



**HAL**  
open science

## Refining the phenotypical and mutational spectrum of Taybi-Linder syndrome

Audrey Putoux, A. Alqahtani, L. Pinson, A.D.C. Paulussen, J. Michel, A.  
Besson, S. Mazoyer, I. Borg, S. Nampoothiri, A. Vasiljevic, et al.

► **To cite this version:**

Audrey Putoux, A. Alqahtani, L. Pinson, A.D.C. Paulussen, J. Michel, et al.. Refining the phenotypical and mutational spectrum of Taybi-Linder syndrome. *Clinical Genetics*, 2016, 90 (6), pp.550-555. 10.1111/cge.12781 . hal-03626085

**HAL Id: hal-03626085**

**<https://hal.science/hal-03626085>**

Submitted on 12 Apr 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Refining the phenotypical and mutational spectrum of Taybi-Linder Syndrome

A. Putoux<sup>a,b</sup>, A. Alqahtani<sup>a</sup>, L. Pinson<sup>c</sup>, ADC. Paulussen<sup>d,e</sup>, J. Michel<sup>a</sup>, A. Besson<sup>b</sup>, S. Mazoyer<sup>b</sup>, I. Borg<sup>f</sup>, S. Nampoothiri<sup>g</sup>, A. Vasiljevic<sup>h</sup>, A. Uwineza<sup>i</sup>, D. Boggio<sup>a</sup>, F. Champion<sup>j</sup>, CE. de Die-Smulders<sup>d,e</sup>, T. Gardeitchik<sup>k</sup>, WK. van Putten<sup>l</sup>, MJ. Perez<sup>m</sup>, Y. Musizzano<sup>n</sup>, F. Razavi<sup>o</sup>, S. Drunat<sup>p</sup>, A. Verloes<sup>p</sup>, R. Hennekam<sup>q</sup>, L. Guibaud<sup>r</sup>, E. Alix<sup>a</sup>, D. Sanlaville<sup>a,b</sup>, G. Lesca<sup>a,b</sup>, P. Edery<sup>a,b</sup>.

a- Hospices Civils de Lyon, Service de Génétique, Lyon, France

b- Centre de Recherche en Neurosciences de Lyon, INSERM U1028, UMR CNRS 5292, Université Claude Bernard Lyon 1, Lyon, France

c- Département de Génétique Médicale, Centre Hospitalier Universitaire, Montpellier, France

d- Department of Clinical Genetics, Maastricht University Medical Centre, PO Box 5800, 6202 AZ, Maastricht, The Netherlands

e- School for Oncology & Developmental Biology (GROW), Maastricht University Medical Centre, Maastricht, The Netherlands

f- University of Malta, Department of Pathology; Mater Dei Hospital, Medical Genetics Unit, Malta

g- Department of Paediatric Genetics, Amrita Institute of Medical Sciences and Research Centre, Cochin, India

h- Hospices Civils de Lyon, Centre de Pathologie et Neuropathologie Est, Lyon, France

i- Centre for Medical Genetics, College of Medicine and Health Sciences, University of Rwanda, Huye, Rwanda

j- Hospices Civils de Lyon, Service de Gynécologie-Obstétrique, Lyon, France

k- Department of Human Genetics, Radboud University Medical Centre, PO Box 9101, 6500 HB, Nijmegen, the Netherlands

l- Paediatric Intensive Care Unit, Radboud University Medical Centre, PO Box 9101, 6500 HB, Nijmegen, the Netherlands

m- Département de Génétique Médicale, Unité de fœtopathologie, Centre Hospitalier Universitaire, Montpellier, France

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cge.12781

n- Département de Pathologie Tissulaire et Cellulaire des tumeurs, Pôle Biologie Pathologie, Centre Hospitalier Universitaire, Montpellier, France

o- Département de Génétique Histologie-Embryologie-Cytogénétique, Hôpital Necker-Enfant Malade, AP-HP, Paris, France

p- Department of Genetics, APHP-Robert DEBRE University Hospital, and Paris-Diderot University, Paris, France

q- Department of Paediatrics, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.

r- Département d'Imagerie Pédiatrique et Fœtale, Centre Pluridisciplinaire de Diagnostic Prénatal, Hôpital Femme Mère Enfant, Lyon-Bron, France.

**Corresponding author:**

Audrey Putoux

Unité de Génétique Clinique

Centre de Référence des Anomalies du Développement et Syndromes Polymalformatifs

Hôpital Femme Mère Enfant

59, boulevard Pinel

69677 BRON Cedex

FRANCE

Tel: +0033427855083

Fax: +0033427855245

E-mail: [audrey.putoux@chu-lyon.fr](mailto:audrey.putoux@chu-lyon.fr)

**Conflict of interest**

The authors have declared no conflicting interests.

**Acknowledgements**

We are sincerely grateful to the families for participating in this study.

**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 fetuses including a twin pair and four unrelated patients with *RNU4ATAC* mutations. We describe uncommon features in the twin fetuses. 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 *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 *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. *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<sup>®</sup> Terminator v3.1 (Applied Biosystems).

