Geleophysic and acromicric dysplasias: natural history, genotype–phenotype correlations, and management guidelines from 38 cases

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Purpose: Geleophysic dysplasia (GD) and acromicric dysplasia (AD) are characterized by short stature, short extremities, and progressive joint limitation. In GD, cardiorespiratory involvement can result in poor prognosis. Dominant variants in the *FBN1* and *LTBP3* genes are responsible for AD or GD, whereas recessive variants in the *ADAMTSL2* gene are responsible for GD only. The aim of this study was to define the natural history of these disorders and to establish genotype–phenotype correlations.

Methods: This monocentric retrospective study was conducted between January 2008 and December 2018 in a pediatric tertiary care center and included patients with AD or GD with identified variants (*FBN1*, *LTBP3*, or *ADAMTSL2*).

Results: Twenty-two patients with GD (12 *ADAMTSL2*, 8 *FBN1*, 2 *LTBP3*) and 16 patients with AD (15 *FBN1*, 1 *LTBP3*) were included. Early death occurred in eight GD and one AD. Among

GD patients, 68% presented with heart valve disease and 25% developed upper airway obstruction. No AD patient developed life-threatening cardiorespiratory issues. A greater proportion of patients with either a *FBN1* cysteine variant or *ADAMTSL2* variants had a poor outcome.

Conclusion: GD and AD are progressive multisystemic disorders with life-threatening complications associated with specific genotype. A careful multidisciplinary follow-up is needed.

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INTRODUCTION

Geleophysic dysplasia (GD, MIM 231050) and acromicric dysplasia (AD, MIM 102370) belong to the acromelic dysplasia group characterized by severe short stature, short extremities, progressive joint limitation, thickened skin, and pseudomuscular build.[1] Patients with GD present with characteristic facial features defined by a happy face with full cheeks, a shortened nose, hypertelorism, a long flat philtrum, a thin upper lip, and tiptoe walking. X-rays reveal delayed bone age, cone-shaped phalangeal epiphyses, shortened long tubular bones, and small capital femoral epiphyses. Natural history is marked by progressive cardiac valvular thickening, tracheal stenosis, respiratory insufficiency, and hepatomegaly, responsible for life-threatening complications.[2,3] AD is distinct from GD mainly because of good prognosis. It is characterized by distinct dysmorphic features such as a round face, well-defined eyebrows, long

eyelashes, a bulbous nose with anteverted nostrils, a long flat philtrum, thick lips with a small mouth, and a hoarse voice. Specific radiographic findings include short metacarpals and phalanges, internal notch of the second metacarpal, external notch of the fifth metacarpal, and internal notch of the femoral heads.[4,5]

Dominant pathogenic variants in the *FBN1*[6] and *LTBP3*[7] genes are responsible for GD and AD, whereas recessive pathogenic variants in the *ADAMTSL2*[8] gene are associated only with a recessive form of GD. These genes encode proteins involved in the microfibrillar network, a key component of the extracellular matrix with an important role in its mechanical function and the bioavailability and activity of the TGF-β superfamily.[9] Alterations of microfibrillar network and enhanced TGF-β bioavailability had been shown in acromelic dysplasia.[6–8,10] Pathogenic variants in *FBN1* are all located in exons 41 and 42 encoding TGFβ-binding

protein-like domain 5 (TB5). The protein product of *FBN1*, Fibrillin-1, is composed of seven TBs domains containing eight cysteine residues linked by four disulfide bonds (these domains are also called cysteine domains), essential for domain structure.[6]

As a consequence of the clinical and molecular overlap between AD and GD, early accurate diagnosis can be difficult. Patient prognosis—especially when cardiorespiratory issues are involved—can differ, highlighting the need for appropriated follow-up. Here, we report clinical and molecular findings in 38 patients from 38 unrelated French families presenting with either AD or GD. The aim of this study was to define the natural history of these patients and establish phenotype–genotype correlation. The final aim was to propose specific guidelines for patient management, adapting medical care to genetic findings.

MATERIALS AND METHODS

Study design
This retrospective, monocentric study was conducted at Necker-Enfants malades Hospital in Paris, France. Between January 2008 and December 2018, 38 patients were diagnosed with either AD or GD confirmed by genetic analyses. Where there were several cases in the same family, only one proband was included in the analysis to avoid bias resulting from familial clustering. Patients' information was gathered from electronic and paper medical records and added to an anonymized database. The data collection was approved by the French National Commission on Informatics and Liberty (CNIL 1698048). Clinical and radiological criteria for diagnosis, detailed in Table S1, were used to assign each patient to either AD or GD. We present the natural history for each group separately.

Statistical analysis
Patients with GD were compared with patients with AD to identify differences of natural history between these two groups. To study the effect of genes and pathogenic variant types, the following patients were compared: (1) patients with *ADAMTSL2* variants and patients with *FBN1* variant, (2) patients with missense *FBN1* variants involving a cysteine with other missense *FBN1* variants, (3) patients with two missense variants in *ADAMTSL2* and patients with one missense variant and one nonsense variant in *ADAMTSL2*, (4) patients with *FBN1* variants involving a cysteine and patients with *ADAMTSL2* variants. We performed univariate analyses using a Fisher test for qualitative data and a Mann–Whitney test for quantitative data. If $p < 0.05$, the difference between two groups was considered as significant. All statistical analyses in this study were performed using GraphPad Prism 5 statistical software program (San Diego, CA, USA).

