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DISSERTATION

“Molekulare und phänotypische Charakterisierung zweier monogener Entwicklungsstörungen des Nervensystems: MCT8 Defizienz & FOXG1 Syndrom”

“Molecular and phenotypic characterization of two monogenetic neurodevelopmental disorders: MCT8 deficiency & FOXG1 syndrome”

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Abstract **German version**

Einleitung Die menschliche Gehirnentwicklung ist komplex. Einzelne Mutationen können zu schweren Entwicklungsstörungen führen. In diesem Dissertationsprojekt habe ich zwei Erkrankungen untersucht. (**I**) Lokal ist die Gehirnentwicklung durch Transkriptionsfaktoren (TF) reguliert. Inaktivierende Mutationen des TF FOXG1 führen zu psychomotorischer Retardierung. Thesen zur Pathophysiologie stützten sich bisher auf Mausmodelle und klinische Daten. Neuropathologische Analysen existierten keine. (**II**) Neben lokalen Einflüssen regulieren endokrine Faktoren, z.B. Schilddrüsenhormone (SD), die zerebrale Genexpression. SD müssen mittels Transportern Zellmembranen der neurovaskulären Einheit überwinden, um intrazelluläre Rezeptoren zu binden. Mutationen des Transporters MCT8 führen zu einem Syndrom mit Entwicklungs-/Bewegungsstörungen. Zur gezielten Therapieentwicklung ist es notwendig, die genaue MCT8 Lokalisation zu identifizieren; für die topographische Diagnostik und für Erkrankungs-spezifische Perzentilen, den neurologischen Phänotyp exakt zu beschreiben.

Methoden (**I**) Wir führten immunhistochemische Analysen an Gehirnen zweier Feten mit *FOXG1* Syndrom und eine systematische Literatursuche zu den Grundlagen der Pathophysiologie durch. (**II**) Wir untersuchten die MCT8 Expression mittels Immunfluoreszenz in adulten humanen Gehirnen. Zur qualitativen und semi-quantitativen Analyse dynamischer Veränderungen, schlossen wir eine Altersserie murinen Gewebes und humane Organoide ein. Zur Bewegungsstörungsanalyse zeichneten wir Patientenvideos auf und werteten diese mittels einer Dystonie Skala aus.

Ergebnisse (**I**) Es zeigten sich ein reduziertes Gehirnvolumen, kortikale Schichtungsdefekte, veränderte neuronale Projektionen und weniger Interneurone. Ich konnte 35 Studien zur Pathophysiologie in Mausmodellen identifizieren. (**II**) MCT8 war konstant in „Barrieren des ZNS“ (Bluthirnschranke, *Plexus choroideus*, Tanyzyten) nachweisbar. In Neuronen konnte MCT8 früh postnatal im Gewebe der Maus, in neuronalen Progenitorzellen der Organoide, nicht aber in adulten Gehirnen detektiert werden. Analysen der Bewegungsstörungen stellten die Dystonie als vorwiegende, jedoch Hypotonie als schwerwiegendste Störung dar.

Diskussion (**I**) Beim FOXG1 Syndrom scheinen kortikale Schichtungsdefekte neuronale Projektionen zu verändern und eine verfrühte neuronale Differenzierung zu einem reduzierten Gehirnvolumen zu führen, assoziiert mit Entwicklungsstörungen. Frühe Strukturierungsdefekte des Gehirns scheinen eine erhöhte Ratio von exzitatorischer/inhibitorischer neuronaler Aktivität zu bedingen und somit zu Hyperkinesen zu führen. (**II**) MCT8 scheint wichtig zu sein, für den SD-Transport über die Bluthirnschranke und für die prä- und früh postnatale neuronale Entwicklung. Bewegungsstörungen der Patienten deuten auf eine wichtige pathophysiologische Rolle des MCT8 in den Basalganglien hin. Das humane „Zeitfenster der MCT8 Expression“ und die Rolle des motorischen Systems sollten Themen zukünftiger Studien sein.

Abstract **English version**

Introduction The achievement of developmental milestones in children depends on healthy brain development. Single gene mutations may have devastating consequences, leading to neurodevelopmental diseases (NDDs). In this dissertation project, I investigated two NDDs. (**I**) Locally, brain development is regulated by transcription factors (TF). Loss-of-function mutations of the TF FOXG1 cause a syndrome with psychomotor retardation. Knowledge about the pathophysiology so far relied on mouse models and clinical descriptions. Neuropathological data did not exist. (**II**) Besides local signals, endocrine factors such as thyroid hormones (THs) regulate cerebral gene expression. To bind their intracellular receptors, THs must be moved across membranes of the neurovascular unit *via* transporters. Mutations of the TH transporter MCT8 lead to a severe NDD, called MCT8 deficiency. For targeted therapies, it is necessary to identify the exact localization of MCT8 and, for topographic diagnostics and disease-specific percentiles to describe the neurological phenotype precisely.

Methods (**I**) We performed immunohistochemical analyses of two fetal brains with *FOXG1* syndrome and systematically searched for murine studies on its pathophysiology. (**II**) We analyzed the MCT8 expression in adult human brains by immunostaining. To test dynamic changes (qualitatively and semi-quantitively), we included a series of murine brains of different age and human organoids. Videos of patients with movement disorders (MDs) were captured and analyzed with a Dystonia Rating Scale.

Results (**I**) FOXG1$^{+/-}$ brains presented with reduced brain volumes, layering defects, deficient neuronal projections, and fewer interneurons. 35 articles were identified studying the pathophysiology. (**II**) MCT8 immunosignals were constantly detectable in the "barriers of the CNS" (blood-brain barrier, choroid plexus, tanycytes), but were only visible in murine neuronal populations early postnatally. Correspondingly, in human organoids, MCT8 immunosignals were present in solitary neuronal progenitor cells, but not in neurons of adult individuals. The analysis of MDs revealed dystonia to be a consistent feature, hypotonia, however, seemed to be the clinically most relevant disability.

