>4/6</td>
<td>5/7</td>
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<tr>
<td>Scoliosis</td>
<td>−</td>
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<td>−</td>
<td>−</td>
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<td>+</td>
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<tr>
<td>Respiratory abnormalities</td>
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<td></td>
<td>5/6</td>
<td>7/7</td>
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<tr>
<td>Respiratory distress</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4/6</td>
<td>7/7</td>
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<tr>
<td>Respiratory failure requiring assisted ventilation</td>
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<td>−</td>
<td>−</td>
<td>−</td>
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<td>−</td>
<td>1/6</td>
<td>7/7</td>
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<tr>
<td>Bronchospasm/pulmonary obstruction</td>
<td>−</td>
<td>u</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>2/6</td>
<td>u</td>
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<tr>
<td>HP:0025428</td>
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<td></td>
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<tr>
<td>Recurrent pulmonary infections</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>u</td>
<td>u</td>
<td>u</td>
<td>1/6</td>
<td>7/7</td>
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<tr>
<td>HP:0006532</td>
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<td></td>
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<tr>
<td>Laryngomalacia</td>
<td>u</td>
<td>+</td>
<td>u</td>
<td>u</td>
<td>u</td>
<td>u</td>
<td>1/6</td>
<td>0/7</td>
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<tr>
<td>HP:0001601</td>
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<tr>
<td>Bronchomalacia</td>
<td>u</td>
<td>−</td>
<td>u</td>
<td>u</td>
<td>u</td>
<td>u</td>
<td>0/6</td>
<td>6/7</td>
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### TABLE 1 (Continued)

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<th>1</th>
<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>Summary of this cohort</th>
<th>Summary from seven individuals described in literature*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial lung disease HP:0006530</td>
<td>u</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>u</td>
<td>–</td>
<td>0/6</td>
<td>5/7</td>
</tr>
<tr>
<td>Other affections of the airways</td>
<td>–</td>
<td>u</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>3/6</td>
<td>1/7*</td>
</tr>
<tr>
<td>Facial dysmorphisms HP:0001999</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5/6</td>
<td>7/7</td>
</tr>
<tr>
<td>Proptosis HP:0000520</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>3/6</td>
<td>2/7</td>
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<tr>
<td>Hypertelorism HP:0000316</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>3/6</td>
<td>5/7</td>
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<tr>
<td>Broad nasal bridge HP:0000431</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>4/6</td>
<td>2/7</td>
</tr>
<tr>
<td>Depressed nasal bridge HP:0005280</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1/6</td>
<td>4/7</td>
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<tr>
<td>Anteverted nares HP:0000463</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>1/6</td>
<td>3/7</td>
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<tr>
<td>Low hanging/low inserted columella HP:0009765/HP:0010763</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5/6</td>
<td>u</td>
</tr>
<tr>
<td>Short philtrum HP:0000322</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5/6</td>
<td>u</td>
</tr>
<tr>
<td>Full lips HP:0012471</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>4/6</td>
<td>2/7</td>
</tr>
<tr>
<td>Thin upper lip vermilion HP:0000219</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>2/6</td>
<td>u</td>
</tr>
<tr>
<td>Broad chin HP:0011822</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>4/6</td>
<td>u</td>
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<tr>
<td>Abnormal form/location of the ears HP:000377/HP:000357</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Neurodevelopmental delay HP:0012758</td>
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<td>–</td>
<td>–</td>
<td>+</td>
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<td>2/6</td>
<td>3/7</td>
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<tr>
<td>Polyhydramnios HP:0001561</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>u</td>
<td>–</td>
<td>0/6</td>
<td>3/7</td>
</tr>
</tbody>
</table>

Abbreviations: f, female; I, individual; u, unknown; +, present; –, absent.

*aBalasubramanian et al., Caro-Contreras et al., Shin et al.

bApnea.
cRestrictive ventilatory insufficiency.
dInterstitial infiltrates.
eSevere tracheomalacia additionally to bronchomalacia in one individual.
Detailed clinical descriptions of the individuals are provided in the Supporting Information. All individuals had the typical hand malformation observed in Chitayat syndrome, consisting of short and small index fingers with ulnar deviation and spontaneously flexed position of the metacarpophalangeal joint, with especially in Individual 2. Note that there is also shortening of the other fingers, especially the middle fingers, and ulnar deviation of all fingers. Photographs of the hands of Individual 3 display additional flexed position of the first metacarpophalangeal joint. Radiographs of Individuals 5 and 6 showed hyperphalangism of the index fingers, consisting of a triangular bone with lateral growth plates in the second metacarpophalangeal joints. In Individuals 1-3, 5 and 6, the triangular bone has lateral growth plates, whereas in Individual 4, it is fused with the proximal phalanx. In Individuals 5 and 6, the third and fourth fingers are also affected. The phalanges of the index finger are small and/or short, and the index fingers are ulnarly deviated. There is also ulnar deviation and shortening of other fingers in all individuals. Clinodactyly of the fifth finger and short middle phalanges can be found in most individuals. In Individual 3, the proximal phalanx of the first finger is ulnarily deviated and has an abnormally shaped growth plate. A detailed description of the radiographs can be found in the Supporting Information.

