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Fabry disease: Four case reports of meningioma and a review of the literature on other malignancies

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ABSTRACT

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by loss of function mutations in the *GLA* gene at Xq22 with subsequent functional deficiency of alpha-galactosidase A, resulting in the accumulation of globotriaosylceramide (GL-3 or Gb_3) in multiple cells types throughout the body. As with other rare metabolic disorders, little is known about the incidence of malignancies in these populations and the relationship to the underlying disease, if any. We report the occurrence of meningioma in four female patients with Fabry disease. Two of the cases are from the same family and shared the same *GLA* mutation. All four patients underwent surgical excision of their tumor. High resolution light microscopy and electron microscopy examination of one case revealed extensive involvement of tumor cells and associated blood vessels by GL-3 accumulation. Because of the small number of Fabry-associated cancer cases reported in the literature, questions about a possible link between lysosomal storage disorders and the development of malignancy remain open.

1. Introduction

Meningiomas are the most common primary CNS tumor in the general population with a prevalence of 97.5 in 100,000 in the United States [1], and while most are benign, they often produce debilitating symptoms via their mass effect on the brain. Over the years, the incidence of this tumor and its various risk factors has been examined. Women's risk of meningioma is twice that of men, and may be linked to the expression of hormone receptors observed in some tumors [1]. Some studies suggest a link with hormone replacement therapy [1]. The incidence of meningioma, similar to other cancers of the breast, colon, pancreas, etc., has also been associated with obesity and its associated low-grade chronic inflammatory state [2]. Family history of meningioma in first degree relatives (2-fold increased risk) and exposure to ionizing radiation are also risk factors [1]. Familial cases have been reported both in association with [3] and in the absence of neurofibromatosis [4,5]. However, little has been reported on the occurrence of meningioma in association with metabolic disorders. These are the first reported cases of meningioma occurring in Fabry disease, an X-linked metabolic disorder caused by a deficiency of lysosomal alpha-galactosidase, resulting in cellular accumulation of the lipid globotriaosylceramide (GL-3) and its deacylated product lyso-Gb_3 [6,7]. We review the existing reports of cancer occurring in patients with Fabry disease, and discuss the possible association of metabolic lipid disorders with respect to the evolution of malignancy.

2. Materials and methods

We received representative wet tissue samples of surgically excised tumor from case 1. A portion of tumor tissue was fixed in 10% NBF, processed into paraffin blocks, sectioned and stained with routine hematoxylin and eosin as well as immunohistochemistry for vimentin (Abcam, Cambridge, MA). A separate portion tumor tissue was fixed in 3% glutaraldehyde in 0.2 M sodium cacodylate buffer, pH 7.3, and processed into epoxy resin blocks for high resolution light microscopy and electron microscopy as previously described [8]. Previously processed paraffin

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blocks from cases 2 and 3 were made available to us and were sectioned and stained with routine hematoxylin and eosin as well as immunohistochemistry for vimentin. All patients and family members provided consent to further examine the pathology and report on these cases.

3. Results

3.1. Case 1

A 41-year old woman was diagnosed with Fabry disease at age 40 as part of a family screening. This patient is the cousin of case 2 and they share the same family mutation in *GLA* (p. Leu415Pro or p.L415P); their mothers were sisters, both heterozygotes for Fabry disease. Her medical history included mild corneal compromise (cornea verticillata) and mild dysesthesias [9]. She had no signs of renal, cardiac or otologic disease and was not on enzyme replacement therapy. She presented with complaints of a non-specific headache over the prior two months. MRI revealed vertebrobasilar dolichoectasia and convexity meningioma located in the left hemisphere (Fig. 1A). The patient underwent surgical excision of the meningioma and the pathology of the patient's tumor was reported as a grade 1 meningothelial meningioma. Immunohistochemical staining performed at the treating hospital was reported as 40% of tumor cells strongly positive for progesterone receptor, and 2% of cells weakly positive for Ki-67.

