Asphyxiating thoracic dysplasia: clinical and molecular review of 39 families

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ABSTRACT

Background Asphyxiating Thoracic Dysplasia (ATD) belongs to the short rib polydactyly group and is characterized by a narrow thorax, short long bones and trident acetabular roof. Other reported features include polydactyly, renal, liver and retinal involvement. To date, mutations in IFT80, DYNC2H1, TTC21B and WDR19 have been reported in ATD. The clinical and molecular heterogeneity leads to difficulties in the evaluation of the long-term prognosis.

Methods We investigated 53 ATD cases (23 living cases and 30 fetuses) from 39 families. They benefited from a combined approach of deep phenotyping and IFT80 and DYNC2H1 molecular screening.

Results Among the 23 postnatal cases, pulmonary insufficiency was noted in 60% of cases, with tracheotomy requirement in five cases. Renal and liver diseases occurred respectively in 17% and 22% of cases, whereas retinal alteration was present in 50% of cases aged more than 5 years. We identified DYNC2H1 mutations in 23 families (59%) and IFT80 mutations in two families (5%). However, in six families, only one heterozygote mutation in either IFT80 or DYNC2H1 was identified. Finally, the two genes were excluded in 14 families (36%).

Conclusions We conclude that DYNC2H1 is a major gene responsible for ATD, while IFT80 is rarely involved. The presence of only one mutation in six families and the exclusion of the two genes in 14 families support the involvement of other causal cilia genes. The long-term follow up emphasizes that the pulmonary prognosis is probably less pejorative and retinal involvement more frequent than previously thought.

INTRODUCTION

Asphyxiating thoracic dysplasia (ATD, Jeune syndrome, MIM208500) is an autosomal recessive chondrodysplasia characterised by narrow thorax, trident acetabular roof, occasional polydactyly and limb shortening associated with possible renal, hepatic, pancreatic and retinal manifestations occurring in the course of the disease.1–3 This disease has a wide spectrum of severity ranging from mild form to lethal condition and overlaps with the Short Rib Polydactyly (SRP) Type III (Verma-Naumoff).4 In the severe form, respiratory failure leads to death in early infancy. The frequency and age of onset of extraosseous manifestations are hitherto unknown. The identification of IFT80 (Intraflagellar transport 80, MIM61177) mutations in ATD has first confirmed that ATD belongs to the spectrum of cilia disorders.5 More recently, mutations in DYNC2H1 (dynein cytoplasmic 2 heavy chain 1, MIM603297), TTC21B (Tetratricopeptide repeat containing Hedgehog Modulator 1, MIM612014) and WDR19 (WD Repeat-Containing Protein 19, MIM608151) have been reported in ATD cases.6–9 IFT80 encodes a 777 residue protein that contains seven WD40 domains and is a component of intraflagellar transport complex B which is involved in the anterograde transport toward the ciliary tip allowing the elongation and the maintenance of the primary cilia.5 DYNC2H1 encodes a subunit of cytoplasmic dynein complex, a component of intraflagellar transport complex A involved in the retrograde transport from the ciliary tip to the basal body of the ciliary axoneme and plays a role in the maintenance of the primary cilia and the recycling of the ciliary protein.6–7 TTC21B encodes the retrograde IFT139 protein and causes isolated nephropthisis and ATD.8 Finally, WDR19 encodes retrograde IFT144 of IFT complex A, involved in nephropathisis, cranioectodermal syndrome and ATD.9

Through a national grant funded in 2007 for 3 years (PHRC AOM06031), we investigated 53 ATD cases. The aim of the study was (1) to better describe the natural history of the disorder and evaluate the frequencies of skeletal and extraskeletal complications (2) to perform the molecular screening of DYNC2H1 and IFT80 genes. These two genes only were screened as they were the only ones identified as ATD disease genes at the commencement of the study.

METHODS

The study was promoted by Assistance Publique-Hôpitaux de Paris, approved by the Institutional Ethic Committee and registered at the National Health Authority and at the International Protocol Registration System (ClinicalTrials.gov, NCT00948376).

Fifty-three ATD cases including 30 fetuses and 23 living cases, belonging to 39 families, were
Genotype-phenotype correlations

recruited between 2007 and 2009. Among these 39 families, five were consanguineous. They originated from France (31), Portugal (2), Turkey (2), Germany (1), Algeria (1), Morocco (1) and Poland (1).

