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Accessibility
Temple-Baraitser Syndrome and Zimmermann-Laband Syndrome: one clinical entity?

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Abstract

Background: KCNH1 encodes a voltage-gated potassium channel that is predominantly expressed in the central nervous system. Mutations in this gene were recently found to be responsible for Temple-Baraitser Syndrome (TMBTS) and Zimmermann-Laband syndrome (ZLS).

Methods: Here, we report a new case of TMBTS diagnosed in a Lebanese child. Whole genome sequencing was carried out on DNA samples of the proband and his parents to identify mutations associated with this disease. Sanger sequencing was performed to confirm the presence of detected variants.

Results: Whole genome sequencing revealed three missense mutations in TMBTS patient: c.1042G > A in KCNH1, c.2131 T > C in STK36, and c.726C > A in ZNF517. According to all predictors, mutation in KCNH1 is damaging de novo mutation that results in substitution of Glycine by Arginine, i.e., p.(Gly348Arg). This mutation was already reported in a patient with ZLS that could affect the connecting loop between helices S4-S5 of KCNH1 with a gain of function effect.

Conclusions: Our findings demonstrate that KCNH1 mutations cause TMBTS and expand the mutational spectrum of KCNH1 in TMBTS. In addition, all cases of TMBTS were reviewed and compared to ZLS. We suggest that the two syndromes are a continuum and that the variability in the phenotypes is the result of the involvement of genetic modifiers.

Keywords: Temple-Baraitser syndrome, Whole genome sequencing, KCNH1, Zimmermann-Laband syndrome

Background

Temple-Baraitser syndrome (TMBTS; MIM: 611816) and Zimmerman-Laband syndrome (ZLS; MIM: 135500) are rare developmental disorders with hypoplasia/aplasia of nails. These syndromes are considered to be distinct entities, with TMBTS defined as a disorder characterized by severe intellectual disability (ID), epilepsy, hypoplasia/aplasia of the nails of the thumb and great toe, a pseudo-myopathic appearance, and marked hypotonia in infancy [1–6], and ZLS characterized by ID, gingival fibromatosis, associated with absence or dysplasia of all nails, hypoplasia of the distal phalanges, scoliosis, hepato-splenomegaly, coarse face, and hirsutism [7].

KCNH1 encodes a voltage-gated potassium channel that is predominantly expressed in the central nervous system, and mutations in this gene have been linked to both syndromes [6, 7].

Here, we report on a Lebanese male patient with TMBTS having a mutation in KCNH1 that has previously been reported in a patient with ZLS. In addition, we have reviewed all published cases of TMBTS and
highlight common features, as well as critical differences, between these two syndromes, and raise the issue of whether their classification into two entities is appropriate.

Methods
Clinical report
The male proband is the third child of healthy unrelated Lebanese parents. He was born at 36 weeks of gestation, after a complicated pregnancy characterized by the therapeutic administration, to the mother, of drugs against early contractions at 32 weeks of gestation. At birth, his weight was 2700 g (60th percentile), his length 48 cm (75th percentile) and his head circumference (OFC) 33 cm (60th percentile). Family history was unremarkable. Marked hypotonia, constipation, and aplasia of thumb and great toe nails were noted in the first two to three days of life.

The propositus was referred for genetic examination at the age of 9 months. His weight was 9750 g (60th percentile), length 71.5 cm (75th percentile), OFC 42.7 cm (10th percentile). He had a flat occiput, a frontal bossing, large ears, mild hypertelorism, epicanthal folds, a broad and depressed nasal bridge, a short columella, long philtrum, a broad mouth with downturned corners, a high arched palate, 2 upper and 2 lower incisors of normal shape, and full cheeks (Fig. 1). Widely spaced nipples and left chest depression were also noted. Both thumbs were held in an adducted posture and were terminally broad with aplasia of the nails bilaterally. Big toes were also broad, long, and with aplasia of nails. No hirsutism, no hypoplasia of the distal phalanges, no hypermobility, no camptodactyly, nor palmar creases were noted.