The pulmonary phenotype in this cohort was milder than the phenotype described previously in individuals with Chitayat syndrome. Although five of six individuals in the present cohort had pulmonary problems, none of the individuals received a diagnosis of bronchomalacia, tracheomalacia or interstitial lung disease, and only one had respiratory distress leading to temporary ventilation. One individual (Individual 2) had laryngomalacia, which has not been described before in individuals with Chitayat syndrome. Individuals 3, 4, 5 and 6 had recurrent bronchospasms and pulmonary obstruction, and Individual 3 had recurrent pulmonary infections. Further diagnostic testing of this individual showed unspecific micronodules in the right hemithorax and a distal airway.
pathology in the left posterobasal segment but no signs of interstitial lung disease. Additionally, Individual 4 was diagnosed with restrictive ventilatory insufficiency whereas chest radiographs of Individual 6 noted interstitial infiltrates. In one individual (Individual 1), there was no history of pulmonary disease.

All individuals had variable facial dysmorphisms. The following features were observed in at least two unrelated individuals and had been previously reported in individuals with Chitayat syndrome: proptosis (3/6), hypertelorism (3/6), broad nasal bridge (4/6), full lips (3/6) and abnormal form or location of the ears (4/6). The features depressed nasal bridge and anteverted nares, which were present in at least three previously described individuals, were found in a single individual of the present cohort. In five individuals we observed a low hanging/low inserted columella and short philtrum, which was previously undescribed. Facial photographs of all individuals were available for systematic evaluation and comparison, consent for publication was available from Individuals 1, 2 and 3 (Figure 2a–f).

Polyhydramnios was not observed during pregnancy in any of the individuals described here, in contrast to those described in the literature, where polyhydramnios had been reported in three of the seven cases. Two individuals in this cohort achieved developmental milestones later than expected and one of them later had learning difficulties and attended a school for children with special needs. No data of formal neurological evaluation is available.

### 3.2 | Genotype

Trio exome sequencing of Individuals 1 and 2, gene panel analysis in Individuals 3, 5 and 6 and Sanger sequencing in Individual 4 identified the recurrent heterozygous variant NM_006494.2: c.266A>G; p.(Tyr89Cys) in ERF. The ERF pathogenic variant occurred de novo in Individuals 1, 2 and 3, whereas Individuals 5 and 6 inherited it from Individual 4.

### 4 | DISCUSSION

To our knowledge, only seven individuals with molecularly confirmed Chitayat syndrome have been described in the literature so far (Balasubramanian et al., 2017; Caro-Contreras et al., 2019; Shin et al., 2019). With this report, the known phenotypical spectrum of Chitayat syndrome is widened by six additional individuals with variable pulmonary manifestations and one of them presenting without any clinically obvious lung disease.

Individuals with Chitayat syndrome show the characteristic combination of hyperphalangism of the index fingers leading to shortening and ulnar deviation, hallux valgus, facial dysmorphism and lung disease. In some of the individuals reported here, clinical diagnosis was complicated by the absence of severe respiratory impairment, and diagnosis was obtained by NGS-based analyses (exome and panel sequencing). In Individual 2 the respiratory problems, which appeared to be rather mild, were documented only retrospectively. Notably, all of the individuals described in the literature with a molecular diagnosis of Chitayat syndrome had respiratory distress postnatally or in the first 8 weeks of life, requiring assisted ventilation, and recurrent lung infections (Balasubramanian et al., 2017; Caro-Contreras et al., 2019; Shin et al., 2019). Six out of seven individuals had bronchomalacia, five out of seven individuals showed interstitial lung disease. The here reported cohort broadens the variability of phenotypes associated...
with Chitayat syndrome with remarkably mild pulmonary manifestations. Most interestingly, Individual 1 of this cohort, a meanwhile 16-year-old girl, does not show any of these complications to date. No respiratory distress or respiratory infections ever occurred. To our knowledge, this is the first individual with molecularly confirmed Chitayat syndrome showing no respiratory involvement, although it should be mentioned that she did not receive any diagnostic test to exclude lung disease and pulmonary manifestation cannot be completely excluded.