Discussion (**I**) In FOXG1 syndrome, premature neuronal differentiation may cause a microcephaly that is associated with developmental delay. Impaired corticogenesis may result in deficient neuronal projections and early patterning defects may lead to an increased exhibition-to-inhibition ratio triggering hyperkinetic symptoms. (**II**) MCT8 seems to facilitate the transport over the blood-brain barrier independent of age and over specific neuronal cell membranes in the pre- and early postnatal phase. MDs of patients indicate a substantial pathophysiological role of the basal ganglia and the white matter. The human "time window of MCT8 expression" and the role of basal ganglia/ white matter still needs to be further defined.

Synopsis **Neurodevelopment in health and disease**

The neural tube develops from a single layer of neuroepithelium (for review see Sauka-Spengler & Bronner-Fraser 2008 [1]). Three primary (forebrain, midbrain, and hindbrain) and later five secondary cerebral vesicles (telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon) form in the fourth and fifth weeks of gestation (WG) (for review see Darnell & Gilbert 2017 [2]). Finally, the mammalian brain enables human children to achieve extraordinary motor, verbal, and social milestones.

This tightly regulated process depends on the expression of transcription factors that regulate gene expression. Forkhead Box G1 (FOXG1) is a transcription factor previously referred to as Brain Factor 1 (BF-1) due to its exclusive expression in the telencephalon [3,4]. Studies in mice suggest that its expression may be necessary for maintaining the pool of proliferating cells in the early ventricular zone [5], while its downregulation allows the migration of neurons from the inside to the outside through the intermediate zone [6]. Its re-expression is indispensable for reaching the final neuronal target – the cortical plate, which later becomes the cerebral cortex [7]. In addition to local factors, endocrine influences also play an important role during brain development. The early fetus obtains thyroid hormones (THs) from the mother through the placenta, but becomes able to synthesize own THs starting form weeks 8-10 of gestation. THs influence the expression of the 1,145 genes that are essential for the process of corticogenesis, such as the proliferation and migration of neurons (for review see Bernal 2017 [8]). Postnatally, THs remain critical for proper brain development, exemplified by untreated children with congenital hypothyroidism who are unable to walk and do not develop age-appropriate cognitive function (for review see Gruters & Krude [9]).

Therefore, subtle molecular changes can fundamentally disrupt neurodevelopment, leading to a diverse group of severe, early-onset neurodevelopmental disorders (NDDs). NDDs affect over 3% of children in the United States of America [10]. Variability in genetic etiology and heterogeneity in clinical phenotypes make the diagnostic process lengthy and costly. However, recent advances in genotype- and phenotype-based diagnostics have enabled the identification of more than 1,000 loci involved in complex NDDs and paved the way for the development of individualized therapeutic approaches [11,12]. In this translational dissertation project I have investigated the neurological phenotype and the pathophysiological mechanisms of two NDDs, **(i)** the Monocarboxylate Transporter 8 (MCT8) deficiency [13], caused by a dysfunctional TH transporter; and **(ii)** the Forkhead box G1 (FOXG1) syndrome [6] caused by dysfunction of a transcription factor.

Part I FOXG1 syndrome

1 Introduction

The action of the transcription factor FOXG1 is essential for the development of the telencephalon in mammals and for controlling the expansion of the dorsal telencephalon by promoting the growth of neurons [5,14] and interneurons [6,15–17] (**Figure 1**). Mutations of a single *FOXG1* allele cause FOXG1 syndrome [18]. Formerly referred to as a "*Congenital variant of Rett syndrome*" [19], descriptions of different phenotypes and advances in molecular diagnostics have led to the delineation of the "*FOXG1 syndrome*" as a distinct clinical entity [6,20,21,21,22] (OMIM #613454). Key features include severe microcephaly, developmental delay, dyskinetic movement disorders, epilepsy, movement stereotypes, and abnormal sleep patterns [6,20,22–32]. Neuroimaging studies in patients show consistent features such as microcephaly, dysgenesis of the *Corpus callosum*, and delayed myelination [28,31,33,34]. Currently, research into the underlying pathophysiology relies only on mouse models and suggests that depression of FOXG1 target genes may cause premature neuronal differentiation at the expense of the progenitor pool [35], as well as patterning and migration defects with impaired formation of cortico-cortical projections [6,36]. It remains an open question to what extent this recapitulates the pathophysiology of neurodevelopment in FOXG1-haploinsufficient patients [6]. In *Part I* of this dissertation project, I performed neuropathological analyses of two fetuses with FOXG1 syndrome [6]. To complement the descriptive data with information about functional analyses, I systematically searched and summarized the available literature for studies investigating the pathophysiological consequences of FOXG1 syndrome on brain development in mouse models.