## RESULTS

*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 *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. A



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 fetuses 1 (e), 2 (f), 3 (g) and 4 (h). For details, see supporting information.

## REFERENCES

1. Ederly P, Marcaillou C, Sahbatou M et al. Association of TALS developmental disorder with defect in minor splicing component U4atac snRNA. *Science* 2011; 332: 240-243.
2. He H, Liyanarachchi S, Akagi K et al. Mutations in U4atac snRNA, a component of the minor spliceosome, in the developmental disorder MOPD I. *Science* 2011; 332: 238-240.
3. Will CL, Luhrmann R. Splicing of a rare class of introns by the U12-dependent spliceosome. *Biological chemistry* 2005; 386: 713-724.
4. Lehalle D, Wieczorek D, Zechi-Ceide RM et al. A review of craniofacial disorders caused by spliceosomal defects. *Clinical genetics* 2015; 88: 405-415.
5. Padgett RA. New connections between splicing and human disease. *Trends in genetics : TIG* 2012; 28: 147-154.
6. Pedrotti S, Cooper TA. In Brief: (mis)splicing in disease. *The Journal of pathology* 2014; 233: 1-3.
7. Abdel-Salam GM, Abdel-Hamid MS, Issa M et al. Expanding the phenotypic and mutational spectrum in microcephalic osteodysplastic primordial dwarfism type I. *American journal of medical genetics Part A*: 158A: 1455-1461.
8. Kroigard AB, Jackson AP, Bicknell LS et al. Two novel mutations in RNU4ATAC in two siblings with an atypical mild phenotype of microcephalic osteodysplastic primordial dwarfism type I. *Clinical dysmorphology* 2015.
9. Jafarifar F, Dietrich RC, Hiznay JM et al. Biochemical defects in minor spliceosome function in the developmental disorder MOPD I. *RNA* 2014; 20: 1078-1089.
10. Abdel-Salam GM, Abdel-Hamid MS, Hassan NA et al. Further delineation of the clinical spectrum in RNU4ATAC related microcephalic osteodysplastic primordial dwarfism type I. *American journal of medical genetics Part A* 2013; 161A: 1875-1881.
11. Abdel-Salam GM, Emam BA, Khalil YM et al. Long-term survival in microcephalic osteodysplastic primordial dwarfism type I: Evaluation of an 18-year-old male with g.55G>A homozygous mutation in RNU4ATAC. *American journal of medical genetics Part A* 2015.
12. Abdel-Salam GM, Miyake N, Eid MM et al. A homozygous mutation in RNU4ATAC as a cause of microcephalic osteodysplastic primordial dwarfism type I (MOPD I) with associated pigmentary disorder. *American journal of medical genetics Part A* 2011; 155A: 2885-2896.
13. Haan EA, Furness ME, Knowles S et al. Osteodysplastic primordial dwarfism: report of a further case with manifestations similar to those of types I and III. *American journal of medical genetics* 1989; 33: 224-227.
14. Kilic E, Yigit G, Utine GE et al. A novel mutation in RNU4ATAC in a patient with microcephalic osteodysplastic primordial dwarfism type I. *American journal of medical genetics Part A* 2015; 167A: 919-921.
15. Klinge L, Schaper J, Wieczorek D et al. Microlissencephaly in microcephalic osteodysplastic primordial dwarfism: a case report and review of the literature. *Neuropediatrics* 2002; 33: 309-313.
16. Nagy R, Wang H, Albrecht B et al. Microcephalic osteodysplastic primordial dwarfism type I with biallelic mutations in the RNU4ATAC gene. *Clinical genetics* 2012; 82: 140-146.

17. Sigaudy S, Toutain A, Moncla A et al. Microcephalic osteodysplastic primordial dwarfism Taybi-Linder type: report of four cases and review of the literature. *American journal of medical genetics* 1998; 80: 16-24.
18. Merico D, Roifman M, Braunschweig U et al. Compound heterozygous mutations in the noncoding RNU4ATAC cause Roifman Syndrome by disrupting minor intron splicing. *Nature communications* 2015; 6: 8718.
19. Fairchild HR, Fairchild G, Tierney KM et al. Partial agenesis of the corpus callosum, hippocampal atrophy, and stable intellectual disability associated with Roifman syndrome. *American journal of medical genetics Part A*: 155A: 2560-2565.