The patient consented to additional histopathologic studies of her tumor, and additional samples of wet tumor tissue were processed for further examination. Hematoxylin and eosin stained paraffin sections revealed a typical meningothelial meningioma with well-defined lobules of meningothelial cells. These cells were positive for vimentin by immunohistochemistry. Vacuolization of tumor cells, mimicking the microcystic and/or clear cell variant of meningioma, as well as vacuolization of associated vascular cells were observed, suggestive of lipid storage (Fig. 1C and F). Epon-embedded sections examined at the light level revealed numerous dense blue granules in the cytoplasm of tumor cells (Fig. 2A), vascular endothelial cells and vascular smooth muscle cells (Fig. 2B), which appeared as zebra bodies, electron dense

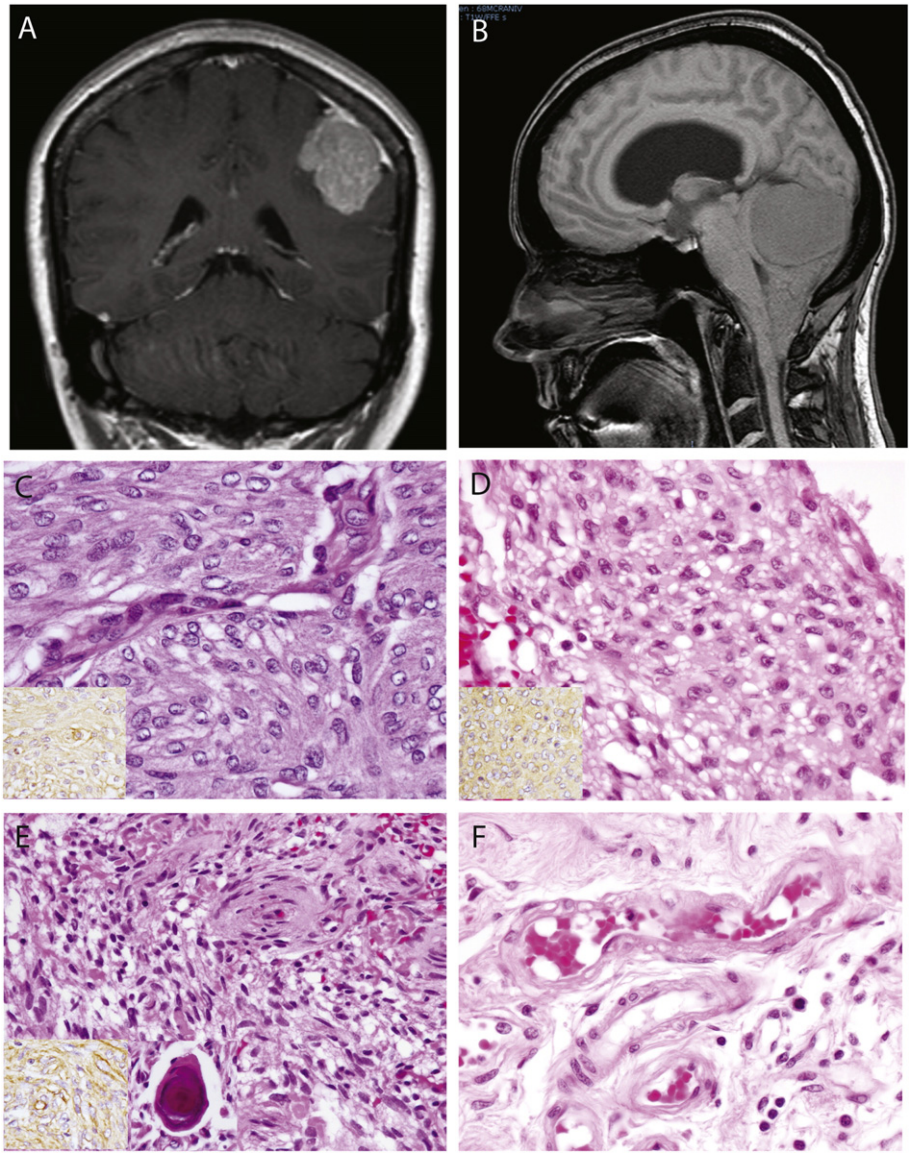

Fig. 1. MRI location and histologic appearance of meningiomas occurring in Fabry patients. Panels A. Case 1, convexity meningioma. Panel B. Case 3, torcular meningioma. Panel C. Case 1 - The tumor cells are meningothelial and arranged in well-defined lobules, with noticeable vacuolization. (paraffin section, H&E, 600× magnification) Tumor cells are also positive for vimentin (insert, 600×). Panel D. histologic appearance of tumor cells in case 2, note vacuolated appearance (paraffin section, H&E, 600× magnification) and vimentin positivity (insert, 600×). Panel E. Histologic appearance of tumor cells in case 3, note vacuolated appearance (paraffin section, H&E, 400× magnification), presence of typical psammoma bodies (insert, 600×) and vimentin positivity (insert, 600×). Panel F. Histologic appearance of associated tumor vasculature, note vacuolated appearance of VSMCs (paraffin section, H&E, 600× magnification).