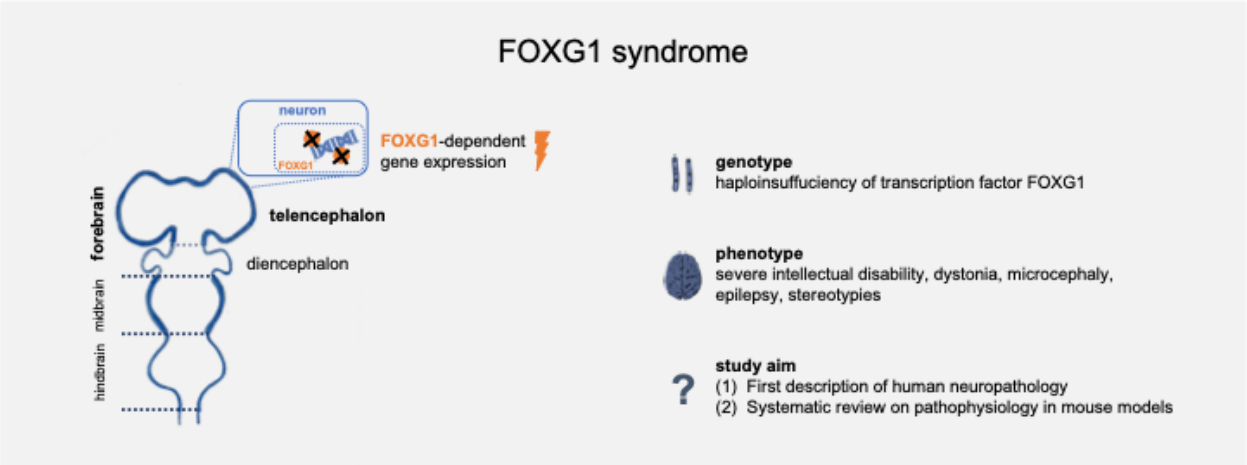

Figure 1. Genotype, phenotype, and study objectives of the FOXG1 syndrome project. Forkhead box G1 (FOXG1) is a transcription factor expressed in the telencephalon. Haploinsufficiency of FOXG1 in humans leads to a severe neurodevelopmental disorder, the FOXG1 syndrome, characterized by severe cognitive and motor dysfunction. To decipher the pathophysiology, we aimed to analyze the neuropathology of fetal cases with *FOXG1* mutations and discuss these descriptive results in the context of functional data from mouse models. [6] additional data. Unpublished figure, copyright by Nina-Maria Wilpert.

2 Results

Human neuropathology (published in Wilpert *et al.* **Eur J Med Genet 2021**)

To investigate the molecular consequences of FOXG1 haploinsufficiency on human brain development, we performed genetic testing and standardized macro- and microscopic neuropathological analyses of two fetal cases with suspected FOXG1 syndrome [6] (**summary in Table 1**). The first female fetal case (33 weeks of gestation, case 1) carried a

FOXG1 insertion of 1 bp at cDNA position 460 (c.460dupG), resulting in a frameshift and a stop codon further downstream (p.Glu154Glyfs*301) [6]. In the second female fetus (36 weeks of gestation, case 2), we identified a *FOXG1* nonsense mutation at the same cDNA position 460 (c.460G>T), but this resulted in an immediate premature termination stop codon (p.Glu154*) [6]. 17% of patients with FOXG1 syndrome carry mutations at cDNA position 460 [31]. Macroscopic analysis revealed that the first fetal brain was eutrophic (50th percentile) and the second brain was hypoplastic (< 5th percentile), despite overall eutrophic biometric data (95th percentile) of the entire fetus; cortical gyrification appeared to be delayed [6]. Interhemispheric connections seemed to be altered: In case 1, the *Corpus callosum* was absent and instead Probst bundles (projected axons unable to cross the midline) and thickened fornices were present [6]. In case 2, the *Corpus callosum* was present but thickened just like the fornices [6]. Furthermore, immunohistochemical qualitative and semi-quantitative analyses revealed severe layering defects with a reduction by one SATB2-positive neuron layer (special AT-rich sequence-binding protein 2; marker for upper layer neurons), more numerous CTIP2-positive neurons in layers II, V-VI (chicken ovalbumin upstream promoter transcription factor interacting protein 2; marker for motor neuron projections of layers V and VI) and ectopically distributed MAP2-positive (microtubule-associated protein 2, marker for migrating neurons), TBR1-positive (t-box brain transcription factor 1, marker for post-mitotic pyramidal neurons) and CUTL1-positive cells (CCAAT displacement protein 1, marker for upper layer neurons) in all layers [6]. In both cases, fewer inhibitory GABAergic and calretinin-positive interneurons were identified in the cortices and ganglionic eminences (GE, a transient structure from which the basal ganglia and most cortical inhibitory interneurons arise) [6]. We also observed a delay of myelination with an excessive occurrence of PDGFRα-positive (platelet-derived growth factor receptor A) oligodendrocyte progenitor cells, but fewer further developed OLIG2-positive (oligodendrocyte transcription factor) pre-oligodendrocytes [6]. Finally, gliosis (GFAP-positive cells, glia fibrillary acidic protein) was conspicuous in both telencephalons; in case 1, numerous neurons in layers II, III and V were calcified [6]. Potential clinical consequences of these macro- and microscopic findings of a reduced brain volume, altered interhemispheric connectivity, disrupted cortical layering, delayed myelination and (un)specific gliosis and neuronal calcification will be discussed in the **Discussion** on **page 10**.

Systematic review of mouse models (unpublished)

We then performed a systematic review of the pathophysiological consequences of *Foxg1* mutations in mouse models to complement our descriptive human data with potential mechanisms of function. After searching the PubMed database for specific search terms, we found 652 hits (**Figure 2**). Six additional studies were found by screening the reference lists of relevant articles. In total, 658 titles and abstracts were screened for eligibility (content dealing with the pathophysiology of FOXG1/Foxg1) which excluded three duplicates and another 596 studies. Then, I applied my specific inclusion and exclusion criteria on the remaining 59 full-text publications. The resulting 35 articles were included into our qualitative literature review (**summary in Table 1**).