Histology
The mitral valve of patient 15 was obtained following valve replacement surgery. The sample was fixed in 10% formalin, embedded in paraffin, cut at 5-μm thickness, and stained with Alcian Blue (glycosaminoglycan) and Mallory trichrome (collagen). Images were viewed using a Nikon eclipse Ci microscope with a Nikon DS-Fi3 camera (objective X1) and analyzed using NIS element F4.60 software.

Modeling
Two-dimensional representations of LTBP3 and ADAMTSL2 proteins were created using Illustrator for Biological Sequence (IBS1.0).[11] Three-dimensional modeling of the TB5 domain of the FBN1 (amino acids 956–1008) was performed using Phyre2[12] homology from crystal structure of TB4 domain of FBN1;[13] the model was then analyzed using ENDscript 2.0 web server[14] and the PyMOL Molecular Graphics System (Version 2.0 Schrödinger, LLC).[15] The potential effect of variants was observed using in silico mutagenesis.

RESULTS

Cohort
Clinical and genetic findings for 38 patients of our cohort are presented in Table S2.

Geleophysic dysplasia
This group included 22/38 patients. Six patients were females and 16 were males with a mean age of 12.3 years at data collection (from 1 month to 35 years, 5 patients were older than 18 years). Eight patients were deceased at the time of the study (Table S2). Twelve of 22 had recessive pathogenic variants in the *ADAMTSL2* gene, 8 de novo heterozygous pathogenic variants in the *FBN1* gene and 2 de novo heterozygous pathogenic variants in the *LTBP3* gene (Table S3). Consanguinity was present in four families with a homozygous pathogenic variants in *ADAMTSL2*.

Acromicric dysplasia
This group included 16/38 patients. Seven patients were females and nine were males with a mean age of 23.6 years at data collection (from 6 to 71 years, seven patients were older than 18 years). One patient died at 6 years secondary to rigid endoscopy. Among them, 15 had a heterozygous pathogenic variant in the *FBN1* gene (5 de novo, 5 inherited from an affected parent, and 5 with an unknown inheritance) and 1 had a de novo heterozygous pathogenic variant in the *LTBP3* gene (Table S3).

Natural history
Perinatal history
Geleophysic dysplasia. Despite prenatal ultrasonographic anomalies in 14 cases, the diagnosis was not suspected during pregnancy. The ultrasound screening detected polyhydramnios in ten patients, short long bones in eight patients, and intrauterine growth retardation in six patients. The mean term at detection of these findings was 31.5 weeks of gestation. The average birth weight was in the 30th percentile and

the average birth length was in the 15th percentile. Ten patients (45%) had a birth length below the 5th percentile. The average occipitofrontal circumference (OFC) was in the 50th percentile. No perinatal complication was observed.

Acromicric dysplasia. During pregnancy, ultrasounds revealed intrauterine growth retardation in one patient (patient 28) (data available in ten patients). The average birth weight was in the 20th percentile and the average birth length was in the 25th percentile. Four of 11 patients (36%) had a birth length below the 5th percentile. The average OFC was in the 30th percentile. No perinatal complications were observed.

Growth

Geleophysic dysplasia. At age of data collection, all patients presented with short stature with an average of −4.6 SD and a weight with an average of −2.5 SD. In all cases, the growth rate falls below the standard growth curve in the first year of life. For the four adult patients, height was 115, 143, 130, and 137 cm for the two males and females, respectively. OFC was between −2.5 and +1 SD.

Acromicric dysplasia. At age of data collection, all patients presented with short stature with an average of −5.2 SD and a weight with an average of −2 SD. In all cases, the growth rate falls below the standard growth curve in the first year of life. The adult heights were 119, 122, and 134 cm for the three females and 140 cm for the male. OFC was normal in all cases.

Cardiac

Geleophysic dysplasia. Fifteen of 22 patients (68%) presented with postnatal cardiac valve thickening: pulmonary stenosis (8/15), mitral insufficiency (5/15), mitral stenosis (5/15), or aortic stenosis (4/15). Five patients (23%) had a multivalvular defect. Two clinical profiles were described among these patients. The first group presented with steady cardiac condition during the follow-up period (six patients). The second group presented with rapidly progressive valvular disease (nine patients).

While nonprogressive valve defects were detected at the mean age of 2.8 years (from 1 to 10 years), progressive valve thickening appeared in the first year of life and was responsible for early heart failure. Among the nine patients with a progressive valve defect, six patients underwent surgical valve replacement: 4/6 in the first year of life, and 2/6 in childhood (6 and 8 years). The three others were recused from cardiac surgery because of poor overall condition. Five patients died because of heart failure and/or comorbidities. In patient 15, postsurgery mitral valve study showed thick leaflets and fused chordae. Histopathological analysis (Mallory trichrome stain) revealed collagen accumulation responsible for severe fibrosis in which chordae tendineae were contained (Fig. 1). Alcian blue stain revealed no mitral valve glycosaminoglycan deposition.