The 30 fetuses, from 18 families, included 15 females and 15 males, issued of terminated pregnancies (TP) between 14 and 35 weeks of gestation (WG) with an average of 25 WG (table 1). Nine families underwent two or three TP because of recurrence. They fulfilled the diagnosis criteria for ATD namely: (1) marked short ribs, severe constricted thoracic cage, trident acetalubar roof, shortening of long bones (2) available detailed foetopathological report (3) available DNA samples for the proband and his parents. Exclusion criteria were clinical or radiological features suggestive of other SRP types.

The 23 living patients, from 23 families, included 8 girls and 15 boys, ranging in age from 6 months to 48 years (mean age 10.6 years) at the beginning of the study. Among them, two families had TP for recurrence (tables 1 and 2, F15/L19 and F10/L13). They fulfilled the diagnosis criteria for ATD namely: (1) short ribs with narrow thorax, trident acetalubar roof, variable long bones shortening (2) availability of DNA samples for the proband and his parents. We excluded patients with Ellis van Creveld syndrome features such as ectodermal defects or orofaciodigital syndrome features. Complete clinical follow-up data were recorded for all postnatal patients. The deep phenotyping study consisted of physical examination with measurements, skeleton x-rays, hepatic, renal and pancreatic function, abdominal and heart ultrasound. Pulmonary functional evaluation (including spirometry and volumes) and electroretinogram were performed only in children older than 5 years.

For molecular studies, genomic DNA was extracted from peripheral blood using QIAamp DNA blood midi/maxi kit (Qiagen S.A., sample and assay technology, France). HEX (hexachloro-fluorescein) or FAM (6 carboxyfluorescein) fluorescently labelled PCR products were run on an ABI 3130 sequencer and analysed using GeneMapper (Applied Biosystems). Linkage analysis was first performed in all consanguineous families and with recurrent sibs using microsatellite markers of the ABI PRISM linkage mapping set (Applied Biosystem) at the IFT80 and DYNC2H1 locus (Microsatellite markers available on request). For the concordant haplotyped cases and for the other non-consanguineous/non-recurrent cases, IFT80 and DYNC2H1 exons and flanking intron sequences were amplified from patient DNA by PCR using 20 pairs of primers for IFT80 and 90 couples of primers for DYNC2H1 designed with the Primer 3 software or UCSC Genome Browser database (see Web Resources). To amplify the 20 coding exons of IFT80 and the 90 coding exons of DYNC2H1 (sequence available on request), we purified the PCR product with exonuclease I (ExoSAPIT; Amersham Bioscience, USA) according to the manufacturer’s instructions. Sequencing reactions were performed on both strands and run on an automatic sequencer (ABI 3130) using the BigDye Terminator cycle sequencing Kit V1.1 (Applied Biosystems, Foster City, California, USA) and then analysed by sequencing analysis (Applied Biosystems).

All families provided written informed consent for clinical and molecular studies, approved by our local Research Ethics Committee.

RESULTS
The clinical, biological and molecular results are listed in table 1 for fetuses and table 2 for postnatal cases.

For the 30 fetuses, TP was based on prenatal ultrasound survey with (i) a diagnosis of severe ATD in 7/30 cases (after 25 WG in six and at 22 WG in one) (ii) a diagnosis of non-specified severe skeletal dysplasia or thanatophoric dysplasia in 9/30 (iii) detection of short ribs and short long bones in recurrence in 14/30 (at 14 WG for 1 and between 15–26 WG for 13). Postaxial polydactyly was present in 7/30 (23%). Renal abnormalities were observed in 10/30 cases (33%, 7/18 families) including cysts (4), hydrenephrosis (4) or renal dysplasia (2). Hepatic abnormalities were observed in 8/30 (26%, 6/18 families) including portal fibrosis (6), portal spaces dilatation and bile duct agenesis (1). Other features were: situs inversus (1), cleft palate (2), pulmonary segmentation abnormalities (2), micropenis (1) and pancreas cyst (1).

Among the 23 postnatal cases, only two were diagnosed as ATD antenatally and 13 were diagnosed at birth. In the eight remaining cases, the diagnosis was performed between 1 month and 9 years of age. However, 14/23 had prenatal skeleton features, detected by ultrasound survey, including short long bones (11), bowing of the femora (2), short ribs (6) and trident acetalubar roof (2). Clinically, all patients presented disproportioned chest narrowing but variable in severity and deformity (figure 1A, B). Neonatal respiratory insufficiency was noted in 11/23 (47%) and respiratory support for more than 3 weeks was required in six cases (26%). In infancy, 15/23 (65%) presented significant pulmonary complications (such as recurrent infections or asthma symptoms). In the course of the disease, five required long term tracheotomy (21%) and three required non-invasive positive pressure ventilation (13%). Two patients underwent chest expansion procedures for severe respiratory insufficiency. In the four adult patients, a significant improvement of the chest narrowing was noted after puberty.