In 1995, Xuan and colleagues were the first to study the consequences of "brain factor 1" mutations on brain development by developing a mouse model in which *Foxg1* was replaced by a lacZ/neo (β-galactosidase/neomycin) cassette [35]. Homozygous offspring exhibited early patterning defects and prematurely differentiating neurons, i.e. a reduced progenitor pool and strikingly reduced cerebral hemisphere volumes [35]. This genotype was lethal at birth [35]. In contrast, heterozygous mice with unaltered brains were described and were thus used as control brains for years [35]. Only one year after the description of the first patient with FOXG1 haploinsufficiency in 2005 [18], Shen

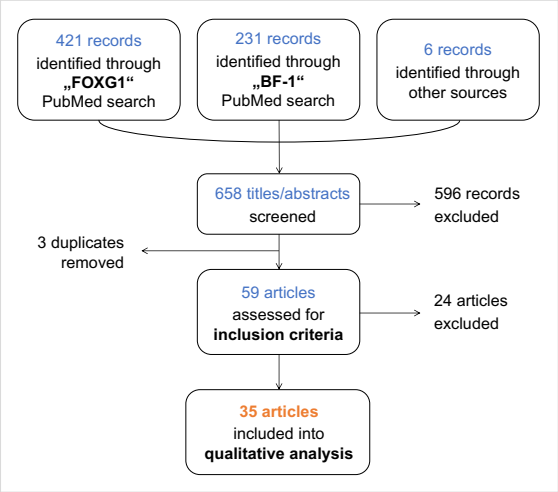

Figure 2. PRISMA flow diagram. A systematic MEDLINE (PubMed) search for defined terms identified 652 entries. Six additional publications were found *via* reference lists. 596 abstracts and titles were screened and excluded; three duplicates were removed. 59 publications were screened for eligibility, and finally 35 studies were included into the final descriptive analyses. FOXG1: Forkhead Box G1, BF-1: Brain Factor 1. Unpublished figure, copyright by Nina-Maria Wilpert.

and colleagues provided the first evidence of impaired neurodevelopment in the heterozygous offspring as well, which may more accurately reflect the human FOXG1 syndrome [37]. Since the genetic background of mice has also been shown to lead to subtle differences between mouse models [38], we have listed the different backgrounds and homo/heterozygosity in the summary of all studies (**Table 1**).

Foxg1 deficiency causes microcephaly, simplified gyrification and gliosis

Pioneering studies in Foxg1-deficient mice reported premature cell cycle exit and subsequent early differentiation at the expense of the progenitor pool in the telencephalon [35,39]. The shortened proliferation time therefore resulted in a reduction of total brain tissue volume with microcephaly [40] and simplified gyrification. Gliosis can either arise from increased initial gliogenesis or be triggered in response to pathological conditions of the central nervous system. Overexpression of *Foxg1* inhibits glial fate *in vitro* [37,41,42], whereas conditional silencing of *Foxg1* leads to increased gliogenesis and neurogenesis in *vivo*, supporting the notion that this may ultimately lead to an increased appearance of astroglia [43]. Furthermore, Tian and colleagues reported pronounced cell death of postmitotic neurons following transiently upregulated neurogenesis [43]. Therefore, the simultaneity of prematurely increased astroglia production and reactive glial expansion following neuronal injury could trigger gliosis in *Foxg1*-mutant mice.

FOXG1 deficiency impairs neuronal insight-out migration and callosal projection neurons

In total, 27 studies have investigated corticogenesis in mouse models with FOXG1 syndrome [5,7,17,34–39,43–60]. Dynamic expression of *Foxg1* critically regulates the maintenance of the progenitor pool in the ventricular zone [5], the migration of differentiating neuronal cells towards the cortical plate and entry into the latter [7]. Finally, Foxg1 continues to be expressed in layers II, III, V and VI, leading to the development of callosal projection neurons [60]. Severe migration defects of late-born through early-born neurons within the cortical plate have been described in homozygous mice with *Foxg1* mutations [36]. Of note, heterozygous *Foxg1* mice also exhibit delayed insight-out migration of upper layer neurons. In addition to impaired migration, it has also been reported that depression of *Foxg1* target genes (e.g. *Tbr1* encoding T-box brain transcription factor 1; *Fezf2* encoding family zinc finger 2; *Nr2f1*

encoding COUP-TFI: chicken ovalbumin upstream promoter transcription factor 1) results in longer deep-layer cell fate at the expense of upper-layer neurons [55,60]. In any case, upper layer neurons are reduced in the postnatal cortices of *Foxg1* mutant mice [36,45,60]. Cargnin and colleagues described underdeveloped glia of the *Indusium griseum* in the midline and impaired formation of the repressive complex Foxg1-Rp58 (repressor protein 58), both of which are critical for axonal guidance [36]. Axonal tracing experiments in *Foxg1* heterozygous mice revealed failure of callosal axons to cross the midline but accumulation of the latter forming misled fiber bundles [36]. Collectively, these findings strongly suggest that Foxg1 haploinsufficiency impairs the identity of projecting neurons, insight-out migration, and guidance of cortico-cortical projections. More recently, semi-quantified immunostaining in Foxg1 heterozygous mice showed that the fornix, another white matter bundle, is enlarged [34]. However, whether similar mechanisms are responsible for the misdirection of these hippocampal efferences needs to be clarified in future studies.

Foxg1 deficiency causes underdeveloped basal ganglia and fewer inhibitory interneurons

During embryogenesis, Foxg1-deficient mice show conspicuous patterning defects with an enlarged dorsal telencephalon and loss of ventral structures [61]; only a remnant of the ganglionic eminence is preserved [35,44,47,62,63]. Moreover, chemotactic signals (Sema3A/3F: semaphorin 3A/3F) and receptors (Robo1: roundabout guidance receptor 1; EphA4: ephrin type A receptor 4; Cxcr4/7: C-X-C chemokine receptor 4/7) of interneurons are severely dysregulated, resulting in tangential and radial migration defects [17,56]. Finally, *Foxg1* mutant mice show postnatally underdeveloped basal ganglia [38,56,63], mis-layered and fewer cortical interneurons, and an increased ratio of excitatory to inhibitory (E/I) synapses [17,38,56,64]. *In vitro*, Chen and colleagues demonstrated decreased electrophysiological excitability of *Foxg1*-deficient somatostatin-positive interneurons [64] and an increased seizure susceptibility to pentylenetetrazole [65,66] in *Foxg1*-mutant mice *in vivo* [17,64]. Overall, *Foxg1* syndrome during murine brain development results in severely impaired differentiation of the ganglionic eminence, impaired interneuron migration, increased cortical E/I ratio and subsequently predisposes to epilepsy.

