Molecular and clinical studies in 8 patients with Temple syndrome


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Temple syndrome (TS14, #616222) is a rare imprinting disorder characterised by phenotypic features including pre- and postnatal growth retardation, muscular hypotonia and feeding difficulties in infancy, early puberty and short stature with small hands and feet and common truncal obesity. It is caused by maternal uniparental disomies, paternal deletions and primary imprinting defects that affect the chromosomal region 14q32 and lead to a disturbed expression of imprinted genes in this region. Here, we present detailed clinical data of 8 patients with Temple syndrome, 4 with an imprinting defect, 2 with an imprinting defect in a mosaic state as well as 1 complete and 1 segmental maternal uniparental disomy of chromosome 14.

KEYWORDS
chromosome 14, genomic imprinting, imprinting defect, imprinting disorder, methylation, mosaicism, Temple syndrome

1 INTRODUCTION

Temple syndrome (TS14; #616222) is a rare imprinting disorder characterised by pre- and postnatal short stature with small hands and feet, muscular hypotonia and feeding difficulties in early infancy followed by weight gain and precocious puberty. It is caused by dysregulation of imprinted genes within the chromosomal region 14q32.1 This region harbours the paternally expressed genes DLK1 and RTL1 as well as the maternally expressed genes MEG3, RTL1as, MEG8, a sno- and a microRNA gene cluster (Figure 1). The parent-of-origin-specific expression is regulated by 2 differentially methylated regions (DMRs) that act as imprinting control regions: the MEG3-DLK1:IG-DMR (previously IG-DMR) located between the DLK1 and the MEG3 gene and the MEG3:TSS-DMR (MEG3-DMR2) located in the promoter region of the MEG3 gene. Both DMRs are methylated on the paternal allele. The germline derived MEG3-DLK1:IG-DMR acts upstream of the secondary-derived, somatic MEG3:TSS-DMR and governs it in a hierarchical fashion.3,4 A third DMR is present in intron 2 of the MEG8 gene (MEG8:In2-DMR). It is also a secondary-derived, somatic DMR and is, in contrast to the 2 others, methylated on the maternal allele.5,6 Methylation analyses are performed using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA; SALSA MS-MLPA kit ME032, MRC Holland) which includes several probes within the MEG3:TSS-DMR (see section 3). At present no methylation-specific probes are included for the MEG3-DLK1:IG-DMR and the MEG8:In2-DMR, which was not yet identified when
the MS-MLPA kit was designed. Temple syndrome was first described in 1991 in a patient with a maternal uniparental disomy 14 (UPD(14)mat) due to a Robertsonian translocation (13;14).\(^7\) Beside maternal UPDs of chromosome 14 with and without Robertsonian translocations, paternal deletions and imprinting defects have been identified as the molecular causes of TS14.\(^5,8,9\)

Since then approximately 120 TS14 patients have been described, the majority with a UPD(14)mat and merely 22 patients with a primary imprinting defect (ID1,5,10,11).

Here, we describe 8 further TS14 patients: 4 with primary IDs, 2 with mosaic IDs, 1 with a full UPD(14)mat and 1 with a segmental UPD(14)mat.

2 | RESULTS

Clinical data are summarised in Table 1, photos are shown in Figure 2.

2.1 | Patient 1

This girl is the second child of healthy, non-consanguineous parents. Her older sister is healthy. During pregnancy oligohydramnios and intrauterine growth retardation (IUGR; starting ~25 weeks of gestation) were reported. She was born after 35 + 4 weeks of gestation with 39 cm (~-2.9 SD), 1460 g (~-2.4 SD) and OFC (occipitofrontal head circumference) (~third percentile). At 9 months she was seen by a clinical geneticist due to disproportionate short stature with relatively short limbs, mild dysmorphic features (prominent forehead, upward slanting palpebral fissures with almond-shaped eyes, downturned corners of the mouth and retrognathia) and muscular hypotonia. Conventional chromosome analysis (46,XX), metabolic investigations, X-rays, cerebral MRI (magnetic resonance imaging), EEG (electroencephalogram) and ophthalmologic investigations were all normal. Motor milestones were normal/slightly delayed. She could walk independently at 23 months and spoke her first words at 2.5 years. She has a round face with full cheeks, clinodactyly, brachydactyly and mild obesity since the age of 6 years. Puberty started early (~9 years) for which she received a GnRH agonist until the age of 26 months.