Renal manifestations were observed in 4/23 patients (17%) including renal failure with transplantation after 20 years (2) and renal cysts diagnosed at 3 and 5 years (2). Five out of 23 (22%) presented with liver abnormalities, namely increased γ-glutamyl transferase (2), liver fibrosis at 14 years old (1) and steatosis associated with renal failure (1). Electroretinogram alteration was found in eight cases among the 16 cases older than 5 years (50%). Combination of renal and liver abnormalities was observed in 3/23, kidney and retina alteration in 2/23, and liver and retina alteration were observed in 4/23 (table 2). Postaxial polydactyly was noted in 2/23 (9%). Birth heights were normal in all and 17/23 patients (74%) were in the normal range while 6/23 presented postnatal short stature. The four adults of the series had a subnormal height, ranging from 1.50 m to 1.78 m. All patients had some degree of brachymetacarpia (especially in the hands and feet) and retina alteration were observed in 4/23 (table 2). Postaxial polydactyly was noted in 2/23 (9%). Birth heights were normal in all and 17/23 patients (74%) were in the normal range while 6/23 presented postnatal short stature. The four adults of the series had a subnormal height, ranging from 1.50 m to 1.78 m. All patients had some degree of brachymetacarpia (especially in the hands and feet) and retina alteration were observed in 4/23 (table 2).
Table 1  Summary of clinical and molecular data in the 30 fetuses

| Families | ATD diagnosis before TP | Autopsy term (weeks) | Postaxial PD | Renal anomalies | Hepatic anomalies | Other features | Mutated gene | cDNA change | Amino-acid change | Location |
|----------|-------------------------|----------------------|--------------|-----------------|-----------------|---------------|--------------|-------------|------------------|----------|
| F1.f1    | Yes                     | 17                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F1.f2    | No                      | 15                   | +            | −               | −               | −             | −            | DYNC2H1     | c.5220delT | p.Phe1740LeufsX26 | Ex 34    |
| F1.f3    | No                      | 25                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5220delT | p.Phe1740LeufsX26 | Ex 34    |
| F2.f1    | Yes                     | 14                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F2.f2    | Yes                     | 17                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5220delT | p.Phe1740LeufsX26 | Ex 34    |
| F3       | No                      | 21                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F4       | No                      | 22                   | +            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F5.f1    | Yes                     | 16                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F5.f2    | Yes                     | 17                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F6.f1    | No                      | 22                   | +            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F6.f2    | No                      | 14                   | +            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F7.f1    | Yes                     | 35                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F7.f2    | Yes                     | 26                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F8       | No                      | 24                   | +            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F9       | No                      | 26                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F10      | No                      | 24                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F11      | No                      | 28                   | +            | −               | −               | −             | −            | IFT80       | c.958–2A>G   | p.Leu1435Pro     | Ex 5     |
| F12      | No                      | 18                   | +            | Hydro nephrosis | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F13.f1   | Yes                     | 27                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F13.f2   | Yes                     | 15                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F14.f1   | No                      | 24                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F14.f2   | No                      | 35                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F15.f1   | Yes                     | 23                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F15.f2   | Yes                     | 20                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F16.f1   | Yes                     | 34                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F16.f2   | Yes                     | 25                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F17      | No                      | 22                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |
| F18      | No                      | 37                   | −            | −               | −               | −             | −            | DYNC2H1     | c.5176C>T   | p.Arg1726*       | Ex 34    |