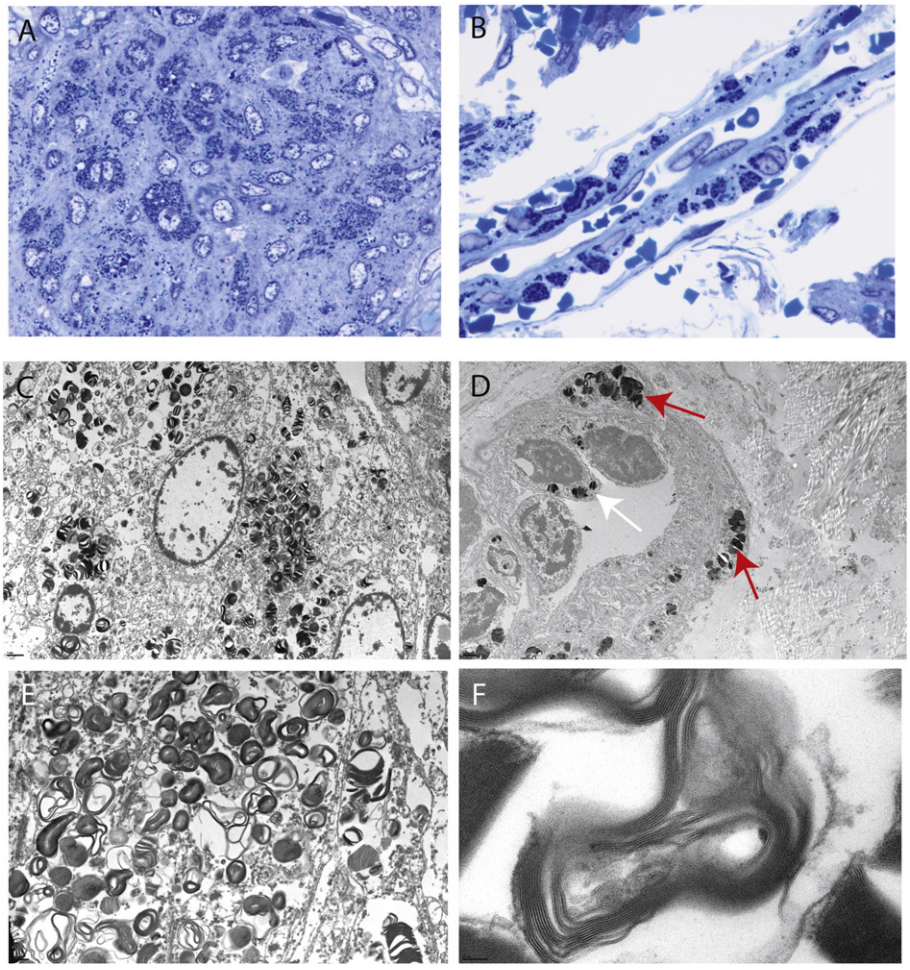

Fig. 2. High resolution light microscopy and electron microscopy of case 1. Panels A and B. High resolution light microscopy sections reveal marked accumulation of GL-3 in both tumor (Panel A) and vascular cells (smooth muscle cells and endothelial cells, Panel B), (1 μm, semi-thin epoxy resin sections, Richardson's stain, magnification 1000×). Panel C. Electron microscopy highlights the electron-dense zebra bodies within tumor cells, characteristic of GL-3 accumulation in Fabry Disease. (scale bar = 1 μm) Panel D. Electron dense GL-3 is also confirmed within endothelial cells (white arrows) and vascular smooth muscle cells (red arrows) of small vessels (scale bar = 1 μm). Panel E. High magnification of typical myelin figures and zebra bodies (electron microscopy, scale bar = 0.5 μm). Panel F. High magnification of Fabry myelin figure highlights the periodicity of the lipid layers (scale bar = 50 nm).

granules, and myelin figures on electron microscopy (Fig. 2C through F), characteristic of the GL-3 accumulation observed in Fabry disease.