Moreover, 3/22 patients presented with atrioventricular septal defect. Ten patients had hepatomegaly; in three patients this was not associated with right heart valve defect.

Acromicric dysplasia. Two of 16 patients developed postnatal cardiac valvulopathy with nonprogressive mitral
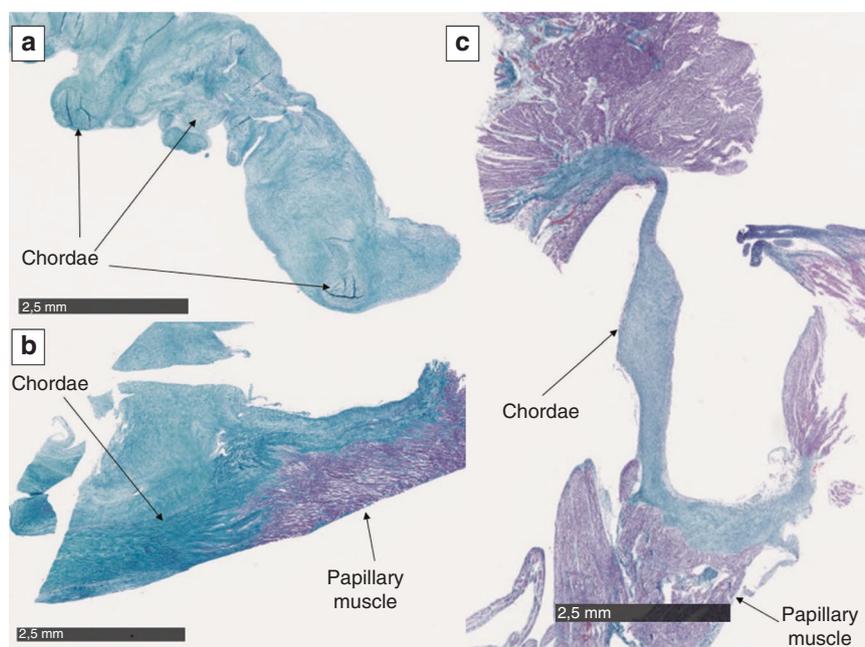

Fig. 1 Postsurgery mitral valve of patient 15 and control with Masson trichrome stain. (**a**) Masson trichrome stain (collagen stains light blue) revealed diffuse valve fibrosis with fused chordae encompassed in dense collagen. (**b**) Mitral valve chordae are severely thickened. (**c**) Control mitral valve chordae.

thickening, detected at 6 and 40 years old. Two patients had hepatomegaly without a heart valve defect.

Pneumological

Geleophysic dysplasia. Obstructive lung disease. Eight patients developed asthma ranging from mild to severe.

Restrictive lung disease. Thoracic tomodensitometry and respiratory function tests were available in nine patients and seven patients, respectively. All patients with progressive cardiac valve defect had severe respiratory insufficiency with chronic interstitial involvement on thoracic tomodensitometry (available in five patients) and a total lung capacity (TLC) below 50% (available in two patients). Of the five other patients with available respiratory function tests, functional studies revealed unexplained restrictive lung disease (TLC <80%) in two patients and decreased TLC below 90% in two patients. Thoracic tomodensitometry was available in four patients and revealed normal lung or mild interstitial syndrome.

Acromicric dysplasia. Obstructive lung disease. Seven patients developed asthma, easily managed by medical treatment and physiotherapy.

Restrictive lung disease. Among seven patients with available pulmonary data, functional studies revealed a restrictive lung disease (TLC <80%) in two patients and a decreased TLC (<90%) in three patients. Thoracic tomodensitometry was available in six patients and revealed normal lung or mild interstitial syndrome.

Ear, nose, and throat (ENT)

Geleophysic dysplasia. Multilevel airway obstruction was identified in 6 of 22 patients. Diagnosis of airway inflammatory stenosis was confirmed during laryngotracheal endoscopy under general anesthesia, mainly before the age of 12 months ($n = 4$). Endoscopy was indicated due to failed extubation ($n = 4$) or obstruction respiratory symptoms ($n = 2$). Four patients had laryngeal stenosis, and two had a tracheal stenosis. Endoscopy revealed malacia in all patients: tracheomalacia ($n = 4$), laryngomalacia ($n = 2$), and bronchomalacia ($n = 1$).

These combined obstructions were progressive and led to respiratory failure and death in four patients despite endoscopic therapy.

Conductive hearing loss was assessed in ten patients. Six patients had recurrent ear infections; six had otitis media with effusion. Ten of 15 suffered from adenoid hypertrophy with six patients requiring surgery. Five patients developed obstructive sleep apnea related to adenoid hypertrophy; one of these patients required continuous positive airway pressure (CPAP).

Acromicric dysplasia. Laryngeal and/or tracheal stenosis was not reported in this subgroup. One patient was diagnosed with tracheomalacia at 63 years of age.