Measurements at 5 years 6 months were: height 107 cm (~-2.1 SD), weight 23 kg (BMI 23) and OFC 52 cm (~-0.4 SD). The placenta was described as small (270 g). She showed postnatal bradycardia and apnoea as well as hypoglycaemia. Muscular hypotonia made tube feeding necessary for the first 10 weeks. Developmental milestones were delayed. She could sit at 11 months (corrected age), walked independently after 26 months, and spoke her first words ~24 to 26 months. Onset of obesity was noted at ~36 months.

Measurements at 5 years 6 months were: height 107 cm (~-2.1 SD), weight 23 kg (BMI 23) and OFC 52 cm (~-0.6 SD) with small hands and feet. Facial characteristics included micrognathia, short philtrum, downturned corners of the mouth, hypertelorism, a hypoplastic mid-face with a broad nasal bridge and a high forehead. Beside that a triangular-shaped face was noted, being more prominent in early childhood as well as clinodactyly and brachydactyly and a mild intellectual disability. Testing for Silver-Russell syndrome (SRS) and Prader-Willi syndrome (PWS) was negative. Chromosome analysis and array CGH (comparative genomic hybridisation) showed a normal female karyotype (46,XX). Spinal muscular atrophy (SMN1 deletion) and hypochondroplasia were excluded. MS-MLPA of 14q32 showed complete loss of methylation at the MEG3:TSS-DMR. Biparental inheritance was ascertained by microsatellite analysis (MSA).
### TABLE 1  Summary of clinical data

| Patient | Gender | Molecular diagnosis | Premature birth | IUGR | Low birth weight | Low birth length | Birth head circumference | Reduced fetal movement | Hypotonia | Feeding problems | Head circumference | Facial dysmorphism | \[ \text{Clinodactyly} \] | \[ \text{Short stature} \] | \[ \text{Overweight/obesity} \] | \[ \text{Small hands/feet} \] | \[ \text{Motor delay} \] | \[ \text{Speech delay (first words)} \] | \[ \text{Intellectual disability} \] | \[ \text{Premature puberty} \] |
|---------|--------|---------------------|----------------|------|----------------|----------------------|------------------------|-----------------------|-----------|----------------|------------------|-----------------|-------------------|-----------------|----------------|----------------|----------------|----------------|-----------------|----------------|----------------|----------------|
| 1       | F      | ID, mosaic          | Yes            | Yes  | Yes            | Yes                  | Low normal             | Not reported           | Yes       | Yes            | Microcephaly     | Yes              | Yes               | Yes             | No             | No             | No             | No             | No              | No             | No             | No             |
| 2       | F      | ID                  | Yes            | Yes  | Yes            | Yes                  | Normal                 | Yes                   | Yes       | Yes            | Normal           | Yes              | Yes               | Yes             | No             | No             | No             | No             | No              | No             | No             | No             |
| 3       | F      | ID                  | No             | Yes  | Yes            | No                   | Low normal             | No                    | Yes       | Yes            | Normal           | Yes              | Yes               | Yes             | Yes            | No             | Yes             | No             | No              | No             | No             | No             |
| 4       | F      | ID, mosaic          | Yes            | Yes  | Yes            | Yes                  | Low normal             | Yes                   | Yes       | Yes            | Microcephaly     | Yes              | Yes               | Yes             | No             | No             | No             | No             | No              | No             | No             | No             |
| 5       | F      | ID                  | No             | Yes  | Yes            | Yes                  | Low normal             | Yes                   | Yes       | Yes            | Normal           | Yes              | Yes               | Yes             | No             | No             | Yes             | No             | No              | No             | No             | No             |
| 6       | F      | UPD(14)mat          | Yes            | Yes  | Yes            | Yes                  | Low normal             | Yes                   | Yes       | Yes            | Microcephaly     | Yes              | Yes               | Yes             | No             | No             | Yes             | No             | No              | No             | No             | No             |
| 7       | M      | Segmental UPD(14)mat| No             | Yes  | Yes            | Yes                  | Low normal             | Yes                   | Yes       | Yes            | Normal           | Yes              | Yes               | Yes             | No             | No             | Yes             | No             | No              | No             | No             | No             |
| 8       | M      |                     | No             | Yes  | No             | Yes                  | Normal                 | Yes                   | No        | No             | Normal           | Yes              | Yes               | Yes             | No             | No             | Yes             | No             | No              | No             | No             | No             |