3.2. Case 2

The patient was a 65-year old female diagnosed at age 63 with Fabry disease (mutation p.Leu415Pro) as part of a family screening. Her son was the index case for the family. The patient is the cousin of aforementioned case 1. Her medical history included corneal involvement (corneal verticillata), mild left ventricular hypertrophy (LVH), and microalbuminuria (150 mg/24 h) with normal eGFR. She had no neuropathic pain in the hands or feet, and had no signs of arrhythmia. The patient was not on enzyme replacement therapy. She presented with a 2 month history of headache and progressive left hemiparesis, and an MRI was performed which revealed periventricular lacunar infarcts and right frontal meningioma adjacent to the motor cortex with mass effect and local compression. She underwent surgical excision of the meningioma, but died 12 days later of sepsis from colonic perforation secondary to diverticular disease. The pathology of this patient's tumor was reported as a meningioma with clear cell and microcystic features, grade 2. The patient's family consented to additional histopathologic studies of her tumor. On hematoxylin and eosin sections, the tumor was composed of a mixture of meningothelial areas with moderate vacuolization of tumor cells, as well as areas with marked vacuolization of tumor cells which resemble the microcystic or clear cell variant of meningioma (Fig. 1D). These features may have been the result of GL-3 accumulation (as in case 1), however, there was no wet tissue available from this case to confirm this observation by electron microscopy. Tumor cells were also positive for vimentin.

3.3. Case 3

This 49-year old female patient was diagnosed at age 41 with Fabry disease as part of a family screening. The index case in her family was her father. She is heterozygous for the known familial mutation p.Gly373Ser in exon 7 of the *GLA* gene. Her father had died at the age of 48 years old, with cardiac and kidney failure. The patient's two sisters and her daughter are all heterozygotes for Fabry disease. Her alpha-galactosidase A activity was 31 nmol/h/mg of protein (within the normal range) in leukocytes. She exhibited random X chromosome inactivation pattern [10]. Her disease was characterized by mild ENT, cerebral and cutaneous impairments. She reported transient tinnitus and has a few angiokeratoma. She has no signs of renal or cardiac disease and is not on enzyme replacement therapy.

At the age of 44 years old she presented with a few months history of chronic fatigue, nausea, vomiting and impaired equilibrium. An MRI with gadolinium was performed and revealed a voluminous tumor in the posterior cranial fossa measuring 45 mm × 40 mm × 50 mm

(Fig. 1B). This extra-axial lesion was attached to the cerebellar tentorium, adjacent to the confluence of sinuses without obvious signs of venous invasion. The patient underwent emergency neurosurgery for tumor excision. Post-operatively, the patient suffered from impaired equilibrium, which improved after a rehabilitation program. Five years later at age 49, MRI showed tumor recurrence at the torcula measuring 14 × 8 mm, which was treated with radiotherapy.

Histopathological examination of the primary tumor revealed a transitional meningioma with a mixture of both meningothelial and fibrous patterns with well-developed whorls and psammoma bodies. Tumor cells appeared vacuolated on H&E stained sections, suggestive of abnormal GL-3 storage (Fig. 1E), however, no wet tissue was available for electron microscopy confirmation of this observation. Immunohistochemistry staining performed at the treating hospital reported that approximately 20% of tumor cells were positive for progesterone receptor, and less than 2% of tumor cells were positive for Ki-67.

3.4. Case 4

This 45-year-old female was diagnosed with late-onset Fabry disease at age 40 as part of her family screening. She is a heterozygote for the well characterized p.Asn215Ser family mutation, which is associated with high residual enzyme activity. Although cardiac hypertrophy was present in all males of her family, she had not developed any cardiac enlargement as of her last examination. Similarly, she had neither the renal nor the cerebral involvement typically associated with classic Fabry disease. She has been on enzyme replacement therapy for the last four years, at the patient's request.