Two patients presented with recurrent ear infections, four with otitis media with effusion, and four with adenoidal hypertrophy requiring surgery for three patients. In three patients, these ENT manifestations were complicated by conductive deafness. Two patients developed obstructive sleep apnea related to adenoid hypertrophy.

Pulmonary hypertension

Geleophysic dysplasia. Eight patients developed chronic or acute multifactorial pulmonary hypertension (PH), likely related to mitral valve disease in six patients, lung interstitial disorder in five patients, and upper airway obstruction in two patients. PH could be fluctuant and associated with acute respiratory failure triggered or enhanced by infection or physical stress such as surgery. One patient presented with unexplained chronic PH associated with restrictive syndrome (total lung capacity of 76% with diffusion capacity of carbon monoxide of 46%); she had no left heart, lung, or respiratory tract disorders.

Acromicric dysplasia. One patient developed acute pulmonary edema with PH secondary to endoscopy and died at 6 years of age. One patient developed unexplained acute respiratory failures with acute PH at 50 years old, likely triggered by viral infections.

Orthopedic

Geleophysic dysplasia. All patients suffered from early joint limitations acquired during childhood. Other orthopedic manifestations included hip dysplasia and osteochondritis ($n = 6$), and carpal tunnel syndrome requiring surgery ($n = 2$) at 11 and 14 years of age.

Acromicric dysplasia. All patients developed early joint limitations. 10 patients developped hip dysplasia and osteochondritis requiring hip osteotomy for two patients 6 patients were diagnosed with carpal tunnel syndrome ($n = 6$) with a mean age at diagnosis of 30 years with 4 patients requiring surgery.

Other

Ophthalmologic findings included classical eye refraction defects (hypermetropia, myopia, and astigmatism) in 18/25 patients during childhood (10 GD, 8 AD). In four patients (3 GD, 1 AD), papillary edema was found during systematic exam and required an emergency brain magnetic resonance image (MRI). Only one patient had intracranial hypertension requiring ventriculoperitoneal shunt at 10 years of age; the three other patients were asymptomatic, and the papillary edema was stable or regressed spontaneously.

Psychomotor development was normal in all patients. Few patients presented with mild language delay due to

conductive deafness and improved after ENT surgery or grommets. A cerebral MRI was available for eight patients, with normal results in all of them.

Genotype–phenotype correlation
Between genes
Applying targeted Sanger sequencing, panel sequencing (PS), or exome sequencing (ES), we identified 17 different *FBN1* variants in 23 patients, 17 different *ADAMTSL2* variants in 12 patients, and 3 *LTBP3* variants in 3 patients (Table S3). Thirteen variants have not previously been reported.

First, we compared patients with *FBN1* and *ADAMTSL2* variants. We did not identify any significant differences in the frequency of major clinical features except for type of cardiac valvulopathy (Table 1). The analysis of cardiac features demonstrated that mitral valvular dysplasia was significantly more frequent in patients with the *FBN1* variant ($p = 0.0256$), whereas pulmonary stenosis was more

Table 1 Clinical comparison between patients with pathogenic variants in the *FBN1* and *ADAMTSL2* genes.

	ADAMTSL2 n = 12	FBN1 n = 23	p value
Death	1	6	0.3800
Heart			
Valve defect	8	8	0.0896
Age at detection (years)	2.5 (0–35)	5 (0–40)	0.3234
Heart surgery	1	5	0.1189
Mitral valve defect	3	8	**0.0256**
Aortic valve defect	3	1	1.000
Pulmonary valve defect	7	1	**0.0101**
Pulmonary disorder			
Restrictive lung disease	2	6	0.6084
Pulmonary hypertension	2	7	0.4496
Asthma	4	8	1
Interstitial involvement	1	7	0.5882
Airway			
Airway obstruction	1	4	0.6399
Tracheostomy	1	4	0.6399
Obstructive sleep apnea	2	4	1
Ear, nose, and throat (ENT)			
Adenoidal hypertrophy	4	7	0.4065
Otitis media with effusion	3	4	0.2745
Conductive deafness	5	5	0.1409
Recurrent ear infections	4	3	0.1414
Orthopedic			
Joint limitations	9	12	0.5743
Tiptoe walking	5	3	0.0623
Hip dysplasia	5	10	0.0703
Hyperlordosis	1	5	0.6126
Carpal tunnel syndrome	2	6	0.6673

Significant results are in bold.

frequent in patients with *ADAMTSL2* variants ($p = 0.0101$). Because of the limited number of patients with *LTBP3* variants, tests did not reach significance.

FBN1 pathogenic variants
All reported subjects with the *FBN1* variant have a simple missense variant in the TB5 domain of the protein, which contains eight cysteine residues linking four disulfide bonds.

In our cohort, five pathogenic variants eliminating and four creating a cysteine residue were identified in eight patients with GD and six with AD. Eight other variants were present in eight patients with AD (Fig. S1). Three-dimensional homology modeling of the TB5 domain using the TB4 domain crystal structure (PDB code: 1UZJ)[13] with 30% sequence identity. Cysteine residues and disulfide bonds were correctly aligned (Fig. S2). Using mutagenesis in silico, we showed that variants substituting a cysteine residue would likely lead to disulfide bond suppression (Fig. 2). The four variants creating a cysteine could potentially introduce a new disulfide bond.