Foxg1 deficiency causes transient oligodendrocyte differentiation defects

Several studies in *Foxg1* mutant mice have revealed distinct patterning defects with underdeveloped ventral specification (Shh) but expanded dorsal markers [47,62,67]. Physiologically, Shh is expressed in the medial ganglionic eminence and anterior entopeduncular area [68,69] and induces Olig2, which is essential for oligodendrocyte lineage differentiation [70–73]. In *Foxg1* mutant mice, only an underdeveloped ganglionic eminence with rare $Olig2^{+}$ cells was observed at E12.5, the time of production of the first oligodendrocyte progenitor cells [63]. Therefore, the lack of Shh-dependent Olig2-induction could be responsible for the reduced formation of oligodendrocyte progenitor cells. However, single-cell analyses show that forebrain oligodendrocyte progenitor cells express high levels of Foxg1 [74]. Therefore, Foxg1 deficiency could also lead to cell autonomous oligodendrocyte differentiation defects. However, this is unlikely since *Foxg1* mutant cells respond adequately to Shh stimulation and show rescued Olig2 expression in *vitro* [62]. Finally, no myelination defect is reported in adult Foxg1-deficient mice, suggesting that the second and third waves of oligodendrocyte progenitor cell production - although they share the same transcriptional profiles but are differentially Shh-dependent - may compensate for the embryonic failure of oligodendrocyte progenitor cell generation [75]. Finally, pre-oligodendrocytes can efficiently mature into myelinating oligodendrocytes. However,

Table 1. Brain abnormalities in human and murine FOXG1/Foxg1 syndrome. GE: ganglionic eminence, na: not applicable, WG: weeks of gestation, E: embryonic days, P: postnatal days, ns: not specified, SW: Swiss Webster. Unpublished table, copyright by Nina-Maria Wilpert.

Studies on humans	Background	Genotype	Age	Early patterning defect	Reduced brain volume	Less proliferation, premature differentiation	Cortical layering defects	Altered neuronal projections	Impaired GE/ basal ganglia	Increased E/I interneurons ratio	Delayed oligodendrocyte differentiation	Astrocytosis	Decreased neuronal survival
Wilpert *et al.* 2021 (Eur J Med Genet) [6]	na	Foxg1 +/-	33, 36 WG		x		x	x	x	x	x	x	x
Studies on mice	**Background**	**Genotype**	**Age**										
Xuan *et al.* 1995 (Neuron) [35]	C57BL/6J	Foxg1-/-	E9.5-12.5	x	x	x			x				
Dou *et al.* 1999 (Cereb Cortex) [44]	C57BL/6J	Foxg1-/-	E10.5-12.5	x	x	x			x				
Hanashima *et al.* 2002 (J Neurosci) [39]	C57BL/6J	Foxg1-/-	E11.5-14.5	x	x	x			x				
Vyas *et al.* 2003 (J Comp Neurol) [40]	ns	Foxg1-/-	E12.5-17.5	x									
Hanashima *et al.* 2004 (Science) [5]	C57BL/6J	Foxg1-/-	E8.5-18.5			x							
Seoane *et al.* 2004 (Cell) [45]	C57BL/6	Foxg1-/-	E12.5			x							
Muzio *et al.* 2004 (J Neurosci) [46]	C57BL/6	Foxg1-/-	E11.5-19.5	x		x			x				
Martynoga *et al.* 2005 (Dev Biol) [47]	CBAxC57BL/6	Foxg1-/-	E8.5-14.5	x	x	x							
Zhao *et al.* 2006 (Brain Res) [48]	ns	Foxg1-/-	E11.5-14.5	x		x							
Shen *et al.* 2006 (Hippocampus) [37]	C57BL/6J, SW	Foxg1+/-	E18.5-P128	x	x								x
Hanashima *et al.* 2007 (J Neurosci) [49]	SW	Foxg1-/-	E11.5-16.5	x		x							
Eagleson *et al.* 2007 (Neuroscience) [38]	C57BL/6J	Foxg1+/-	P4-60	x	x		x						
Siegenthaler *et al.* 2008 (Dev Biol) [51]	C57BL/6	Foxg1+/-	E12.5-13.5			x							
Siegenthaler *et al.* 2008 (Cereb Cortex) [50]	C57BL/6J	Foxg1+/-	E13.5-P6		x	x	x						
Fasano *et al.* 2009 (Genes Dev) [52]	SW	Foxg1-/-	ns				x						
Manuel *et al.* 2010 (Development) [62]	CBAxC57BL/6	Foxg1-/-	E12.5-16.5	x							x		
Manuel *et al.* 2011 (Neural Dev) [53]	129Sv	Foxg1-/-	E12.5			x							
Tian *et al.* 2012 (J Neurosci) [43]	ns	Foxg1-/-	P5-97		x	x						x	x
Miyoshi *et al.* 2012 (Neuron) [7]	SW	Foxg1-/-	E14.5-19.5			x							
Kumamoto *et al.* 2013 (Cell Rep) [54]	CD1	Foxg1-/-	E11.5-18.5			x	x						
Toma *et al.* 2014 (J Neurosci) [55]	ns	Foxg1-/-	E14.5-18.5				x						
Frullanti *et al.* 2015 (Eur J Hum Genet) [76]	ns	Foxg1+/-	P30						x				
Vezzali *et al.* 2016 (Oncotarget) [57]	ns	Foxg1-/-	E11.5-16.5			x							
Yang *et al.* 2017 (Cereb Cortex) [56]	ns	Foxg1-/-	E13.5-18.5	x		x			x	x			
Godbole *et al.* 2017 (Development) [77]	C57BL/6	Foxg1-/-	E12.5-14.5	x									
Cargnin *et al.* 2018 (Neuron) [36]	C57BL/6N	Foxg1-/-	E14.5-P7		x		x	x					
Han *et al.* 2018 (Front Cell Neurosci) [58]	ns	Foxg1-/-	E14.5-18.5	x			x						
Quintana-Urzainqui *et al.* 2018 (iScience) [59]	ns	Foxg1-/-	E13.5-15.5			x							
Liu *et al.* 2018 (Mol Brain) [78]	CD1	Foxg1-/-	E12.5-18.5					x					
Shen *et al.* 2019 (Cereb Cortex) [17]	ns	Foxg1-/-	P2-14							x			
Hou *et al.* 2019 (Nat Commun) [60]	ns	Foxg1-/-	E14.5-P8				x	x					
Yu *et al.* 2019 (Mol Brain) [79]	C57BL/6J, ICR	Foxg1-/-	P90					x					
Du *et al.* 2019 (Cereb Cortex) [63]	ns	Foxg1-/-	E11.5-18.5	x					x	x			
Pringsheim *et al.* 2019 (Ann Clin Trans Neurol) [34]	C57BL/6	Foxg1+/-	P70		x			x	x				
Chen et al. 2019 (Cereb Cortex) [64]	C57BL/6J	Foxg1-/-	E18.5-P60				x			x			