At 15 months old, his weight was 11 kg (75th percentile), length 79 cm (50th percentile), and OFC 45.7 cm (10th percentile). Delays in developmental milestones were striking, as he could not stand up alone or walk with help, and could not follow or respond to simple commands. He had a myopathic face with poor visual contact, a wide open mouth and mild gingival enlargement (Fig. 1). Skeletal survey revealed nearly absent distal phalanges of the thumbs and great toes, very small femoral and humeral epiphyses, and an osteosclerosis of the anterior arc of the right 10th rib (Fig. 2).

Magnetic resonance imaging, abdominal and heart ultrasound, brain stem auditory evoked responses, and EEG were normal. Complete blood count, hemoglobin electrophoresis, serum electrolytes, blood glucose levels, urinalysis, thyroid, liver and renal function tests were all unremarkable. Array CGH analysis and Chromosomal Microarray Analysis did not reveal any abnormalities (data not shown).

DNA extraction and Whole Genome Sequencing (WGS)
Whole genome sequencing was carried-out on the patient and his parents using the HiSeq 2500 sequencer (Illumina, San Diego, CA, USA). Libraries were generated from 1 μg of genomic DNA [8] using the Illumina TruSeq DNA PCR-Free Sample Preparation Kit. Genomic DNA was sheared using the Covaris system (Woburn, MA, USA). Isolated DNA fragment ends were blunted, A-tailed and ligated with sequencing adaptors with index sequences. Excess adapters and enzymes were removed using AMPure beads (Beckman Coulter Genomics, Danvers, MA, USA). Indexed libraries were size selected to 350 bp range using bead-based capture and the concentration of amplifiable fragment was determined by qPCR relative to sequencing libraries with known concentration. Normalized libraries were clustered on a c-BOT machine and 125 bp paired-end sequencing was performed on the HiSeq2500 system.
WGS data analyses

Raw data was mapped to the human genome reference build 19 (http://www.broadinstitute.org/ftp/pub/seq/ references/Homo_sapiens_assembly19.fasta) using BWA aligner [9] version 0.7.7-r441 and variant call was performed using GATK [10] version 3.3.2. The rare variant analysis was performed using the xbrowse tool (https://xbrowse.broadinstitute.org/). For the parents and the child, a ‘De novo Dominant’ inheritance model was selected, with severity of the variant effect set to ‘moderate to high impact’ (Nonsense, essential splice sites, missense frameshift and in frame), call quality as high (genotype quality > 20 and allele balance ratio > 25 %) and allele frequency < 1 % in 1000 genomes and The Exome Aggregation Consortium (ExAC) v0.3 datasets. Functional consequences of amino acid substitutions have been predicted using various tools [11–14].

Sanger sequencing

Genomic sequences of KCNH1, STK36, and ZNF517 were obtained from UCSC Genome Browser (December 2013). A flanking region around each sequence variant site was amplified by PCR with the following primer pairs: forward primer (5′-TCAACGCTTTTGAGAACGTG-3′) and reverse primer (5′-TGTCTTGGTGCTCCTGTCAA-3′) for KCNH1 (NM_002238); forward primer (5′-CATCCCTCATCTCTGGCCCTG-3′) and reverse primer (5′-ACTTTTACCTTGCCCTGAATCA-3′) for STK36 (NM_001243313); and forward primer (5′-GCAAAGCTCCTCACTCCCT-3′) and reverse primer (5′-GTTGTGAACTTCTGTGTCCT-3′) for ZNF517 (NM_213605). Primers for the PCR amplifications were designed using Primer3 Software. PCR reactions were performed using Taq DNA polymerase (Invitrogen Life Technologies, Carlsbad, CA, USA). PCR fragments were run on 1 % agarose gel. The fragments were purified using the Illustra_GFX_ PCR DNA and Gel Band Purification Kit (GE Healthcare) and then sequenced using the Big Dye_ Terminator v 1.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA). Sequence reaction was purified on Sephadex G50 (Amersham Pharmacia Biotech, Foster City, CA), and then loaded into an ABI 3100 system after the addition of Hidi formamide. Electrophrograms were analyzed using Sequence Analysis Software version 5.2 (Applied Biosystems) and then aligned with the reference sequences using ChromasPro version 1.22 (Technelysium, Queensland, Australia).

Results

Whole Genome Sequencing identified 3 missense mutations in TMBTS patient (Table 1). We validated and confirmed the de novo origin of these variants by Sanger sequencing.

