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Refining the phenotypical and mutational spectrum of Taybi-Linder Syndrome

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**Conflict of interest**
The authors have declared no conflicting interests.

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ABSTRACT

Taybi-Linder Syndrome (TALS, OMIM 210710) is a rare autosomal recessive disorder belonging to the group of microcephalic osteodysplastic primordial dwarfisms (MOPD). This syndrome is characterized by short stature, skeletal anomalies, severe microcephaly with brain malformations and facial dysmorphism, and is caused by mutations in RNU4ATAC. RNU4ATAC is transcribed into a non-coding small nuclear RNA which is a critical component of the minor spliceosome. We report here four foetuses and four unrelated patients with RNU4ATAC mutations. We provide antenatal descriptions of this rare syndrome including unusual features found in two twin foetuses with compound heterozygosity for two rare mutations who presented with mild intrauterine growth retardation and atypical dysmorphic facial features. We also carried out a literature review of the patients described up to now with RNU4ATAC mutations, affected either with TALS or Roifman Syndrome, a recently described allelic disorder.

KEY WORDS

Corpus callosum agenesis, dwarfism, microcephalic osteodysplastic primordial dwarfisms, microcephaly, RNU4ATAC, spliceosome, Taybi-Linder Syndrome
INTRODUCTION

Taybi-Linder Syndrome (TALS), also called microcephalic osteodysplastic primordial dwarfism type I (MOPD I, OMIM 210710), is a rare autosomal recessive disorder belonging to the group of microcephalic osteodysplastic primordial dwarfisms. In 2011, we and He et al. identified either homozygous or compound heterozygous RNU4ATAC mutations in all typical TALS patients studied (1, 2). RNU4ATAC is transcribed into a non-coding small nuclear (sn) RNA, U4atac snRNA. U4atac is a component of the minor spliceosome, a ribonucleoprotein complex involved in the splicing of particular introns called U12-type introns (3). U12-type introns have been found in about 800 genes and represent 0.5% of all introns in the human genome. Splicing regulates gene expression and splicing defects may cause several human diseases (4-6), but to date, RNU4ATAC is the only known RNA component of the spliceosome associated with human disorders.

The main features observed in TALS are severe microcephaly with brain malformations including abnormal gyral pattern, corpus callosum agenesis or hypoplasia, vermis hypoplasia and intracranial cysts, psychomotor retardation, dwarfism, skeletal dysplasia, dry skin, sparse hair, flexion contractures, round face with beaked nose and protruding eyes and premature death with a majority of patients who die before the age of 28 months for unknown reasons (7). This syndrome is easily distinguished from other microcephalic dwarfisms such as MOPD II (OMIM 210720), Seckel Syndromes (OMIM 614728; 210600; 615807; 613676; 614851; 613823; 606744) or Meier-Gorlin Syndrome (OMIM 224690; 613800; 613803; 613804; 613805; 616835).

Here, we report on four foetuses including a twin pair and four unrelated patients with RNUATAC mutations. We describe uncommon features in the twin foetuses. This work provides an antenatal description of this rare syndrome and expands the phenotypical spectrum associated with RNU4ATAC mutations.
PATIENTS AND METHODS

Foetuses and patients
Four foetuses and four patients with a clinical phenotype suggestive of TALS belonging to seven families were referred to our laboratory for \textit{RNU4ATAC} analysis. All foetuses have been examined in a foetopathology unit and all patients have been examined in a Department of Clinical Genetics. We obtained informed written parental consent for the genetic study in all cases. Clinical data and molecular results are summarized in Table 1 and each case is described in details in Supporting Information. Photographs are presented in Figure 1. Radiographs and brain MRI are presented in Supplemental Figure 1.

Genetic analyses
We analysed \textit{RNU4ATAC} in all eight cases. Genomic DNA was extracted from a peripheral blood sample from patients and both parents and from frozen foetal tissues or foetal blood in foetuses. \textit{RNU4ATAC} analysis was performed by Sanger sequencing. The amplicon, including the non-coding RNA sequence (NR_023343.1) and 100 surrounding nucleotides was PCR-amplified (Forward primer: TAGGGCGAGGCTCACGAATT, Reverse primer: AGACTACTGGGCTGACTCAG) and sequenced on an ABI 3730xl DNA Analyzer or an ABI 3130xl DNA Analyzer with BigDye® Terminator v3.1 (Applied Biosystems).