the function of Foxg1 within the oligodendrocyte lineage remains highly speculative and it would be interesting to clarify it in future studies

3 Discussion

Mouse models have led to the identification of important pathophysiological principles in Foxg1/FOXG1 syndrome. In general, it is difficult to draw direct pathophysiological conclusions from the study of mouse brain development to the human situation, given the fact that mouse brain development proceeds at a different time scale and the number of synaptic connections are much less [80]. Nevertheless, the present results in human fetuses confirm most of these findings from the field of mouse genetics: FOXG1 haploinsufficiency can lead to severe layering defects that primarily affect upper layer projecting neurons, resulting in altered interhemispheric connections [6]. Yet, clinical consequences remain to be determined since even a complete agenesis of the *Corpus callosum* causes a wide variety of phenotypes [81] ranging from asymptomatic to severely affected patients with cognitive deficits. In addition, a reduced number of inhibitory interneurons may cause the dyskinetic-epileptic symptoms. Further, in humans the maturation of the oligodendrocyte lineage may be delayed but compensated [6]. The improvement of myelination, however, is not going in parallel with substantial developmental steps by the patients, thereby remaining clinically rather unsignificant. Reduced brain volumes could be observed in one case; clinically microcephaly is present in ~50% of patients, which is associated with cognitive and motor developmental delay as present in ~67% of children with FOXG1 syndrome. Finally, we provide first evidence of neuronal calcification and gliosis [6], which may be either a sign of hypoxic neuronal damage with subsequent reactive gliosis or of a primarily increased gliogenesis.

These observations provide a crucial starting point to decipher the pathophysiology of human patients with FOXG1 syndrome in the future. For detailed discussion, we refer to the published data (**page 37**), which we do not wish to repeat here.

4 Methods and contributions

Trio-based panel sequencing and standardized macroscopic, immunohistochemical, and semi-quantitative analyses were performed to describe human neuropathology [6]. Detailed methods can be found in the published data (**page 34**) [6].

Table 2. Inclusion and exclusion criteria. 59 studies as of September 1, 2019 were screened for eligibility using criteria on tissue, species, methods, reported data, and type of publication. Unpublished table, copyright by Nina-Maria Wilpert.

	Inclusion	Exclusion
Tissue	cerebral tissue	other tissue
Species	human rodents	other species
Methods	characterization of loss-of-function models	characterization of gain-of-function models
Reported data	peer-reviewed journals full text in English up to September 2019	non-peer-reviewed publications abstracts only
Type of the publication	original articles	review articles expert opinions conference proceedings

A systematic review of mouse models was done through a MEDLINE (PubMed) search using the search terms (**"BF-1" OR "FOXG1")** in all fields by September 1, 2019. In addition, references of eligible publications were subsequently filtered for relevant studies. Criteria deciding on the inclusion of studies were defined depending on the type of tissue, the species, applied methods, reported data, and the type of publication (**Table 2**).

A first reviewer (Nina-Maria Wilpert, NMW) checked titles and abstracts and applied defined inclusion and exclusion criteria to full-text articles. A second reviewer (Nadia Bahi-Buisson, NBB) was consulted if there was uncertainty about the inclusion of a publication. The following data were extracted: (i) study design, (ii) genetic background of the mouse strain, (iii) genetic methods used to obtain a *Foxg1* knock-out, (iv) age of the mice, (v) brain regions studied, (vi) brain alterations, and (vii) methods. Finally, the data were summarized descriptively with a focus on the effects of *Foxg1* mutations on brain development.

Table 3. Methods and contributions of neuropathological analysis of FOXG1 syndrome. In a first step, a standardized neuropathological analysis of two fetal cases with *FOXG1* mutations was performed. In a second step, the literature was systematically searched for functional data on the effects of *Foxg1* mutations on mouse brain development. WG: weeks of gestation, SD: Séverine Drunat, TAB: Tania Attié-Bitach, JM: Jelena Martinovic, AT: Aude Tessier, YC: Yline Capri, FG: Fabien Guimiot, AL: Annie Laquerrière, FR: Ferechté Razavi, FM: Florent Marguet, CM: Camille Maillard, NMW: Nina-Maria Wilpert, NBB: Nadia Bahi-Buisson. [6] additional data. Unpublished table, copyright by Nina-Maria Wilpert.