The mutation in KCNH1 (c.1042G > A) has a damaging effect according to all different effect predictors tested. STK36 has a missense mutation (c.2131 T > C), which also has damaging effects according to half of the effect predictors tested. ZNF517 has a missense mutation (c.726C > A) predicted as disease causing by one of the effect predictors.

The KCNH1 mutation results in a substitution of Glycine by Arginine. Same mutation is found in both isoforms of this protein: p.(Gly348Arg) in short isoform (NM_002238.3) and p.(Gly348Arg) in long isoform (NM_172362) in the ion transport domain. The p.(Gly348Arg) mutation maps to the connecting loop
between helices S4-S5 as reported by Kortum et al., and exerts a strong impact on function [18].

**Discussion**

We report on a male Lebanese patient in which a *de novo* missense heterozygous mutation c.1042G>A in the KCNH1 gene led to TMBTS.

KCNH1 is a member of voltage-gated potassium channel proteins. It is recognized as an important regulator of cell proliferation in bone-marrow derived mesenchymal stem cells, and is involved in fundamental cellular and developmental processes [15, 16].

Mutations in KCNH1 have been recently associated with TMBTS [6]. Moreover, *de novo* gain-of-function mutations in KCNH1 have also been reported in individuals with ZLS [7].

Generally, TMBTS and ZLS can be distinguished by their characteristic phenotypic features, which include absence or dysplasia of all nails and hypertrichosis in ZLS vs hypoplasia or aplasia of only the great toe and thumb’s nails in TMBTS (Table 2). With this in mind, we considered that our patient had TMBTS. These syndromes are currently considered to be two separate entities, but their common characteristics suggest that these two syndromes may be different presentations of the same disorder. In fact, many common characteristics of patients with TMBTS and ZLS have been noted, such as, seizures, hypertrichosis, hypotonia, aplasia of nails, etc., which sometimes occur in some but not all patients (Table 2). It is noteworthy to mention that many clinical databases do not even mention TMBTS as a differential diagnosis for ZLS because of the absence of hypertrichosis, even though not all reported patients with ZLS present this characteristic.

Interestingly, the same mutation (c.1042G>A) identified in our patient has never been reported with TMBTS, but was previously detected in patients with ZLS (patient 7 in Abo-Dalo et al. or subject 3 in Kortüm et al.) [17, 18]. This substitution leads to a gain of function effect and mutants carrying this mutation exhibit an accelerated channel activation and a slower deactivation [18].

Along with the previously identified p.Ile494Val mis-

Table 1 Variants identified with the WGS analysis while running a *de novo* dominant model using xbrowse

| Gene   | Position | Function       | Software prediction          |
|--------|----------|----------------|------------------------------|
| KCNH1  | c.1042G>A| Sift: damaging | Mutation taster: disease     |
|        | p.(Gly348Arg) | Mutation taster: disease causing | Fathmm: damaged |
| STK36  | c.2131T>C | Sift: damaging | Mutation taster: disease     |
|        | p.(Cys711Arg) | Mutation taster: disease causing | Fathmm: tolerated |
| ZNF517 | c.726C>A | Polyphen: possibly damaging | Mutation taster: disease     |