The probability of heart valve disease was significantly higher with missense variants involving a cysteine compared with other variants (43% vs. 0%, Fisher test, $p = 0.0072$). Valve defects appeared in the first year of life and were progressive in 7/8 patients. Even though PH, lung, and ENT disorders seemed to be more frequent in patients with a variant involving a cysteine, our data did not show any significant differences (Table 2).

ADAMTSL2 pathogenic variants
Patients with recessive *ADAMTSL2* variants had either two missense variants or one missense variant associated with one nonsense variant. None of the patients had two nonsense variants. Figure 3 shows the protein architecture of ADAMTSL2, with all variants of our cohort and their distribution across different protein domains. Variants are distributed throughout the protein. No significant difference was found for any clinical parameters between patients with two missense variants and those with a missense variant associated with a nonsense variant. Furthermore, no significant difference was found between patients with *ADAMSTL2* variants and patients with missense variants involving a cysteine in *FBN1* (Table 2).

LTBP3 pathogenic variants
A donor splice site variant (exon 12: c.1846+5G>A) and a stop-loss variant (exon 28: c.3912A>T: p.1304Cysext*12) were associated with GD whereas one missense variant was associated with AD.

DISCUSSION
We report here the natural history and genotype–phenotype correlation of 38 patients from 38 unrelated French families presenting with AD or GD.
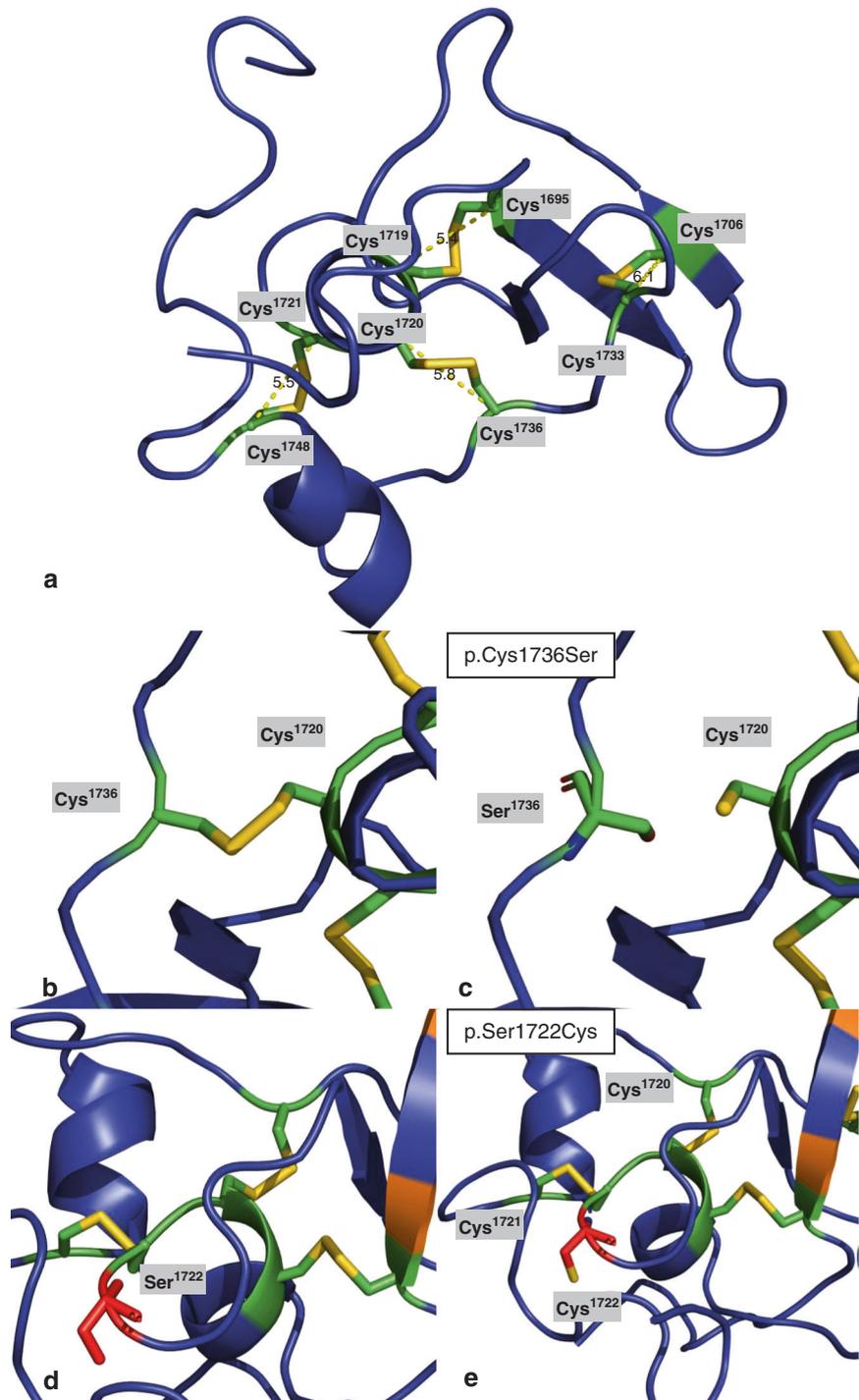
Fig. 2 Structure analyses of missense pathogenic variants involving a cysteine in the TB5 domain of the FBN1 protein. (**a**) The three-dimensional (3D) structure of the wildtype TB5 domain had been created based on the Protein Data Bank (PDB) template 1UZJ (30% sequence homology) by PyMOL 1.1r1. Green represents cysteine residues. The yellow lines between cysteines represent disulfide bridges. The arrows represent the β-sheets. (**b**) The unaffected fourth and seventh cysteines of the domain, which form a disulfide bond. (**c**) The potential conformational change of the variant p.Cys1736Ser with the disulfide bond suppression. (**d**) The unaffected serine1722 is represented in red. (**e**) The variant p.Ser1722Cys is located close to three cysteines of the domain.