At age 41, she began to complain of occasional mild to moderate headache. On routine ophthalmic examination, a progressive axial proptosis was noted in the left eye, with no restriction of the extraocular movements. There was no history of visual loss or diplopia of the left eye. The remainder of the neurological examination was normal, however, the patient reported hearing loss in the left ear, vertigo and dizziness, and intermittent tinnitus.

At age 42, brain MRI performed as part of her annual evaluation revealed a left lateral orbital bone remodeling and thickening (9.6 mm) of the meninges. Based on the imaging and clinical findings, a diagnosis of meningioma was made. Annual MRI surveillance of the lesion over the next three years remained unchanged.

At age 45, she experienced aggravation of the exophthalmos, daily headaches, nausea and vomiting. Brain MRI revealed an increase in tumor size with atrophy of the optic nerve due to local compression and peritumoral edema. The patient underwent left frontal craniotomy with left orbitotomy for surgical removal of the tumor. Her postoperative course was uneventful. She had no neurological sequellae except a temporarily left upper lid ptosis, and mild language disorders, treated with orthoptics and language therapy.

Histopathological examination performed at the treating hospital reported meningothelial meningioma WHO grade 1 [11]. Microscopic analyses reported lobules of meningothelial cells devoid of nuclear atypia, without mitotic activity, organized into small solid layers with a few whorls, and absence of necrosis. Immunohistochemistry staining performed at the treating hospital reported 90% of the tumor cells were positive for progesterone receptor and 6% of the tumor cells were positive for Ki-67.

4. Discussion

A review of the literature reporting malignancies in Fabry patients is shown in Table 1. In addition to our four meningioma cases, three hematologic malignancies [12,13] and three cases of renal carcinoma [14,15,16] have also been reported. Interestingly, all four of our meningioma cases occurred in female Fabry patients; none reported any family history of neurofibromatosis. This may be related, in part, to the female predominance (3:1) of this tumor in the general population

Table 1
Case summaries of four study patients with meningiomas and literature review of malignancies in patients with Fabry disease.

Reference	Tumor type	Gender	Age at cancer diagnosis	Cancer treatment	Age at Fabry disease diagnosis	ERT treatment	Follow-up	*GLA* mutation
Thurberg et al., case 1	Meningioma	F	42	Surgical removal	40, family screening	None	Alive at age 43	p.Leu415Pro (cousin of case 2)
Thurberg et al., case 2	Meningioma	F	66	Surgical removal	63, family screening	None	Patient died 12 days post-op, unrelated to neurosurgery	p.Leu415Pro (cousin of case 1)
Thurberg et al., case 3	Meningioma	F	44	Surgical removal of primary tumor at age 44; tumor recurrence at age 49 treated with radiotherapy	41, family screening	None	Alive at age 50	p.Gly373Ser exon 7
Thurberg et al., case 4	Retro-orbital meningioma	F	42	Surgical removal	40	Yes	Alive at age 45	p.Asn215Ser exon 5
Cybulla et al. [12]	AML	M	30, presented with chronic renal failure	NA	Post-mortem	None	Died at age 32	NA
Cybulla et al. [12]	ALL	M	3	NA	40, presenting with chronic renal failure	Yes	Alive at age 43	NA
Tisi et al. [13]	Small lymphocytic lymphoma	F	62	Chemotherapy	52, presenting with proteinuria	Yes	In remission	c.644A>G, p.Asn215Ser, exon 5
Blanco et al. [14]	Renal cell carcinoma, bilateral	M	69	Bilateral nephrectomy (sequential nephrectomies, 3 years apart)	69, diagnosed in first resected kidney	none	Died at age 72	p.Phe113Leu, exon 2
Cassiman et al. [15]	Renal cell carcinoma, bilateral	M	60	Bilateral nephrectomy	67, diagnosed based on history and low enzyme activity	none	Alive at age 67	c.427G>A, exon 3
Pagni et al. [16]	Renal cell carcinoma, unilateral	F	51	Nephrectomy	45, presenting with proteinuria	yes	Alive at age 51	g.1170C>T, exon 1

[17] and/or its reported hormonal dependence/receptor positive status in many cases [1]. Cases 1, 3 and 4 were all reported as progesterone receptor positive by immunohistochemistry performed at the treating hospitals. However, due to the absence of epidemiologic reports on the occurrence of meningioma in the setting of Fabry disease, the female predominance reported here may be due to chance. In addition, the familial relationship between cases 1 and 2 may indicate an inherited susceptibility in those patients. Therefore, we cannot state at this time whether the possible association we report here is statistically significant.