RESULTS
\textit{RNU4ATAC} missense mutations were identified in all cases in the homozygous or compound heterozygous state (Table 1). Three patients and one foetus carry the g.51G>A mutation at the homozygous state. The other affected individuals are compound heterozygotes. One patient carries the g.51G>A and the g.55G>A mutations. One foetus carries the g.51G>A and the g.124G>A mutations. The twin foetuses carry the g.40C>T and the g.124G>A mutations. Segregation analysis showed that parents of each case are heterozygous for one mutation identified in their child. These mutations have been previously shown to impair either the \textit{RNU4ATAC} structure (8) and/or function (8, 9) by various mechanisms.
DISCUSSION

Forty-two RNU4ATAC-associated TALS cases belonging to 28 families have been reported to date (1, 2, 7, 8, 10-17). We report here on eight additional cases, and provide the first detailed description of foetuses with RNU4ATAC mutations.

The diagnosis was suggestive of TALS in all cases, despite twin foetuses 3 and 4 present uncommon features including mild growth retardation whereas it is usually severe. Moreover, they do not have any flexion contractures, which are frequently observed in TALS (Table 2). Finally, they do not show the typical TALS facial dysmorphism (Fig. 1g,h), suggesting that the phenotypical spectrum of TALS may be wider than previously suspected.

To date, 11 different RNU4ATAC mutations have been reported in association with TALS. These mutations are located in the U4atac intramolecular 5’ stem-loop of the U4atac/U6atac complex (g.30G>A, g.40C>T, g.46G>A, g.50G>A, g.50G>C, g.51G>A, g.53C>G and g.55G>A), in the stem I domain (g.66G>C), in the intramolecular 3’ stem-loop (g.111G>A, g.16_100dup) and nearby the U4atac Sm protein binding site (g.124G>A).

A genotype-phenotype correlation is emerging concerning survival in TALS. While poor survival is associated with homozygosity for the g.51G>A mutation, patients with long-term survival harbour other mutations, mostly g.55G>A (4, 12, 16), g.46G>A (14) and g.30G>A in association with g.111G>A (16). No clear genotype-phenotype correlation can be made yet regarding other features observed in TALS. It is difficult to correlate the occurrence of any feature with mutations other than g.51G>A or g.55G>A, because of the very small number of cases. However, it is interesting to note that foetuses 3 and 4, who carry the g.40C>T mutation in association with the g.124G>A mutation, do not exhibit the characteristic dysmorphic features of TALS and present mild intrauterine growth retardation, compared to the other foetuses and patients (Table 1). The g.40C>T was reported in two siblings in the heterozygous state, in association with a g.101 tandem duplication (bp 16–100) (8). These patients also present an atypical phenotype with long-term survival (alive at ages of 24 and 17 years respectively) and absence of contractures. Finally, the g.66G>C mutation has been reported in association with the g.124G>A mutation in one patient who appears to have a typical but mild phenotype without flexion contractures (7).

Two other RNU4ATAC mutations have been described in six patients presenting Roifman Syndrome (OMIM 616651), a very rare congenital disorder characterized by cognitive impairment, growth retardation, spondyloepiphyseal dysplasia and specific antibody deficiency, a phenotype distinct from TALS (18). However, many features are common to
both syndromes but are more severe in TALS (Table 2). Spondyloepiphyseal dysplasia is a cardinal feature of Roifman Syndrome and TALS. Bone dysplasia in both syndromes includes ossification delay of femoral epiphyses, widened femoral neck, horizontal acetabulum, shortened long bones, changes of the vertebral plates and short metacarpals. Growth retardation and microcephaly are observed in both syndromes but are more severe in TALS. Dry skin and/or eczema may also be observed in Roifman and TALS Syndromes, as is retinal dystrophy (Table 2). Conversely, premature death, sparse hair and severe structural brain abnormalities, which are recognizable features of TALS, have not been described in Roifman Syndrome, although one Roifman Syndrome patient had partial corpus callosum agenesis and hippocampal atrophy (19). In addition, dysmorphic facial features are distinct in these two disorders. Finally, severe and recurrent infections are constant in Roifman Syndrome, due to impaired production of specific antibody in response to antigens stimulation, whereas serum level of IgG, IgA and IgM are generally normal or moderately low. In TALS, recurrent infections have been reported in only 3 cases (8, 11, 14), one of them having an IgG level reported as low (14). These statements suggest a continuous spectrum between these two disorders but require the description of additional patients with RNU4ATAC mutations. All six Roifman Syndrome patients have one RNU4ATAC variant overlapping the 5’ stem–loop critical region or the Sm protein-binding site, while the other variant occurs at highly conserved positions in stem II, which have not been associated with TALS. The authors suggest that the localisation of the stem II variants may affect the PRPF4/PRPF3/PPIH protein complex binding. They hypothesize that these stem II variants have a weaker effect on minor spliceosome function than TALS mutations.