Given the results, our data supports the evidence that the mutated KCNH1 is a major cause of TMBTS and ZLS, while other genetic modifiers could be responsible for the observed differences in clinical phenotype.
| Complicated Pregnancy | + | - | + | - | - | + | - | + | + and of all fingers | 8/8 |
|----------------------|---|---|---|---|---|---|---|---|---|---|---|
| Birth weight         | 2,700 g (50th percentile) | 3,370 g | 3,980 g (50th percentile) | 3,590 g (50th percentile) | 2,980 g (40th percentile) | 3,600 g (50th percentile) | 3,544 g (50th percentile) | 7 pounds 7 ounces | 3,544 g (50th percentile) |
| Height at birth      | 48 cm (25th percentile) | ND | ND | 45 cm (10th percentile) | 52 cm (50-75 percentile) | 52 cm (50-75 percentile) |
| Head circumference at birth | 33 cm (60th percentile) | 35.5 cm | ND | 34 cm (30th percentile) | 33 cm (40th percentile) |
| Clinical findings    | Age (years) | 0 9/12 | 3 5/12 | 4 4/12 | 6 10/12 | 1 7/12 | 3 7/12 | 6 11/12 | 5 6/12 | 7/7 |
| Consanguinity        | - | - | - | - | - | - | - | - | - | - |
| Limbs                | Absence/hypoplasia of thumb nail | + | + | + | + | + | + | + | + and of all fingers | 8/8 |
| Absence/hypoplasia of hallux nail | + | + | + | + | + | + | + | + | + | 8/8 |
| Broad thumbs terminally | + | - | + | + | + | + | - | + | + | 6/8 |
| Thumbs; long/proximaly set | + | ND | + | + | + | + | + | + | + | 7/7 |
| Adductus deformity of distal thumb | + | ND | + | + | + | + | + | + | + | 7/7 |
| Pseudosyntophysis of the thumb | + | ND | + | ND | ND | ND | ND | ND | ND | 3/5 |
| Pseudosyntophysis of the great toe | + | ND | + | ND | ND | ND | ND | ND | ND | Absence of the secondary ossification center and longer great toes |
| Hypoplasia of distal phalanges (0-4) | + | ND | + | ND | ND | ND | ND | ND | ND | 5/8 |
| Delay in epiphysial maturation | + | ND | ND | ND | ND | ND | ND | ND | ND | 6/8 |
| Neurologic finding   | Intellectual disability | + | + | + | + | N/A | + | + | + | 7/7 |
| Poor visual contact | + | + | ND | ND | N/A | ND | ND | ND | ND | 5/5 |
| Autistic behavior   | - | + | + | ND | ND | ND | ND | ND | ND | 3/4 |
| Seizures            | - | ND | + | + | + | One seizure | + | + | + | 6/7 |
| Hypotonia/motor retardation | + | + | + | + | + | + | + | + | + | 8/8 |
| Occipitofrontal circumference (percentile) | 10th | 10th | 25-50th | 25-50th | 25th | ND | ND | ND | ND | ND |

Table 2: Review of all cases with the Temple-Baraitser Syndrome and a comparison to the Zimmermann-Laband syndrome characteristics

| Present Patient | Temple-Baraitser (1991) [1] | Gabbett et al. (2008) [2] or Simons et al. (2014) Patient A | Jacquinet et al. (2010) [3] Patient 1 or Simons et al. (2014) Patient D | Jacquinet et al. (2010) [3] Patient 2 or Simons et al. (2014) Patient E | Yesil et al. (2013) or Simons et al. (2014) Patient C | Shen (2015) [5] Patient 1 or Simons et al. (2014) Patient F | Shen (2015) [5] Patient 2 or Simons et al. (2014) Patient B | Total of affected patients with TMBTS with KCNH1 mutations |
|-----------------|-----------------------------|------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------------------------------------|---------------------------------|
| Age (years)     | 0 9/12 | 3 5/12 | 4 4/12 | 6 10/12 | 1 7/12 | 3 7/12 | 6 11/12 | 5 6/12 | 7/7 |
| Consanguinity   | - | - | - | - | - | - | - | - | - |
| Limbs           | Absence/hypoplasia of thumb nail | + | + | + | + | + | + | + | + and of all fingers | 8/8 |
| Absence/hypoplasia of hallux nail | + | + | + | + | + | + | + | + | + | 8/8 |
| Broad thumbs terminally | + | - | + | + | + | + | - | + | + | 6/8 |
| Thumbs; long/proximaly set | + | ND | + | + | + | + | + | + | + | 7/7 |
| Adductus deformity of distal thumb | + | ND | + | + | + | + | + | + | + | 7/7 |
| Pseudosyntophysis of the thumb | + | ND | + | ND | ND | ND | ND | ND | ND | Absence of the secondary ossification center and longer great toes |
| Pseudosyntophysis of the great toe | + | ND | + | ND | ND | ND | ND | ND | ND | 5/8 |
| Hypoplasia of distal phalanges (0-4) | + | ND | + | ND | ND | ND | ND | ND | ND | 6/8 |
| Delay in epiphysial maturation | + | ND | ND | ND | ND | ND | ND | ND | ND | 6/8 |
| Neurologic finding | Intellectual disability | + | + | + | + | N/A | + | + | + | 7/7 |
| Poor visual contact | + | + | ND | ND | N/A | ND | ND | ND | ND | 5/5 |
| Autistic behavior | - | + | + | ND | ND | ND | ND | ND | ND | 3/4 |
| Seizures | - | ND | + | + | + | One seizure | + | + | + | 6/7 |
| Hypotonia/motor retardation | + | + | + | + | + | + | + | + | + | 8/8 |
| Occipitofrontal circumference (percentile) | 10th | 10th | 25-50th | 25-50th | 25th | ND | ND | ND | ND | ND |
### Table 2  Review of all cases with the Temple-Baraitser Syndrome and a comparison to the Zimmermann-Laband syndrome characteristics (Continued)