Patient care

Medical management of patients with GD and AD dysplasia involves a multidisciplinary team with geneticist, pediatrician, cardiologist, pulmonologist, airway team, ENT, orthopedist, and ophthalmologist. Although acromicric and geleophysic dysplasias are two distinct disorders, clinical and genetic

Table 2 Clinical comparison between (1) patients with *FBN1* pathogenic variants involving a cysteine and patients with other *FBN1* pathogenic variants, and (2) patients with *FBN1* pathogenic variant involving a cysteine and patients with *ADAMTSL2* pathogenic variants.

	FNB1 variants involving a cysteine $n = 14$	(1)		(2)	
		Other *FNB1* variants $n = 9$	*p* value	*ADAMTSL2* $n = 12$	*p* value
Death	6	0	**0.0481**	1	0.0809
Valve defect	8	0	**0.0072**	8	0.7015
Heart surgery	5	0	**0.0451**	1	0.0671
Pulmonary hypertension	6	1	0.1760	2	0.2164
Restrictive lung disease	5	1	0.5000	2	0.5581
Asthma	6	2	0.1880	4	1
Obstructive sleep apnea	3	1	0.5692	2	0.6084
Airway obstruction	4	0	0.1038	1	0.3304
Tracheostomy	4	0	0.1038	1	0.3304

Significant results are in bold.

overlap result in challenges in diagnosis and disease management.

Perinatal history
Prenatal findings were detected more frequently in patients with GD than in patients with AD (70% vs. 10%, $p = 0.0051$). The higher proportion of patients with AD reaching adulthood compared with patients with GD explains the missing prenatal data. Although 70% of our subjects with GD presented with antenatal ultrasonographic signs such as intrauterine growth retardation, polyhydramnios, and/or short long bones, none of these signs were specific and no prenatal diagnosis of acromelic dysplasia was made. Prenatal signs were not associated with higher level of mortality in our cohort.

Growth and development
No significant difference in growth and development was observed between GD and AD. Sixty percent of our patients had a normal birth length and weight. In both GD and AD, severe growth retardation appeared in the first year of life, ranging from −4 and −8 SD. Neither developmental delay nor intellectual disability were reported. Few patients presented with mild language development delay due to conductive deafness and improved after grommets. Indeed, recurrent ear infections, otitis media with effusion, and adenoidal hypertrophy were frequently found. Audiometry must be regularly tested to prevent language development delay.

Orthopedic management
Patients with GD and AD have similar orthopedic complications with progressive joint limitations. Only two patients required surgery in our cohort. Physiotherapy should be part of multidisciplinary care to maintain join amplitudes and avoid surgery. Our center previously suggested a high prevalence of hip dysplasia in patients with GD and AD.[16] This study confirms this first observation with a frequency of

70% of hip dysplasia and two patients requiring an osteotomy. Moreover, 43% of patients developed hip osteochondritis. Clinical and radiographic follow-up is needed every 2 or 3 years to provide joint preserving treatment. Moreover, 35% of patients presented with carpal tunnel syndrome, thus continuity of follow-up is a necessity during adulthood.

Ophthalmologic findings
Refractive disorders are present with a higher frequency in AD and GD than in the general population. During ophthalmologic review, three patients presented with optic disc swelling without intracranial hypertension, as described in pseudoedema, without signs of optic disc drusen. In a previous study, two patients with acromicric and geleophysic dysplasia had been described with pseudopapilledema without any etiology.[17] Whereas these previous patients presented with headaches, our patients were asymptomatic. Pseudopapilledema is also described in Myhre syndrome, another acromelic dysplasia.[18]