Further reports of additional patients with TALS, Roifman Syndrome or possibly other disorders which remain to be identified will certainly help to delineate the phenotypical spectrum associated with RNU4ATAC mutations.

CONCLUSION

In conclusion, we report on eight cases with TALS, carrying four different RNU4ATAC mutations. We show that although RNU4ATAC-associated TALS is a recognizable phenotype, an atypical presentation is sometimes observed, thus expanding the clinical spectrum. Life expectancy is usually short in TALS and patients die of an unknown cause often in the context of an apparently benign infection with a progressive neurological deterioration.
better knowledge of molecular pathways affected by *RNU4ATAC* mutations may allow better understanding and prevention of premature death.

**LEGENDS OF FIGURES**

**Figure 1:** Photographs of patients 1 (a), 2 (b), 3 (c) and 4 (d) and foetuses 1 (e), 2 (f), 3 (g) and 4 (h). For details, see supporting information.
REFERENCES

# Table 1 Clinical and molecular data of TALS patients in this series

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<tr>
<th>Case</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Foetus 1</th>
<th>Foetus 2</th>
<th>Foetus 3 (twin 1)</th>
<th>Foetus 4 (twin 2)</th>
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<td>Rwanda</td>
<td>France</td>
<td>Netherland</td>
<td>France</td>
<td>France</td>
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<td>Homozygous g.51G&gt;A</td>
<td>Homozygous g.51G&gt;A</td>
<td>Homozygous g.51G&gt;A</td>
<td>Homozygous g.51G&gt;A</td>
<td>Heterozygous g.51G&gt;A and g.124G&gt;A</td>
<td>Heterozygous g.40C&gt;T and g.124G&gt;A</td>
<td>Heterozygous g.40C&gt;T and g.124G&gt;A</td>
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<td></td>
<td></td>
<td></td>
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<td>36</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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| Other features       | Large optic discs
Enamel hypoplasia
Short first metacarpal
Dislocated patella
Oedema of feet
Fused anterior fontanel
Asymmetric corneal size
Oedema of feet, mild syndactyly 2-4 of toes
Small anterior fontanel
Rigid cranial sutures
Trigonocephaly
Choanal atresia
Small and pedunculated thumb
Pelvic right kidney
Small anterior fontanel
Low set thumbs
Oedema of feet
Small scrotum
Small anterior fontanel
Small anterior fontanel
Small anterior fontanel
Small scrotum
Small anterior fontanel
Small anterior fontanel
Small scrotum
Small anterior fontanel
Small scrotum
Small anterior fontanel
Small scrotum
Small anterior fontanel
Small scrotum
Small anterior fontanel
Small scrotum
Small anterior fontanel
Small scrotum |
| Age and cause of death| Alive at 6 years
19 months
Encephalomyelitis
6.5 months
Respiratory tract infection
Alive at 6 months
25 GW
21 GW
30 GW
30 GW
25 GW
21 GW
30 GW
30 GW
25 GW
21 GW
30 GW
30 GW |
Table 2 Clinical and molecular data of the patients with *RNU4ATAC* mutations reported so far