CS, consanguinity ATD, Asphyxiating Thoracic Dysplasia; TP, terminated pregnancies; PD, polydactyly; BD, brachydactyly.
| Patient | Age   | CS | Family origin | Respiratory distress | Neonatal complications | Long term complications | Postaxial PD | BD with core shaped epiphysis | Renal features | Retinal involvement | Height | Other features | Mutated gene | cDNA change | Amino-acid change | Location |
|---------|-------|----|---------------|---------------------|------------------------|-------------------------|-------------|-----------------------------|--------------|---------------------|--------|----------------|-------------|------------|------------------|----------|
| L1      | 25    | No | France        | +                   | -                      | -                       | +           | -                           | -            | -                   | 1.78 m   | -               | DYNC2H1     | c.8283delT   | p.Met2873Val     | Ex 51    |
| L2      | 7     | No | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.2549T>A    | p.Leu850*         | Ex 17    |
| L3      | 6 months | No | France        | -                   | -                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.6043C>T    | p.Arg2015*        | Ex 42    |
| L4      | 5     | No | France        | +                   | +                      | -                       | -           | +                           | -            | -                   | -       | -               | DYNC2H1     | c.7981C>T    | p.Arg2661Cys     | Ex 49    |
| L5      | 2     | No | France        | -                   | +                      | +                       | -           | +                           | -            | -                   | -       | -               | DYNC2H1     | c.3719T>C    | p.Ile1240Thr     | Ex 12    |
| L6      | 16    | No | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.9044A>G    | p.Asp3015Gly     | Ex 57    |
| L7      | 8     | No | Poland        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.3719T>C    | p.Ile1240Thr     | Ex 66    |
| L8      | 16 months | Yes | Morocco       | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.11284A>G   | p.Met3762Val     | Ex 78    |
| L9      | 16 months | No | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | FISH probe     | p.Ser3557Pro    | Ex 25    |
| L10     | 9     | Yes | Turkey        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.7981C>T    | p.Arg2015*        | Ex 47    |
| L11     | 4     | No | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.7078G>T    | p.Asp3015Gly     | Ex 43    |
| L12     | 9     | No | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.3719T>C    | p.Ile1240Thr     | Ex 57    |
| L13     | 7     | No | same family   | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.11284A>G   | p.Met3762Val     | Ex 25    |
| L14     | 14    | No | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | DYNC2H1     | c.11284A>G   | p.Met3762Val     | Ex 19    |
| L15     | 36    | No | France        | -                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L16     | 16 months | No | France        | -                   | -                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L17     | 7     | Yes | Algeria       | -                   | -                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L18     | 24    | No | France        | -                   | -                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L19     | 5     | Yes, same | France       | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L20     | 9     | No | Portugal      | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L21     | 10    | Yes | Algeria       | -                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L22     | 48    | No | France        | -                   | -                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |
| L23     | 3     | Yes | France        | +                   | +                      | -                       | -           | -                           | -            | -                   | -       | -               | IFT80       | c.2155C>T    | p.Arg719Cys       | Ex 20    |

GT, glutamyl transferase.
to assume an exon 71 deletion inherited from the father. The deletion was confirmed by FISH (Fluorescence In Situ Hybridization) analysis using the probe RP11-2I22 in L9 and his father. No cases with two heterozygous or homozygous nonsense mutations were identified. Mutations were located throughout the gene, without any hotspot and recurrent mutations were located in exons 12, 25, 30, 38, 39, 42 and 56–57. In two families, we identified IFT80 (5%) mutations including one missense and one splice site (F11), and only one missense mutation in one patient (L15, figure 3). For both genes, missense mutations were responsible for the change of conserved amino-acid across species (http://genetics.bwh.harvard.edu/pph), not present in 200 control chromosomes and predicted as damaging using the Alamut software (See Web resources). Finally, DYNC2H1 and IFT80 were excluded in 14 families.

DISCUSSION
We report here the clinical and molecular study of a series of 53 ATD patients from 39 families. This series confirms the prevalence of ATD in France.10 Within the SRP group, ATD is one of the less rare conditions. 42 ATD cases were diagnosed (TP or after birth) between 2004 and 2010 and referred to the national Reference Center for skeletal dysplasia. Considering the non-referred and missed cases, this leads to one ATD case out of 100 000 births (annual births rate: 700 000 in France).

In the postnatal period, we observed a significant variability in the severity of respiratory insufficiency from severe to mild forms. Decrease in vital capacity was associated with frequent respiratory complications (infections, asthma) and 65% of recurrent pulmonary complications in infancy were observed as previously reported,11 apart from the Dutch series characterised by 80% cases with respiratory problems in the first 2 years of life.3 The thoracic perimeter improved with age in the oldest patients and the four adults of the series had a good pulmonary function. No correlation between the pulmonary prognosis and the stature insufficiency was observed and some patients with persistent tracheotomy had a normal stature. The frequency of renal complications (17%) was almost similar to the recent reported series (0/8,11 3/1212 and 2/133). However, only few patients are older than 15 years and the two patients with severe renal involvement presented with hypertension after 15 years of age with rapid renal failure supporting the need for a long-term follow-up. The frequency of liver involvement (26% of living cases) was also similar to previous