Hematologic malignancies were observed in both male and female patients as was renal cell carcinoma. Of the 9 cases, 3 patients received a cancer diagnosis prior to the diagnosis of their metabolic disorder: one 6 years later, one 37 years later, and one post-mortem [12,15]. A fourth case was not diagnosed until features of Fabry pathology were noted in the kidney resected with the tumor mass [14]. Such a delay in diagnosis is unfortunate, but not uncommon for patients with rare lysosomal disorders. In these cases in particular, the initial cancer diagnosis may have overshadowed the clinical picture such that diagnosis of a rare underlying illness was difficult to discern and easily overlooked.

In addition to the cancer cases in Fabry patients discussed here, malignancies have also been reported in other lysosomal storage diseases. In Gaucher disease, a sphingolipidosis due to the deficient activity of lysosomal beta-glucosidase [18], patients were shown to have a 2–3 fold higher risk of certain malignancies, including non-Hodgkin lymphoma, malignant melanoma and pancreatic cancer [19]. Other researchers have observed an increased risk of multiple myeloma in these patients [20] and suggested that the accumulation of lipid storage in Gaucher cells may lead to chronic stimulation of the immune system leading to lymphoproliferation. A review of the literature on Gaucher disease and associated malignancies has reported several cases of hepatocellular carcinoma, colon cancer, breast cancer and other tumor pathologies [21]. Colon cancer and hepatocellular carcinoma have also been reported in Niemann-Pick type B patients [22,23].

Fabry disease, along with Gaucher disease and Niemann-Pick type B, fall into a sub-category of lysosomal storage disorders, the sphingolipidoses, or disorders of sphingolipid metabolism. These disorders share dysregulation of sphingolipid metabolism, with a shared consequence of altered or lowered ceramide levels. Ceramide is bound within the chemical structure of the accumulating glycosphingolipid which cannot be metabolized into it individual components to release free ceramide, as occurs in normal cells. Ceramide is a molecule with pro-apoptotic and anti-proliferative properties, and recent reviews examine the role of ceramide as an anti-cancer molecule [24,25] and the association of elevated glucosylceramide with Gaucher-associated malignancies [26]. Similar links between low ceramide and colon cancer have also been suggested in the setting of Niemann-Pick type B disease [22]. Chemotherapeutic agents which increase ceramide levels promote cell death of cancer cells [27], and conversely, altered sphingolipid metabolism in cancer cells lead to carcinogenesis, cancer progress and chemotherapeutic resistance [27]. Whether the dysregulation of lipid inherent in these disorders has any relationship to the promotion of malignancy in these patients is unknown. Electron microscopy of our case 1 and the renal cell carcinoma case in Pagni et al. [16], demonstrated the presence of the characteristic “zebra bodies” derived from GL-3 accumulation in tumor cells, confirming that the cancer cells themselves possess dysregulated lipid biology/metabolism. The accumulation of this sphingolipid in the setting of a lysosomal storage disorder would prevent the release of free ceramide, thus inhibiting its normal apoptotic function and possibly contribute to increased cancer susceptibility. The treatment of such disorders would release ceramide, permit its normal anti-proliferative and pro-apoptotic function [24], and possibly reduce any potential increased cancer risk in these rare disease populations. Consistent with this hypothesis is the recent report of successful treatment of a mouse model of renal cell carcinoma with a glycosphingolipid inhibitor [28]. Such an inhibitor would increase the availability of free ceramide and allow it to exert its anti-tumor effect [28].

The small numbers of cancer cases reported in these populations make it difficult to reach a definitive conclusion about a causal link between sphingolipid accumulation and cancer risk; it may well be that authors do not systematically report all cases of malignancies in association with rare lysosomal disorders. The further study of cancer biology in tumors arising in these rare disease patient populations may also help to shed additional light on our current understanding of lipid dysregulation in the cancer biology of the general population.

Disclosures

BL Thurberg is an employee of Sanofi Genzyme. The other authors declare that they have no competing interests in relation to this work. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. D.P. Germain has received a site grant from the French Ministry of Health (Plan National Maladies Rares du Ministère des Affaires Sociales et de la Santé).

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