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<tr>
<th>TALS</th>
<th>Roifman</th>
<th>He et al. 2011</th>
<th>Haan et al. 1989</th>
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<th>Kilic et al. 2015</th>
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<td>5/5</td>
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<td>11/11</td>
<td>8/8</td>
<td>100% (47/47)</td>
<td>83% (5/6)</td>
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<td>CC anomalies</td>
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<td>4/5</td>
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<td>1/1</td>
<td>1/1</td>
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<td>97% (34/35)</td>
<td>0% (0/3)</td>
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<td>AGP</td>
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<td>5/5</td>
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<td>0/1</td>
<td>1/1</td>
<td>8/8</td>
<td>6/7</td>
<td>94% (31/33)</td>
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<tr>
<td>Intracranial cysts</td>
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<td>5/5</td>
<td>0/1</td>
<td>0/1</td>
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<td>4/10</td>
<td>3/7</td>
<td>34% (12/35)</td>
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<tr>
<td>Small vermis</td>
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<td>3/3</td>
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<td>1/3</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>3/8</td>
<td>1/7</td>
<td>32% (10/31)</td>
<td>0% (0/3)</td>
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</tr>
<tr>
<td>Skeletal anomalies</td>
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</tr>
<tr>
<td>Ossification delay</td>
<td>NR</td>
<td>1/1</td>
<td>2/2</td>
<td>3/3</td>
<td>3/3</td>
<td>1/1</td>
<td>1/1</td>
<td>NR</td>
<td>9/9</td>
<td>6/6</td>
<td>100% (26/26)</td>
<td>100% (6/6)</td>
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</tr>
<tr>
<td>Brachydactyly</td>
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<td>2/2</td>
<td>1/2</td>
<td>2/4</td>
<td>1/1</td>
<td>2/2</td>
<td>1/1</td>
<td>2/2</td>
<td>8/8</td>
<td>91% (31/34)</td>
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<tr>
<td>Flexion contractures</td>
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<td>3/3</td>
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<td>1/1</td>
<td>2/2</td>
<td>1/1</td>
<td>0/2</td>
<td>1/1</td>
<td>8/10</td>
<td>6/8</td>
<td>85% (34/40)</td>
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<tr>
<td>Short limb</td>
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<td>1/2</td>
<td>3/3</td>
<td>3/3</td>
<td>1/1</td>
<td>2/2</td>
<td>NR</td>
<td>6/6</td>
<td>6/8</td>
<td>88% (23/26)</td>
<td>0% (0/6)</td>
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</tr>
<tr>
<td>Thumb anomalies</td>
<td>NR</td>
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<td>2/2</td>
<td>0/3</td>
<td>0/5</td>
<td>0/1</td>
<td>0/2</td>
<td>0/1</td>
<td>1/1</td>
<td>3/8</td>
<td>19% (7/36)</td>
<td>0% (0/6)</td>
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<td>Skin and skin appendage</td>
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<tr>
<td>Sparse hair/eyebrows</td>
<td>8/8</td>
<td>1/3</td>
<td>2/2</td>
<td>2/2</td>
<td>5/5</td>
<td>1/1</td>
<td>2/2</td>
<td>1/1</td>
<td>9/9</td>
<td>4/4</td>
<td>95% (35/37)</td>
<td>0% (0/6)</td>
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<tr>
<td>Dry skin / eczema</td>
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<td>0/2</td>
<td>3/3</td>
<td>1/1</td>
<td>2/2</td>
<td>1/1</td>
<td>5/8</td>
<td>2/4</td>
<td>76% (25/33)</td>
<td>33% (2/6)</td>
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<td>Condition</td>
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<td>2/2</td>
<td>1/1</td>
<td>NR</td>
<td>1/2</td>
<td>70% (7/10)</td>
<td>NR</td>
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<td>-------------------------------</td>
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<td>Enamel hypoplasia</td>
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<td>2/2</td>
<td>1/1</td>
<td>NR</td>
<td>1/2</td>
<td>NR</td>
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<tr>
<td>Retinal dystrophy</td>
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<td>0/2</td>
<td>0/2</td>
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<td>0/1</td>
<td>2/2</td>
<td>NR</td>
<td>NR</td>
<td>0/1</td>
<td>25% (3/12)</td>
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<td>NR</td>
<td>NR</td>
<td>4/6</td>
<td>2/7</td>
<td>42% (8/19)</td>
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<td>NR</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>100% (6/6)</td>
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</table>

CC: corpus callosum. AGP: abnormal gyral pattern. NR: not reported.