| Feature                                      | Temple-Baraitser Syndrome | Zimmermann-Laband Syndrome |
|----------------------------------------------|---------------------------|---------------------------|
| Hearing loss                                 | -                         | ND                        |
| Abnormal MRI findings                        | Widespread cerebral atrophy | Mild frontotemporal atrophy |
| Dysmorphic features                          |                           |                           |
| Thoracic abnormalities                       | +                         | ND                        |
| Spine abnormalities                          | -                         | ND                        |
| Coarse face                                  | +                         | ND                        |
| Myopathic appearance                        | +                         | +                         |
| Low anterior hairline                        | -                         | +                         |
| Coarse thick hair                            | -                         | Hypertrichosis            |
| Flat forehead                                | Bulging                   | +                         |
| Mild hypertelorism                           | +                         | -                         |
| Epicanthal folds                             | +                         | +                         |
| Broad depressed nasal bridge                 | +                         | +                         |
| Short columella                              | +                         | +                         |
| Long philtrum                                | +                         | +                         |
| Thick/full vermilion border of upper lip     | -                         | +                         |
| Broad mouth with downturned corners          | +                         | +                         |
| Gingival enlargement                         | -                         | -                         |
| Narrow and high palate                       | +                         | -                         |
| Inverted nipples                             | Widely spaced             | ND                        |
| Systemic manifestations                      |                           | Widely spaced             |
| Gastrointestinal symptoms                    | Constipation              | -                         |
| Small genitalia/endocrine anomalies          | -                         | +                         |
| Cardiovascular system anomalies              | -                         | -                         |

**Note:** ND = Not documented. Values indicate frequencies of the described features.
| Castori et al. (2013) | Kortüm et al. (2015) | Bramswig et al. (2015) |
|--------------------|---------------------|-----------------------|
| Zimmermann-Laband syndrome | KCNH1 mutations | Individual 1 |
| Zimmermann-Laband syndrome | ATP6V1B2 mutations | Individual 2 |
| Kortüm et al. (2015) | Individual 3 |
| Individual 4 |

| ND | ND | ND |
| 2,710 g | 2,850 g | 3,354 g |
| 45 cm | 50 cm | 52 cm |
| 34 cm | 35 cm | NA |

| 14/12 | 4/12 | 3/12 |
| 13 |
| - | - | - |

| 52/52 Hypoplasia/aplasia of nails/phalanges | 5/6 Hypoplasia/aplasia of nails | 2/2 Hypoplasia/aplasia of nails |
| 5/6 | 2/2 | + |
| ND | ND | + |
| 3/4 | ND | - |
| 0/4 | ND | + |

| 2/2 | Hypoplasia/aplasia of terminal phalanges; 1 NA |
| 2/2 | Hypoplasia/aplasia of terminal phalanges |
| ND | ND | ND |
| ND | ND | + |
| ND | ND | ND |
| ND | ND | ND |
| ND | ND | ND |

| 52/52 Hypoplasia/aplasia of nails/phalanges | 4/5 Hypoplasia/aplasia of terminal phalanges; 1 NA |
| 2/2 | Hypoplasia/aplasia of terminal phalanges |
| ND | ND | ND |
| ND | ND | ND |
| ND | ND | ND |
| ND | ND | ND |

| 21/52 | 6/6 | 2/2 |
| 6/6 | 2/2 | + |
| ND | ND | + |
| ND | ND | + |

| 7/52 | 6/6 | 0/2 (patients ages: 22 and 5 years) |
| 6/6 | 2/2 | + |
| ND | ND | + |
| ND | ND | + |