The most specific feature of Chitayat syndrome is hyperphalangism with shortening and ulnar deviation of the index fingers. There are only few other conditions presenting with a similar type of hyperphalangism and hand malformation, including Catel-Manzke syndrome (MIM 616145), Desbuquois dysplasia 1 (DBQD1; MIM 251450), Temtamy preaxial brachydactyly syndrome (TBPS; MIM 605282) and chondrodysplasia with joint dislocations (GPAPP deficiency) (MIM 614078). Catel-Manzke syndrome is due to pathogenic variants in TGDS (MIM 616146) (Ehmke et al., 2014; Manzke, Lehmann, Klopocki, & Caliebe, 2008). DBQD1 is caused by mutations in CANT1 (MIM 613165) (Faivre et al., 2004; Huber et al., 2009), while TBPS is secondary to pathogenic variants in CHSY1 (MIM 601882) (Li et al., 2010; Temtamy, Meguid, Ismail, & Ramzy, 1998). GPAPP deficiency is caused by pathogenic variants in IMPAD1 (MIM 614010) (Vissers et al., 2011). Furthermore, brachydactyly type C due to certain variants in GDF5 can be associated with similar hand malformations (Farooq et al., 2013; Gutierrez-Amavizca et al., 2012; Schwabe et al., 2004; Stange et al., 2015). DBQD1, TBPS, GPAPP deficiency and possibly Catel-Manzke syndrome are resulting from defects in proteoglycan metabolism and are characterized by micro-retrognathia and cleft palate, short stature, congenital heart defects and developmental delay, hearing loss and joint dislocations additionally to hyperphalangism. These additional features are not present in Chitayat syndrome, which facilitates differentiation from the aforementioned conditions. Only in Catel-Manzke syndrome pathogenic features of the aforementioned proteoglycan-related disorders can be absent or very mild, which makes the differential diagnosis to Chitayat syndrome challenging, especially when no respiratory distress occurs. In this context, an analysis of the hand malformation can be conclusive: Catel-Manzke syndrome is usually associated with radial deviation of the index finger, but ulnar deviation is observed in individuals with Chitayat syndrome.

When comparing individuals with Chitayat syndrome to individuals with GDF5-related brachydactyly type C, especially to the individual reported by Schwabe et al. (Schwabe et al., 2004), a striking similarity between the hand malformations is detectable. The molecular mechanism of ERF-related hyperphalangy remains unclear, but due to the phenotypic overlap, a misregulation of GDF5 could be considered. Nevertheless, the reduced proteoglycan content in the cartilaginous skeleton of mice overexpressing ETS2 (Sumarsono et al., 1996) could present a link to proteoglycan-related skeletal dysplasias.

Facial dysmorphism was present in all of the individuals reported here, but were variable. The characteristic facial features described before (hypertelorism, depressed nasal bridge, anteverted nares) were not detectable in all individuals, which is in line with previous reports. In addition, we observed a long hanging/low inserted columella and a short philtrum in all but one individuals.

Interestingly, none of the individuals with Chitayat syndrome displayed signs of craniosynostosis. ERF-related craniosynostosis is characterized by sagittal, lambdoid and multisutural synostosis as well as pansynostosis, often with postnatal onset (Glass et al., 2019; Twigg et al., 2013; Wilkie, Johnson, & Wall, 2017). Additionally, individuals diagnosed with ERF-associated craniosynostosis appear to have a high risk for pathologically elevated intracranial brain pressure leading to visual impairment, Chiari-1 malformation, language and speech delay, poor fine and/or gross motor skills and behavioral problems/hyperactivity (Glass et al., 2019; Twigg et al., 2013; Wilkie et al., 2017). In many of these individuals, a diagnosis of Crouzon syndrome had been suspected initially. The pathomechanism of ERF-related craniosynostosis is predominately linked to haploinsufficiency and causative missense variants are located in the DNA-binding domain, just like the variant associated with Chitayat syndrome (Glass et al., 2019; Wilkie et al., 2017). Wilkie et al. suggested that the distinct phenotype of ERF-related craniosynostosis might result from altered DNA-binding properties associated with the missense variant NM_006494.2:c.266A>G; p.(Tyr89Cys), but the etiological mechanisms remain unknown (Wilkie et al., 2017).

Individuals with Chitayat syndrome typically have a normal intelligence. According to Caro-Contreras et al., the developmental delay described in 3/7 individuals in the literature improved over time in at least two of them (Caro-Contreras et al., 2019). When last seen, Individual 1 in the present report attended a special needs school due to mild developmental delay, whereas Individual 4 experienced learning difficulties at a regular school. Unfortunately, no data of formal neurological evaluation were available for this study. Nevertheless, these findings could be further evidence that developmental problems are part of the phenotypic spectrum associated with Chitayat syndrome.

In conclusion, we present six further individuals with Chitayat syndrome, at least one of them lacking clinical pulmonary manifestations, and only one presenting with respiratory problems requiring assisted ventilation. This report extends the range of clinical features of individuals with Chitayat syndrome and will help to improve the diagnosis of individuals with hyperphalangism.

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AUTHOR CONTRIBUTIONS

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Aude-Annick Suter https://orcid.org/0000-0003-2252-3497
Fernando Santos-Simarro https://orcid.org/0000-0002-1201-9118
Nadja Ehmkhe https://orcid.org/0000-0003-1449-9909

REFERENCES


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