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

Case	Patient 1	Patient 2	Patient 3	Patient 4	Foetus 1	Foetus2	Foetus 3 (twin 1)	Foetus 4 (twin 2)
Origin	India	Malta	Turkey	Rwanda	France	Netherland	France	France
Mutation	Heterozygous g.51G>A and g.55G>A	Homozygous g.51G>A	Homozygous g.51G>A	Homozygous g.51G>A	Homozygous g.51G>A	Heterozygous g.51G>A and g.124G>A	Heterozygous g.40C>T and g.124G>A	Heterozygous g.40C>T and g.124G>A
Growth								
At birth (GW)	40	38	36	39	25	21	30	30
Weight (SD)	-3.7	-4.5	-5.6	-4.1	-3.5	-3.2	-3.1	-3.9
Length (SD)	-6.3	NA	NA	-6.8	-7.5	-7	-2	-3.6
HC (SD)	-5.2	-7.1	NA	-2.5	-4.5	NA	-3.7	-4.4
Post-natal (age in years)	1	NA	NA	0.5	/	/	/	/
Weight (SD)	-4	NA	NA	-8.7	/	/	/	/
Length (SD)	-4.5	NA	NA	-10	/	/	/	/
HC (SD)	-9.4	NA	NA	-8.7	/	/	/	/
Developmental delay	+	?	?	?	/	/	/	/
Brain anomalies								
Corpus callosum	NA	agenesis	agenesis	NA	agenesis	agenesis	hypoplasia	partial agenesis
AGP	+	+	+	NA	+	-	+	+
Small vermis	-	-	+	NA	-	-	-	-
Intracranial cysts	-	+	+	NA	-	-	-	+
Skeletal anomalies								
Short limb	-	+	-	+	+	+	+	+
Brachydactyly	+	+	+	+	+	+	+	+
Tapering fingers	-	+	+	-	-	-	+	+
Ossification delay	+	+	NA	NA	+	+	+	+
Platyspondyly	-	-	NA	NA	-	-	-	-
Flexion contractures	+	+	+	+	+	+	-	-
Skin and skin appendage								
Dry skin	-	+	-	+	/	/	/	/

Sparse hair/eyebrows	+	+	+	+	/	/	/	/
Small nails	+	-	+	-	-	-	+	+
Cardiac abnormalities	-	ASD	VSD	NA	-	-	-	-
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 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 TOP	21 GW TOP	30 GW TOP	30 GW TOP

GW: gestational week. SD: standard deviation. AGP: abnormal gyral pattern. NA: not assessed. ASD: atrial septal defect. VSD: ventricular septal defect. TOP: termination of pregnancy.

**Table 2** Clinical and molecular data of the patients with *RNU4ATAC* mutations reported so far

	TALS											Roifman
	He et al. 2011 Nagy et al. 2012	Haan et al. 1989 Klinge et al. 2002 Nagy et al. 2012	Abdel-Salam et al. 2011	Abdel-Salam et al. 2012	Abdel-Salam et al. 2013	Kilic et al. 2015	Kroeigaard et al. 2015	Abdel-Salam et al. 2015	Edery et al. 2011 Sigaudy et al. 1998	Present cases	Total	Merico et al., 2015
Number of cases	14	3	2	3	5	1	2	1	11	8	50	6
Number of families	1	3	1	2	3	1	1	1	8	7	28	4
Growth Retardation	11/11	3/3	2/2	3/3	5/5	1/1	2/2	1/1	10/10	8/8	100% (46/46)	100% (6/6)
Brain anomalies												
Microcephaly	11/11	3/3	2/2	3/3	5/5	1/1	2/2	1/1	11/11	8/8	100% (47/47)	83% (5/6)
CC anomalies	3/3	3/3	2/2	3/3	4/5	1/1	1/1	1/1	10/10	6/6	97% (34/35)	0% (0/3)
ACP	3/3	3/3	2/2	2/2	5/5	1/1	0/1	1/1	8/8	6/7	94% (31/33)	0% (0/3)
Intracranial cysts	0/3	0/3	0/2	0/2	5/5	0/1	0/1	0/1	4/10	3/7	34% (12/35)	0% (0/3)
Small vermis	0/3	3/3	0/2	0/2	1/3	1/1	0/1	1/1	3/8	1/7	32% (10/31)	0% (0/3)
Skeletal anomalies												
Ossification delay	NR	1/1	2/2	3/3	3/3	1/1	1/1	NR	9/9	6/6	100% (26/26)	100% (6/6)
Brachydactyly	11/11	1/1	2/2	1/2	2/4	1/1	2/2	1/1	2/2	8/8	91% (31/34)	100% (6/6)
Flexion contractures	11/11	3/3	1/1	1/1	2/2	1/1	0/2	1/1	8/10	6/8	85% (34/40)	0% (0/6)
Short limb	NR	1/1	1/2	3/3	3/3	1/1	2/2	NR	6/6	6/8	88% (23/26)	0% (0/6)
Thumb anomalies	NR	1/3	2/2	0/3	0/5	0/1	0/2	0/1	1/11	3/8	19% (7/36)	0% (0/6)
Skin and skin appendage												
Sparse hair/eyebrows	8/8	1/3	2/2	2/2	5/5	1/1	2/2	1/1	9/9	4/4	95% (35/37)	0% (0/6)
Dry skin / eczema	8/8	2/3	1/1	0/2	3/3	1/1	2/2	1/1	5/8	2/4	76% (25/33)	33% (2/6)

Enamel hypoplasia	NR	0/1	2/2	1/1	NR	0/1	2/2	1/1	NR	1/2	70% (7/10)	NR
Retinal dystrophy	NR	1/1	0/2	0/2	0/3	0/1	2/2	NR	NR	0/1	25% (3/12)	50% (3/6)
Cardiac anomalies	NR	NR	0/1	0/2	1/2	1/1	NR	NR	4/6	2/7	42% (8/19)	33% (2/6)
Specific antibody deficiency	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	100% (6/6)

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