| 2/52 | 1/4 | 1/2 |
| 2/52 | 1/2 |
| 1/2 | ND |
| ND | ND |

| ND | 2/4 | 1/1 |
| 2/4 | 1/1 | Hypoplastic corpus callosum, cystic lesion pineal gland |
| 2 NA | 1 NA | Cystic lesion pineal gland |

| 1 has Pectus carinatum and thoracic kyphosis. Others ND | 1 has pectus carinatum | ND |
| ND | ND | ND |
| ND | ND | ND |
| ND | ND | ND |
| ND | ND | ND |
| 8/52 | 5/6 | 1 | Scoliosis | ND | ND | ND | ND |
|------|-----|---|-----------|----|----|----|----|
| at least 1. Others ND | 6/6 | 2/2 | ND | ND | + | + | ND |
| ND | 4/5 | ND | + | + | + | + | ND |
| ND | 1/6 | ND | ND | ND | ND | ND | ND |
| Facial hypertrichosis in 8/52, body hypertrichosis in 19/52 | Hypertrichosis 3/6 | Marked hypertrichosis 2/2 | + | + | + | + |
| ND | ND | Prominent | ND | Broad and prominent | ND |
| 6/52 | 4/5 | ND | + | + | + | + |
| ND | 1/6 | ND | - | + | + | - |
| ND | 2/4 | 5/5 | depressed broad | + | + | + | Only broad |
| ND | 4/4 | ND | + | + | + | - |
| ND | 2/6 | 1 | short philtrum | ND | ND | ND | ND |
| 27 thick lips/macrostomia | 5/6 | ND | + | + | + | + |
| ND | 4/4 | ND | + | + | + | + |
| 52/52 | 5/6 | 2/2 | + | + | + | + |
| 11/52 | ND | ND | ND | ND | ND | ND |
| ND | ND | ND | ND | ND | ND |
| 3/52 abnormal genitalia | 3/6 | have gastroesophageal reflux and/or constipation | ND | Constipation | Slight feeding problem | Constipation | Severe feeding problem |
| 3/52 abnormal genitalia | ND | 1 has macroorchidism | ND | ND | ND | ND |
| 6/52 | ND | ND | - | ND | - | Open ductus bodalli |

**Abbreviations:** +, present; −, absent; NA not analyzed, ND not documented, N/A not applicable, MRI magnetic resonance imaging

* no standard deviation noted
| Table 3 | Clinical comparison between the patient here described with TMBTS and the patient described by Kortüm et al. (subject 3) |
|---------|-------------------------------------------------------------------------------------------------------------|
| Patients having the p.(Gly348Arg) mutation                                                                 |
| Gender  | Present patient                                                                                           | Subject 3 in Kortüm et al. (2015)            |
|         | M                                                                                                          | F                                                                                   |
| Complicated Pregnancy | +                                                              | ND                                                                                       |
| Milestone |                                                                                                         |                                                                                      |
| Birth weight  | 2.700 g (60th percentile)                                                                                        | 3,290 g (39 weeks) (54th percentile)                                               |
| Height at birth | 48 cm (75th percentile)                                                                                        | 55 cm (99th percentile)                                                                |
| Head circumference at birth | 33 cm (60th percentile)                                                                                        | ND                                                                                       |
| Clinical findings |                                                                                                         |                                                                                      |
| Age (years) | 0.9/12                                                                                                    | 19                                                                                     |
| Consanguinity | -                                                                                                          | ND                                                                                       |
| Absence of nails | Nails of thumb and hallux                                                                                  | Nails of hands and feet                                                              |
| Broad, long thumbs terminally | +                                                                                                          | ND                                                                                       |
| Adductus deformity of distal thumb | +                                                                                                          | ND                                                                                       |
| Hypoplasia of terminal phalanges of hands and feet | Nearly absent                                                                                             | +                                                                                       |
| Delay in epiphyseal maturation | +                                                                                                          | ND                                                                                       |
| Neurologic |                                                                                                           |                                                                                      |
| Intellectual disability | +                                                                                                          | Severe                                                                              |
| Poor visual contact | +                                                                                                          | ND                                                                                       |
| Seizures | -                                                                                                          | Started in adolescence                                                                |
| Hypotonia/motor retardation | +                                                                                                          | +                                                                                       |
| Hearing loss | -                                                                                                          | -                                                                                       |
| Abnormal MRI findings | -                                                                                                          | NA                                                                                      |
| Dysmorphic features |                                                                                                           |                                                                                      |
| Thoracic abnormalities | +                                                                                                          | Thoracic scoliosis                                                                   |
| Coarse face | -                                                                                                          | +                                                                                       |
| Myopathic appearance | +                                                                                                          | ND                                                                                       |
| Hypertrichosis | -                                                                                                          | -                                                                                       |
| Coarse thick hair | -                                                                                                          | -                                                                                       |
| Flat forehead | Bulging                                                                                                    | ND                                                                                       |
| Mild hypertelorism | +                                                                                                          | ND                                                                                       |
| Epicanthal folds | +                                                                                                          | ND                                                                                       |
| Broad depressed nasal bridge | +                                                                                                          | ND                                                                                       |
| Short columella | +                                                                                                          | ND                                                                                       |
| Long philtrum | +                                                                                                          | ND                                                                                       |
| Thick vermilion border of upper lip | -                                                                                                          | ND                                                                                       |
| Broad mouth with downturned corners | +                                                                                                          | ND                                                                                       |
| Gingival enlargement | +                                                                                                          | Noticed in childhood prior anticonvulsant treatment                                   |
| Central incisors | +                                                                                                          | +                                                                                       |
| Narrow and high palate | +                                                                                                          | ND                                                                                       |
| Inverted nipples | Widely spaced                                                                                              | ND                                                                                       |
genes can act as disease modifying roles. Understanding the molecular mechanisms by which these genes exert disease modifying roles might help in the better understanding of the pathogenesis of these syndromes.