Figure 1  (A) Pictures and (B) x-rays of thorax (A–F). A1–A3 and B1–B3: patients with 2 DYNC2H1 mutations; C1–C3 patients with only one DYNC2H1 mutation; D1–D3 patients with no mutation in DYNC2H1 and IFT80. E1–E6: variable thoracic aspects in patients with DYNC2H1 mutations. (C) Hands x-rays (F1–F6). Note the mild brachydactyly and hypoplasia of distal phalanges in F1–F3 and the short hands with cone shaped epiphysis in F4–F6.
series and of good prognosis with spontaneous resolution of liver dysfunction or efficiency of ursodeoxycholic acid treatment. By contrast, we observed a higher frequency of eye alterations (50%) compared with the literature, which might be due to the systematic eye survey performed in patients older than 5 years. We also observed orthopaedic features including cervical spine compression, scoliosis and lumbar spine stenosis supporting spine follow-up during the course of the disease. All patients had a normal or sub-normal birth height and only 36% developed short stature in the postnatal period. Based on our results and the previously published series, we propose guidelines for the postnatal follow-up of ATD patients (table 3).

We identified 59% of DYNC2H1 mutations in 39 ATD families supporting that DYNC2H1 is a major gene for ATD. We confirmed that ITF80 is rarely involved in ATD, with only 1/39 family with two mutations. Because we identified a fair number of DYNC2H1 mutations, we tried to establish genotype-
phenotype correlations. Among the 26 cases with two DYNC2H1 mutations, we observed a low frequency of renal (2/26, cyst) or liver involvement (3/26), polydactyly in 6/26 and a relatively high frequency of retina impairment (2/7, 29%). Other rare features observed were micropenis, situs inversus and microdontia. Stature was always in the normal range between

Table 3

| Inclusion of                              | Start                        | Minimal frequency                  |
|------------------------------------------|------------------------------|-----------------------------------|
| **Physical examination**                 |                              |                                   |
| Respiratory parameters                   | At diagnosis                 | Every year until 15 year           |
| Anthropometrics measurements (thoracic,  |                              | Then on indication                 |
| standing and sitting height, weight,     |                              |                                   |
| limb segments)                           |                              |                                   |
| Neuromuscular evaluation (muscular       |                              |                                   |
| testing)                                 |                              |                                   |
| Arterial blood pressure                  |                              |                                   |
| Abdominal examination                    |                              |                                   |
| Back static examination                  |                              |                                   |
| **Pulmonary function testing**           |                              |                                   |
| Polygraphic sleep study                  | 6 months                     | Systematic, per 1 or 2 years       |
| Spirometry and volumes measurements      | 5 years                      | If pulmonary involvement, per 2 year|
| **Renal tests**                          | At diagnosis                 | Per year until 15 year             |
| Urinary and blood tests (tubular and     |                              | Then less frequently but at least per 3 years |
| glomerular evaluation)                   |                              |                                   |
| **Liver evaluation**                     | At diagnosis                 |                                   |
| Liver function                           |                              |                                   |
| Abdominal ultrasound                     |                              |                                   |
| **Pancreatic function**                  | At diagnosis                 |                                   |
| Pancreatic function                      |                              |                                   |
| Abdominal ultrasound                     |                              |                                   |
| **Eye evaluation**                       |                              |                                   |
| Electretinogram                          | 5 years                      | Every 2–3 years                    |
| **Orthopaedics**                         |                              |                                   |
| Cervical spine MRI                       | 6 months or at diagnosis     | Systematic then on indication      |
| Spine and hips X-rays                    | 8–10 years                   | On clinical indication             |
| **Others**                               |                              | Regularly                          |
| Genetic counselling and molecular analysis| At diagnosis                |                                   |
| Psychological support                    | After diagnosis               |                                   |

ATD, Asphyxiating Thoracic Dysplasia.

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–1 SD and +2 SD. The hands were mildly short, without cone shaped epiphysis. By contrast, the three patients with symptomatic renal involvement presented also marked brachyactyly with cone shaped epiphysis and short stature and none of them had DYNC2H1 mutation.

The presence of only one heterozygote mutation in six cases may be due to the limit of our molecular screening. One cannot exclude partial intragenic deletions or mutations in the introns or the promoter region. It may also suggest digenic allelic inheritance or the presence of two causal pathogenic mutations in other cilia genes with the heterozygote DYNC2H1/IFT80 mutation acting as a second site modifier.8

For the 26 remaining cases with only one heterozygote mutation or with no mutation, ongoing exome sequencing will hopefully lead to identify other cilia genes. Further correlation genotype-phenotype studies on larger series will be essential to get better prognosis elements that will help families and medical teams in genetic counselling and long-term management of the disease.

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