Cardiorespiratory outcome
The prognosis of patients with GD depends on cardiorespiratory complications. Valve defects detected after one year of age often remain stable and are associated with good prognosis,[19] whereas progressive cardiac valve thickening and/or upper airway obstruction detected in the first year of life are associated with significant morbidity and mortality in patients with GD in our cohort and the literature.[20,21] Early detection is essential to prevent progression with life-threatening complications. Some patients developed respiratory insufficiency associated with interstitial syndrome, which was at least partially explained by valvulopathy. Our study reveals a high susceptibility of acute respiratory failure and a high prevalence multifactorial PH (cardiac, pulmonary, upper airway obstruction) in patients with GD. Notably, one patient with AD developed acute pulmonary edema with PH secondary to endoscopy and died at 6 years of age.
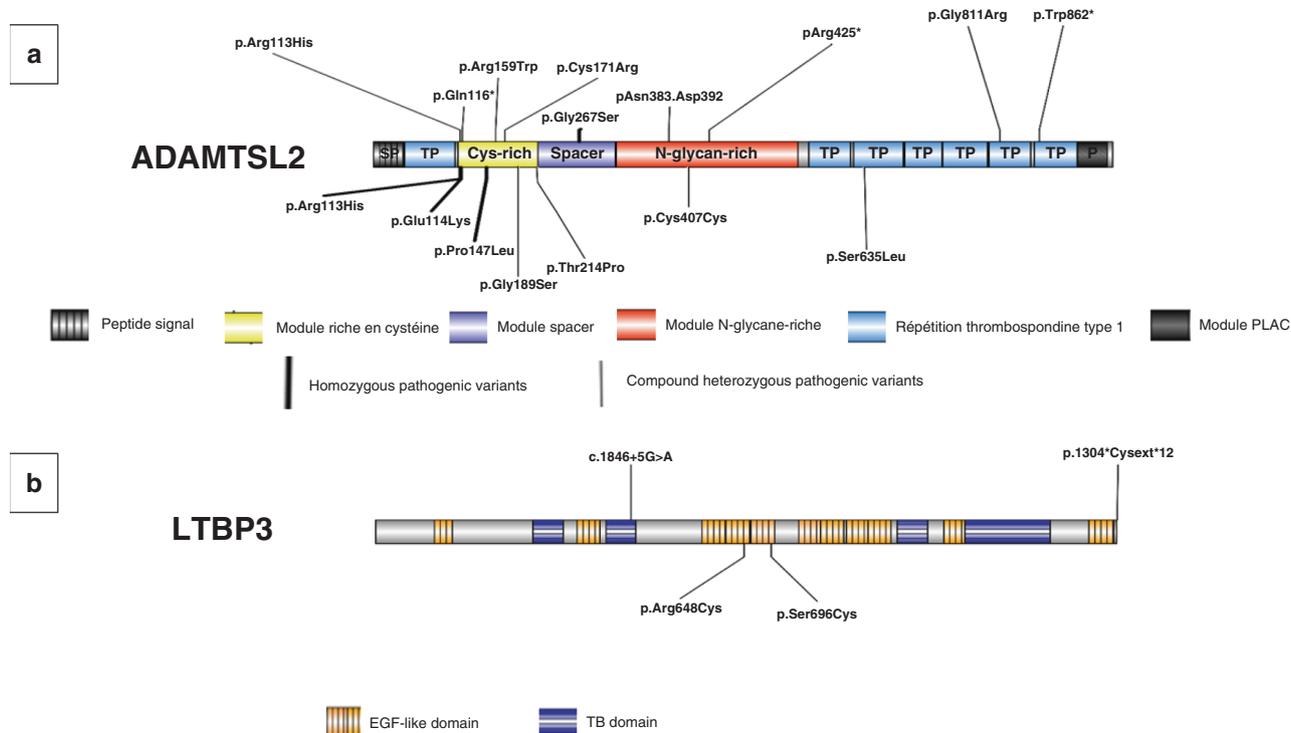
Fig. 3 Two-dimensional representations of ADAMTSL2 and LTB3 proteins. (**a**) ADAMTSL2 protein scheme with pathogenc variants reported in our cohort. Homozygous variants appear as bold lines. Composite heterozygous variants are on the same height. *Cys-rich* cysteine-rich module, *N-glycan rich:* N-glycan-rich module, *P* PLAC module, *PS* peptide signal, *Spacer* spacer module; *TP* Thrombospondin type 1 repeat. (**b**) LTBP3 protein scheme with pathogenic variants reported in the literature and in our cohort. Variants associated with geleophysic dysplasia and acromicric dysplasia are above and below the protein, respectively. EGF-like domains are represented with vertical bars, TB domains are represented with horizontal bars.

Some patients with acromelic dysplasia underwent surgery, such as cardiac or orthopedic procedures; however, several patients required tracheostomy after failed extubating, with unsuccessful attempt to remove the tracheostomy.[22] Interestingly, one patient previously reported required tracheostomy after a cesarean.[7] Anesthetists should be warned of this risk before scheduling any surgery for these patients and a smaller tube should be used.

Inflammatory upper airway stenosis is very likely to appear, at the larynx level or at the tracheal level. These stenoses are difficult to deal with, because they are active lesions and because any stimulation could worsen the stenosis. Tracheostomy can be performed in a life-threatening emergency but should not be considered as a definitive solution because secondary stenoses may appear below. The airway team should keep in mind that after the onset of the first stenosis, the airway is at high risk.