Finally, both ZLS and TMBTS patients with KCNH1 mutations show similar phenotypes. Nevertheless, two other ZLS patients were also described with mutations in the ATP6V1B2 gene that encodes a component of the vacuolar ATPase (V-ATPase). These mutations present a more pronounced phenotype characterized mostly by hypertrichosis and a coarser facial phenotype (Table 2). But due to the limited number of individuals described, a conclusion about whether probands with mutations involving ATP6V1B2 lead to a more severe syndrome might not be accurate. On the other hand, Kortüm et al. screened a cohort of 24 ZLS patients, of which only 8 had mutations in KCNH1 and ATP6V1B2 suggesting further the genetic heterogeneity in the ZLS disorder [18].

Conclusions

In summary, this study shows that the same KCNH1 mutation can lead to both ZLS and TMBTS. The phenotypic variability could be the result of a modifier gene or genes, and identification of such genes would be of great importance. A careful analysis of genetic polymorphisms in various loci should be taken into consideration for clinical diagnosis. Further investigations are needed to confirm if ATP6V1B2 mutations lead to a more severe phenotype.

Abbreviations

ID, intellectual disability; TMBTS, Temple-Baraitser syndrome; WGS, whole genome sequencing; ZLS, Zimmermann-Laband syndrome.

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Availability of data and materials

Data from this study are freely available and can be obtained by contacting the corresponding author.

Authors’ contributions

AM carried out the clinical genetic diagnosis of the patient and collected blood samples. AM, FM, DM and LC made substantial contribution to conception, design, and analysis of data. AM, NC, LC, KS, and AC drafted the manuscript, its revisions for important intellectual content and interpretation of data. RTh, EW, ST, WL and KS carried out sample processing and DNA isolation. MLe, RA, RT, PJ and EW performed bioinformatics data analysis and validation. All authors have read and approved the final version of the manuscript and its submission for publication.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from legally authorized representatives of the patient (parental consent) to participate in this study and its publication and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Ethical approval and consent to participate

This study has been approved by the Saint Joseph University of Beirut’s Committee on Clinical Investigation and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from legally authorized representatives of the patient (parental consent) to participate in this study and its publication and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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d| Systemic manifestations | Gastrointestinal symptoms | Constipation | ND
| Small genitalia/endocrine anomalies | - | Solitary renal cyst | ND
| Cardiovascular system anomalies | - | ND |

Abbreviations: +, present; –, absent; ND not documented
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