Methods	Material	Contributions
1 Neuropathology, immunohistochemical analysis		
1.1 Genetic analysis	Foetal brain, case 1 (33 WG),	SD, TAB
1.2 Collection of clinical data	Foetal brain, case 2 (36 WG)	JM, AT, YC
1.3 Autopsy		FG, JM
1.4 Standardized neuropathological, IHC labeling		FG, AL, FR
1.5 Visual analysis, interpretation		NMW, FM, CM, AL
1.6 Imaging		FM
2 Publication		
3.1 Creating figures, tables	First human neuropathological	FM
3.2 Writing first draft of manuscript	results of FOXG1 syndrome	NMW, AL
3.3 Editing and reviewing manuscript		all authors
3 Systematic literature search		
2.1 Defining search terms, exclusion/inclusion criteria	Published data on	NMW (NBB)
2.2 Database search	FOXG1 syndrome mouse models	NMW
2.3 Applying exclusion/inclusion criteria		NMW
2.4 Data collection and interpretation		NMW (NBB)

The author of this dissertation project (NMW) conducted the systematic literature search starting from the definition of the search terms to the interpretation and discussion of the extracted data under the supervision of NBB (**Table 3**). In addition, NMW, together with FM (Florent Marguet), CM (Camille Maillard) and AL (Annie Laquerrière), analyzed and interpreted the standardized macro- and microscopic analyses of two fetal cases [6]. The first draft of a manuscript was written by NMW and AL; edits and revisions were dynamically incorporated into the manuscript by NMW [6].

Part II MCT8 deficiency

5 Introduction

The development of the mammalian brain critically depends on the action of THs. However, it should be noted that the uptake of THs into the shielded neurons is a complex process that requires a number of players (**Figure 3**) [13]. The neurons are shielded from the blood stream by the blood-brain barrier (BBB) [82], which is formed by the neurovascular unit (NVU), which comprises endothelial cells, scattered pericytes and the *glia limitans*, which is formed by astrocytic end feet [13,83,84]. Consequently, L-thyroxine (T4) and the more active TH 3,3',5-triiodothyronine (T3) require transmembrane transporters to transport T3/T4 across the luminal and abluminal membranes of each cell type in the NVU [13,85]. It is now well established that a wide range of transmembrane transporters are involved in cellular TH uptake, including Monocarboxylate Transporter 8 (MCT8) [86,87].

The consequences of inactivating mutations of a single TH transporter – here MCT8 – illustrate the fragility of spatiotemporal regulation of cerebral TH transport and hormone action [88,89]. While the first phenotypic descriptions of this disease were published in 1944 [90], the underlying molecular causes remained unknown for a long time. Finally, in 2004, X-linked mutations in the *SLC16A2* (Solute Carrier Family 16 Member 2, encoding MCT8) gene were identified as the cause of the syndrome formerly known as Allan-Herndon-Dudley syndrome (AHDS, OMIM #300523) [88,89]. Since then, more than 320 individuals with a variety of different *SLC16A2* mutations have been identified worldwide (for review see Grijota-Martínez *et al.* 2020 [91]). However, the condition may still be far under-diagnosed because the usual screening parameter, the serum levels of thyroid stimulating hormone (TSH), is not altered and T3 measurements (which would be expected to be extremely high) are not usually performed [92]. In the phenotypic descriptions of larger cohorts, the most striking features were axial hypotonia, dystonia, spasticity, intellectual disability, cachexia, and the inability to walk or talk in most cases [92,93].

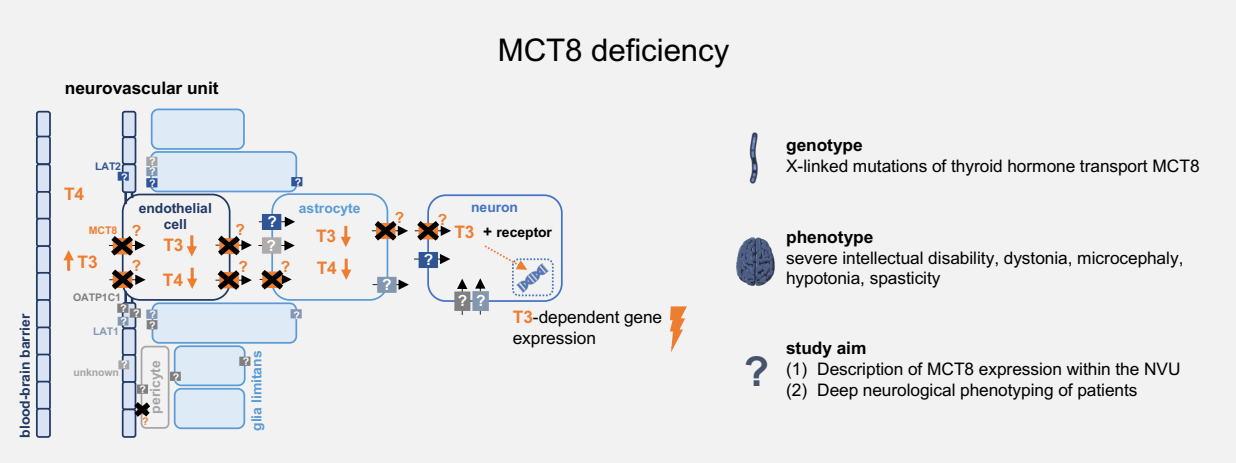

Figure 3. Genotype, phenotype and study objectives of the MCT8 deficiency project. Thyroid hormones (THs) must be transported across multiple neurovascular unit (NVU) membranes to reach their neuronal TH receptor, which affects gene expression. X-linked mutations of the TH transporter monocarboxylate transporter 8 (MCT8) lead to a severe neurodevelopmental disorder, MCT8 deficiency. To develop targeted therapies, we wanted to describe the precise localization of MCT8 within the NVU. We also wanted to describe the phenotype in detail. This could provide a topographical understanding of patient pathophysiology and serve for disease-specific percentiles of motor, verbal, and social milestones. [13,94], additional data. Unpublished figure, copyright by Nina-Maria Wilpert.