- **Gender:** F = Female, M = Male
- **Molecular diagnosis:** ID = Idiopathic, mosaic = mosaic
- **Premature birth:** Yes
- **IUGR:** Yes
- **Low birth weight:** Yes
- **Low birth length:** Yes
- **Birth head circumference:** Low normal
- **Reduced fetal movement:** Not reported
- **Hypotonia:** Yes
- **Feeding problems:** Yes (tube feeding for a few days only)
- **Head circumference:** Microcephaly
- **Facial dysmorphism:** Frontal bossing/prominent forehead
- **Short philtrum:** Yes
- **Broad nose:** Yes
- **Depressed nasal bridge:** Yes
- **Almond-shaped eyes (epicanthus):** Yes
- **Micrognathia:** Yes
- **High palate:** Not reported
- **Anteverted nares:** No
- **Other:** Full cheeks
- **Clinodactyly:** Yes
- **Short stature:** Yes
- **Overweight/obesity:** Overweight
- **Small hands/feet:** Yes
- **Motor delay:** Yes (slightly)
- **Speech delay (first words):** Yes (~30 mo)
- **Intellectual disability:** Mild learning difficulties
- **Premature puberty:** Yes (~9 y)
2.3 Patient 3

She was born as the first child of healthy, non-consanguineous parents in the 39 + 6 weeks of gestation with 46 cm (−2.3 SD), 2320 g (−2.4 SD) and OFC 33 cm (−1.2 SD). IUGR was noted around the 32th week of gestation; fetal movements were reported as normal. After birth, muscular hypotonia was present leading to feeding difficulties (breast feeding for 6 months, but drank only little) but tube feeding was not required. She could walk independently and spoke her first words at ~18 months. Obesity started when she was 4 to 5 years old. Puberty was prematurely (menarche at 9 years) and her skeletal age is accelerated (14 years when the patient was 12 years 2 months). She has small hands and feet, a short philtrum, hypotelorism and a high forehead. Mild dyscalculia was reported as was a hypothyroidism. At the age of 12 years 7 months her measurements were 147.5 cm (−0.9 SD) and 59.9 kg (BMI 27.5) with a normal OFC (53 cm [0.1 SD]).

After birth, PWS was molecularly excluded. MS-MLPA for chromosome 14q32 showed complete loss of methylation at the MEG3: TSS-DMR. UPD(14) was ruled out by MSA.

2.4 Patient 4

The patient is the second child of non-consanguineous parents. She was born spontaneously after 40 weeks of gestation with low normal measurements: length 51 cm (+0.05 SD), weight 2790 g (−1.1 SD) and OFC 32.5 cm (−1.8 SD). The pregnancy was complicated by reduced fetal movements and oligohydramnios. After birth pronounced muscular hypotonia and severe feeding problems were present, which necessitated a percutaneous endoscopic gastrostomy (PEG) until 2 years of age. Psychomotor development was slightly delayed; walking without support was achieved at 13 months. Although speech development was normal in the beginning, she needed to attend a school for speech handicapped.

At 8 years, she presented with bulging abdomen and truncal obesity (27 kg [+0.1 SD]). Other body measurements were low normal (height 125 cm [−0.7 SD], OFC 50 cm [−1.6 SD]), hands and feet were small. No signs of a precocious puberty were present. Psychomotor development was still slightly delayed, behaviour was normal.

Muscular hypotonia and feeding problems at the age of 13 months led to a tentative diagnosis of PWS but molecular genetic testing was negative. In addition, myotonic dystrophy type 1 was excluded, and CGH-array analysis revealed normal results. At the age of 8 years, TS14 was suspected. SNP Array-CGH analysis was unsuspicious and no deletion in 14q32 was observed. MS-MLPA revealed mosaic hypomethylation at the MEG3:TSS-DMR. Thus, TS14 is caused by a sporadic imprinting defect.

In addition, there is a history of juvenile Polyposis in this family. The father of our proband, her sister and the patient herself carry a pathogenic variant in the SMAD4 gene.
FIGURE 2  Legend on next page.
labour since month 4. In addition, reduced fetal movements were noted. APGAR scores were 7, 8, and 10, respectively. Feeding problems persisted until today (aged 2 years 11 months). She started walking alone with 19 months. Speech development is delayed. At the last examination (2 years 11 months) her height was 75.7 cm (−3 SD), weight 8 kg (−0.7 SD), OFC 44.3 cm (−3.5 SD). She showed frontal bossing, almond-shaped eyes, a short philtrum and a small chin. Due to the clinical findings TS14 was suggested. MS-MLPA showed complete loss of MEG3:TSS-DMR methylation confirming the diagnosis. MSA showed biparental inheritance and confirmed an imprinting defect.