As previously described,[5] apart from the short stature, AD is associated with a "good" prognosis. The long-term follow-up showed that nonprogressive valve thickening or upper airway obstruction may appear during adulthood.[23] Moreover, patients can develop unexplained restrictive lung disease. Some patients with AD presented with fluctuant acute respiratory failure associated with PH suggesting flare-ups of noncardiogenic pulmonary edema triggered by infection or physical stress.

Finally, many patients with GD and AD have asthma, which easily managed by corticoids and β2-agonists in most cases.

The three genes responsible for GD and AD are involved in the microfibrillar network, a main component of extracellular matrix and TGF-β reservoir. Microfibrillar network disorganization and enhanced TGF-β signaling are observed in GD/AD fibroblasts.[6–8] Interestingly, pathogenic mechanisms of progressive valve disorders,[24] PH,[25] bronchopulmonary insufficiency,[26] and upper airway stenosis[27,28] are associated with dysregulated TGF-β signaling in others disorders. This signaling pathway plays a key role in the inflammatory response contributing to the fibrotic process.[29,30] TGF-β enhancement may induce inappropriate inflammation leading to aberrant fibrosis in the upper airways and heart valve as observed in patient 15. If this hypothesis is confirmed by further studies, it suggests that anti-TGF-β could be efficient as future therapies and thus slow the progressive cardiorespiratory involvement.

Differential diagnosis

Acromelic dysplasia also includes Weill–Marchesani syndrome (WMS) and Myhre syndrome, two skeletal dysplasias with striking clinical overlap with GD and AD. Myhre syndrome is defined by specific dysmorphic features, mild to moderate intellectual disability, and mixed hearing loss. Arterial hypertension, bronchopulmonary insufficiency, laryngotracheal stenosis, pericarditis may be responsible for

life-threatening complications for patients.[27] WMS is characterized by abnormalities of the lens of the eye including microspherophakia and dislocation of the lens. Similar to patients with GD, patients with WMS could develop progressive cardiac valvular thickening, tracheal stenosis, and/or bronchopulmonary insufficiency.[31]

Phenotype–genotype correlations

To address the high phenotype variability, we aimed to establish genotype–phenotype correlations. Variants in *FBN1* are localized in exons 41–42 encoding the TB5 domain characterized by eight cysteine residues, which are involved in FBN1 folding via intradomain disulfide linkage. In our cohort, four of five variants eliminating a cysteine were associated with a severe phenotype with life-threatening complications. These variants are responsible for the suppression of a disulfide bond that is essential for TB domain structure.[32] This conformational modification could explain the clinical impact of variants and thus the severe phenotype. The functional impact of variants creating a new cysteine residue is less predictable. The variants p.(Tyr1696Cys) and p.(Tyr1699Cys) are associated with a severe phenotype whereas the variants p.(Tyr1700Cys) and p.[Ser1722Cys]) of the TB5 domain are associated with AD. Three of these four variants eliminated a tyrosine residue. Tyrosine residue is a large aromatic group and its suppression could easily disturb the chemical environment within the β-sheet structure.[33] Without structural data, it is difficult to predict whether the impact of these variants is due to the addition of cysteine or removal of tyrosine. *FBN1* is also associated with Marfan syndrome in which variants involving a cysteine are responsible for a more severe phenotype than other variants.[34,35]

Most patients with *ADAMTSL2* variants developed moderate to severe cardiorespiratory complications. To date, no patients with two nonsense variants have been reported, suggesting embryonic lethality. Our study shows that patients with variants in *FBN1* involving a cysteine and those with variants in *ADAMTSL2* seem to have a similar, severe phenotype (Table 2).

The small number of patients with *LTBP3* variants limits any phenotype–genotype correlation. In our cohort and literature, four variants are associated with acromelic dysplasia.[7] A splice variant and a stop-loss variant are responsible for a severe phenotype, whereas missense variants seem to be associated to a nonthreatening disease (Fig. 3). Interestingly, patients from the same family presented with a similar phenotype. Finally, all 13 patients with severe cardiorespiratory outcome had variants in the *ADAMTSL2* gene, a variant involving a cysteine in the *FBN1* gene, or a splice or stop-loss variant in the *LTBP3* gene. No patients with good cardiorespiratory outcome have a variant involving a cysteine in the *FBN1* gene.

Conclusion

Patients with GD and AD require a multidisciplinary approach with a cardiologist, pulmonologist, ENT, orthopedist, ophthalmologist, and geneticist (clinical management in Supplementary material). Cardiac valve thickening and upper airway obstruction detected in the first year of life were associated with a poor prognosis. Physicians should be aware of the potential rapid worsening of patients with GD and the need for early detection of complications. Because of the risk of acute cardiorespiratory insufficiency, patients with AD or GD require organized long-term follow-up. Moreover, coordinated surveillance by a multidisciplinary team through childhood and into adulthood is essential as the natural history continues to be delineated. Genotype–phenotype correlations emerge from this study. These new findings provide precious tools to adapt the management for each patient according to their variant. Finally, physiopathology of acromelic dysplasia remains unclear and further studies, especially specific mouse models, are needed to improve to provide optimal medical treatment.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-020-00994-x) contains supplementary material, which is available to authorized users.

DISCLOSURE

The authors declare no conflicts of interest.

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