2.6 | Patient 6

She was born in the 38th weeks of gestation after an uneventful pregnancy as the first child of a healthy, non-consanguineous couple with low birth measurements: 44 cm (−2.8 SD), 1825 g (−3.2 SD), OFC of 31.5 cm (−2.2 SD). After birth she showed clinodactyly, muscular hypotonia and feeding problems and her motor and speech development was slightly delayed. Further growth measurements showed a decreasing body height curve with −3.44 SD at the age of 5 years when growth hormone therapy was initiated. Herewith her body length was within the lower normal range (>10th percentile). Premature puberty was observed starting with 8 years and was treated with a GnRH agonist until the age of 10 years. Due to a scoliosis, successfully treated by surgery, growth hormone therapy was stopped at 12.5 years. At this time her height was 143 cm (−1.87 SD) and she had a normal weight (−0.7 SD). Her intellectual development is good (German gymnasium/grammar school). Beside her small stature, she shows small hands with clinodactyly and small feet, but is not overweight (photographs in Reference 13). She has minor facial dysmorphisms including a high forehead and a short philtrum, as well as a broad nasal tip, almond-shaped eyes and mild micrognathia and high palate. The tentative clinical diagnosis of SRS was made before the Netchine-Harbison score was published in 2015 (Patients’ score 3/614), but methylation analysis by MS-MLPA for chromosomes 11 and 7 were normal (ME030 and ME032, MRC Holland). Hypomethylation of the MEG3:TSS-DMR was detected by MS-MLPA confirming TS14. UPD(14)mat was excluded by MSA.

2.7 | Patient 7

The patient was born after 39 + 4 weeks of gestation with low birth measurements: 47 cm (−2.1 SD), 2270 g (−2.8 SD) and OFC 33.5 cm (−1.4 SD). He had a spastic-hypertrophic pyloric stenosis that was surgically corrected when he was 1 month old. Nevertheless feeding difficulties persisted. His development was normal with a slight delay in gross motor skills noted at 3 years 4 months and 3 years

10 months. At the same time bone age was slightly delayed (2.8 years at age 3.4 years). With 4 years 3 months he was small (93 cm, −2.9 SD), with normal weight (16 kg, BMI 18.5) and OFC (49.5 cm, −1.4 SD). His muscle tonus was normal-low. At the age of 9 years 6 months premature puberty was detected. He was still small (129.1 cm, −1.8 SD) with truncal obesity (BMI 23.8), normal OFC (52 cm, −0.8 SD) and small hands and feet. His facial appearance included slightly down slanting palpebral fissures, a small mouth, micrognathia and full cheeks. Cytogenetic analyses showed a normal male karyotype 46,XY. At 9 years TS14 was suspected due to the pubertas précox. Complete loss-of-methylation at the MEG3:TSS-DMR was detected by MS-PCR and MS-MLPA. MSA showed a maternal heterodisomy of chromosome 14.

2.8 | Patient 8

The patient is the first child of healthy non-consanguineous parents. He has 2 healthy younger brothers. A first pregnancy ended in a spontaneous early loss.

He was born after 37 + 5 weeks of gestation by Caesarean section with 48 cm (−0.9 SD), 2470 g (−1.4 SD) and an OFC of 34 cm (−0.3 SD). The pregnancy was complicated by early vaginal bleedings and later oligohydramnios. Reduced fetal movements were noted. After birth muscular hypotonia was present. He needed assisted ventilation (CPAP - continuous positive airway pressure) for some hours and was tube fed for 10 days. Feeding remained difficult for the first 2 years of life. Later on he started to eat more and did not show real satiation. Mental development was slightly delayed. He could sit at 12 months, walked alone at 14 months and spoke first words at 3 years 6 months.

At the age of 10 years he showed normal stature (135.5 cm [−0.9 SD]) and OFC (55 cm [+1.2 SD]) but had small hands and feet and was obese (69 kg [+2.8 SD; BMI 37.6]). No signs of precocious puberty were present. He showed a slight developmental delay, but no behaviour abnormalities.

Due to neonatal muscular hypotonia and feeding problems, a tentative diagnosis of PWS was suggested but molecular genetic testing was negative. However, MS-PCR and later on MS-MLPA showed a severe hypomethylation of the MEG3:TSS-DMR and confirmed TS14. MSA showed biparental inheritance for markers of the proximal region of chromosome 14 while the distal markers showed an isodisomic maternal UPD (Table S18). To determine its extent a SNP array analysis (Genome-Wide Human SNP Array 6.0, Affymetrix) was conducted showing loss of heterozygosity over 36 Mb (arr[hg19] 14q24.2q32.33(71,323,248-107,285,437) hzm; Figure 3A).

FIGURE 2 Patient photos. A, Patient 1 at the ages of 4, 8, 11, 13 and 17 years. She shows mild facial dysmorphism with a prominent forehead, a short philtrum, a broad nose with a depressed nasal bridge, almond-shaped eyes, micrognathia and full cheeks. B, Patient 3 at 12 years 7 months. Facial features include a prominent forehead and a short philtrum. C, Patient 2 at the age of 3 months, 1 year 3 months, 4 and 5 years. Note the prominent forehead, hypertelorism, a hypoplastic midface with a broad nasal bridge, micrognathia, a short philtrum and downturned corners of the mouth. A triangular-shaped face was noted, being more prominent in early childhood. D, Patient 5 at 2 years 11 months. She also shows a prominent forehead, a short philtrum, almond-shaped eyes and micrognathia. Additionally hypertelorism is present. E, Patient 4 at the age of 8 years. The depicted truncal obesity together with the short stature was the clinical signs that led to genetic counselling. F, Patient 7 at 9 years 6 months. The patient shows small hands and feet. Most of the patients show mild facial dysmorphism but there is no specific recognisable facial phenotype. Note the small hands and feet present in all patients.
3 | DISCUSSION

Temple syndrome can be caused by different molecular mechanisms. The majority of cases described have a maternal UPD of chromosome 14 while imprinting defects and deletions are much rarer.1,11 We have identified 8 patients with typical clinical features of TS14, among them 6 with imprinting defects in a non-mosaic or mosaic state, and 2 with complete or segmental maternal uniparental disomy of chromosomes 14.

3.1 | Uniparental disomy 14

Uniparental disomies can result from Robertsonian translocations, non-disjunction errors in meiosis or mitosis followed by trisomy or monosomy rescue or gamete complementation or can arise due to crossing over events as well as postfertilisation errors.15,16

While UPD(14)mat cases have been described frequently with and without Robertsonian translocations, segmental UPD(14) has only been reported in a small number of cases (Figure 3B). Two of these segmental maternal UPDs are located outside the imprinted region and do not lead to TS14, while no position is given for the third case.17–19 The paternal UPD(14) cases described span differently sized regions all including 14q32 and leading to Kagami-Ogata syndrome (KOS14, #60814920–25).

Patient 8 described in this study is, to the best of our knowledge, the first patient with proven TS14 due to a segmental UPD(14)mat. The affected region spans ~36 Mb and is isodisomic (Figure 3A) while the remaining part shows biparental inheritance suggesting a mitotic crossing-over event as the most likely mechanism.

3.2 | Non-mosaic and mosaic imprinting defects

Imprinting defects are errors of the methylation imprint. In TS14 the paternal allele harbours a maternal epigenotype with the MEG3/DLK1:IG-DMR and the MEG3:TSS-DMR being hypomethylated and the MEG8:Int2-DMR being hypermethylated.3,26,27

IDs can be either secondary arising due to, for example, deletions of a regulatory element in cis or primary without an underlying change in the DNA sequence.28 Primary IDs are due to a failure in imprint erasure, establishment or maintenance. All 6 TS14 ID cases described in this report are primary IDs.

So far 22 TS14 ID patients have been described, merely 5 of them with the ID in a mosaic state.1,5,10,26,29 In these individuals cells with a normal methylation imprint and cells with an ID coexist and the ID is therefore thought to occur due to a postfertilisation error in imprint maintenance. Mosaic IDs have been reported for Angelman, Beckwith-Wiedemann and SRS with different frequencies.30,31

3.3 | Clinical findings and differential diagnoses

Intrauterine growth retardation, low birth weight, early neonatal muscular hypotonia and feeding problems are the clinical hallmarks of TS14 (Table 1). Most of our patients show short stature in the first year of life. Due to precocious puberty and consequent acceleration of bone age final height is lower than expected from parental heights. Truncal obesity is present in about half of the here described patients starting after the age of ~2 years. Seven of 8 patients show mildly delayed speech development. Intellectual disability was present in 5 of 8 but only in very mild forms, whereas 2 patients had normal intelligence. Most of our patients show mild facial dysmorphism characterised by frontal bossing, almond-shaped eyes and mild micrognathia; however, there is no specific recognisable facial phenotype. Early clinical diagnosis of TS14 can be suggested because of IUGR, low birth weight, early feeding problems and muscular hypotonia. Later on, short stature and especially precocious puberty, at least in females, should lead to the clinical TS14 diagnosis.1

In the cohort of 8 TS14 patients described here 5 were initially suspected of having PWS and/or SRS before the correct diagnosis was obtained. Both disorders show phenotypic overlap with TS14: neonatal muscular hypotonia is a key feature of PWS, but is usually more prominent than in TS14. Later on short stature and obesity are present in PWS and TS14, but are more severe in PWS. IUGR, low birth measurements and postnatal short stature are present in SRS and TS14 patients.32 Therefore it is not surprising that the number of TS14 patients identified in presumed PWS and SRS cohorts is increasing.5 In addition, there is rising awareness of the TS14 phenotype as a recognisable syndrome and differential diagnosis for PWS and SRS. With the refined description of the phenotypic spectrum in TS14 the number of molecular diagnoses increased but it is probably still underdiagnosed, especially in patients with low-grade mosaic IDs as the phenotype might be less severe in those patients.

3.4 | Diagnostic testing

The most promising approach for the molecular diagnosis of TS14 (and KOS14) is a methylation analysis of the MEG3:TSS-DMR in combination with a gene dosage analysis followed by MSA of chromosome 14. An effective and cost efficient method to study methylation is the MS-MLPA. Here, methylation is tested at multiple sites within the MEG3:TSS-DMR in combination with the gene dosage across the imprinted region (MRC Holland, ME032).

Gene dosage analyses are crucial to estimate the recurrence risk. Deletions of various sizes have been reported, some only 4 to 6 kb.34 Most deletions are associated with a 50% recurrence risk leading to either TS14 or KOS14 depending on the sex of the transmitting parent. These deletions cannot be silently transmitted over generations in contrast to other imprinting disorders, for example, AS and PWS.4,8,26,33

The extent of large deletions should be investigated to identify affected genes such as the recurrent 1.1 Mb deletion spans YY1 which leads to intellectual disability.34,35

Without a detectable deletion differentiation between ID and UPD(14)mat must ensue using MSA. In case of UPD(14)mat cytogenetic analyses should be performed to rule out structural rearrangements like Robertsonian translocations while primary IDs are usually sporadic and not associated with a higher recurrence risk.
FIGURE 3  (A) SNP array results of Patient 8 and (B) overview of maternal and paternal segmental uniparental disomies (UPDs) of chromosome 14 described in the literature. Part (A) shows a schematic overview of chromosome 14 on the left hand side. Cytobands and the region showing loss of heterozygosity indicating the maternal UPD in the patient are given. A more detailed view is pictured on the right hand side. Log2 ratio is stable indicating that no deletion is present. Analysis was conducted using the software genotyping console and chromosome analysis suite (Affymetrix). Part (B) of the figure shows the schematic overview of chromosome 14 with the reported segmental maternal uniparental disomy 14 (UPD(14)mat) (UPD(14)mat) on the left hand side in red and the segmental UPD(14)pat on the right hand side in blue. The segmental UPD described in this study is shown in purple. Note that the maternal UPDs are interstitial and do not encompass the imprinted region on 14q32. The patient described by Martin et al has a phenotype reminiscent of TS14 but the UPD is confined to the region 14q23q24.2. Bruno et al do not give a location of the UPD(14) they detected and only sparse phenotypic features are available. The segmental UPD(14)pat described by Carvalho et al is 8.6 Mb in size and extends until telomeres. SNP - single nucleotide polymorphism.
4 | CONCLUSIONS

We here present detailed clinical characterisation of 8 patients with Temple syndrome: 4 with TS14 due to a primary imprinting defect, 2 patients with an imprinting defect in a mosaic state, 1 with a maternal UPD of chromosome 14 and the first description of a TS14 patient with a segmental maternal UPD of chromosome 14 including the imprinted region14q32.

Our cohort emphasises that differential diagnoses of PWS and SRS are quite common and PWS- and SRS-negative patients should be tested for TS14 as part of the diagnostic workup. Methylation analyses of/within the MEG3:TSS-DMR together with gene dosage analyses by MS-MLPA, followed by MSA of chromosome 14, should be used for diagnostic testing.

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Conflict of interest

The authors declare that they have no competing interests.

Ethics approval

The study was approved by the ethics committee of the university hospital Essen. Written informed consent was obtained from all patients.

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