Postnatal treatment trials with MCT8-idependent TH analogues have so far failed to improve the neurological phenotype [95]. Only recent prenatal T4 substitution of an affected male fetus appeared to allow age-appropriate development of the 31-month-old child described [96]. The development of targeted therapies in the future critically depends on (1) knowing the precise localization of MCT8 within the NVU, (2) identifying the temporal changes in MCT8 expression during brain development to define the window of opportunity for therapies, and (3) accurately describing the neurological phenotype.

6 Results

Cerebral MCT8 expression (published in Wilpert *et al.* **Thyroid 2020**)

Ther reader can find the detailed results in the published data (**page 48**). In summary, antibodies targeting MCT8/Mct8 were tested using stably MCT8-transfected cell lines and Mct8 knockout (KO) mice [13]. No false-positive or -negative immunosignals were detected [13]. We then optimized the protocol for the preparation of highly sensitive human brain tissue and for the discrimination of autofluorescence based on, e.g. lipofuscin accumulation and erythrocytes in human brains that have not been perfused prior to fixation [13]. Finally, we performed immunolabeling studies in 19 different brain regions (frozen tissue, ethanol-fixed) from human body donors (age ≥78 years) [13]. Surprisingly, we found that MCT8 immunosignals were restricted to endothelial cell membranes only (**summary in Table 4**) [13].

Table 4. Overview of cerebral MCT8/Mct8 expression analyses. In immunolabeling studies of human, murine, and human organoid tissues, we found that MCT8/Mct8 is consistently expressed in the central nervous system barriers. However, neuronal expression appeared to disappear during postnatal development. E: embryonic stage, P: postnatal day, na: not assessed, +++: very strong immunolabeling (IL) signal, ++: strong IL signal, +: positive IL signal, -: no IL signal. After Wilpert *et al.* 2020 [13].

		E	P6	P12	P21	≥P83
RODENTS	cortical neurons	na	+++	++	+	-
	hippocampal neurons	na	+++	++	+	-
	islands of Calleja	na	+++	++	+	-
	amygdala neurons	na	+++	++	+	-
	cerebellar neurons	na	+++	-	-	-
	other neurons	na	-	-	-	-
	choroid plexus	na	+++	+++	+++	+++
	tanycytes	na	+++	+++	+++	+++
	endothelial cells	na	+++	+++	+++	+++
HUMAN		**organoid**	**child**	**adolescent**		**adult**
	neurons	+++	na	na	na	-
	endothelial cells	na	na	na	na	+++

To exclude false-negative results due to tissue destruction (*post mortem* delay of 20-48 hours), we validated our results in a cortical postoperative brain sample (age 50 years) and obtained similar results [13]. To test for possible dynamic changes in Mct8 expression during brain development, we systematically analyzed mouse brains from postnatal day six to postnatal day 83 [13]. Mct8 immunosignals were found – as in humans – within the blood-brain barrier as well as in other "central nervous system barriers" such as ependymal cells of the choroid plexus and in tanycytes [13]. No dynamic changes in Mct8 expression were detected in these structures [13]. In contrast, Mct8 immunosignals were observed in the membranes of specific neuronal populations only during early postnatal stages [13]. Semi-quantitative analyses of immunolabeling results underscored these visual impressions [13]. To test whether human progenitor cells

also express MCT8, as observed in mice, we repeated our protocol on human forebrain-like organoids [13]. Indeed, MCT8 immunosignals were present in developing human neurons [13].

Movement disorders in MCT8 deficiency (published in Masnada *et al.* **Mol Genet Metab 2021**)

For topographic diagnostics, we have contributed to an in-depth characterization of movement disorders in patients with MCT8 deficiency [94]. Detailed results can be found in the published data (**page 66**). The investigators recorded a total of 27 standardized videos of the movement disorders in MCT8 patients, and two pediatric neurologists analyzed the video material [94]. A dystonic movement disorder was observed [94] in the majority of children (25/27). However, using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), dystonia was found to be the predominant movement disorder in only a minority of cases (5/27), and the severity of dystonia was quite low (average 18.7/104.0) [94]. The mean disability score of the patients was 25.4/30.0 [94]. However, muscle hypotonia was also present in 25/27 of the patients and appeared to be the predominant movement disorder in 19/25 patients [94].

7 Discussion

Children with MCT8 deficiency suffer the consequences of a reduced TH supply to the brain and an excess of systemic THs leading to peripheral hyperthyroidism (e.g. leading to increased heart rate, muscle wasting, and low body weight) (for review see van Geest *et al.* 2020 [97]). Knowledge of the precise localization of MCT8 within the NVU is critical for the development of targeted therapies. In our histological analyses of brain tissue, we found that MCT8/Mct8 is constantly expressed in the barriers of the central nervous system during development and at the adult stage [13]. In contrast, MCT8/Mct8 expression was restricted to specific neuronal membranes of progenitor cells in human cerebral organoids or in early differentiated neuronal populations in mice [13]. However, the transferability of MCT8/Mct8 expression data and conclusions therefrom may be limited by species differences [13,98]. These differences are suspected because mouse models of MCT8 deficiency do not remotely recapitulate the human phenotype [99,100]. Other TH transporters (OATP1C1: organic anion transporter1 C1) have been found to compensate for TH transport across the BBB in *Mct8* knockout mice [99,100], but not in humans. Whether the time- and region-specific neuronal Mct8 expression also applies to humans needs to be clarified in future studies. It will be necessary **(i)** to investigate a time window of human MCT8 expression for potential postnatal therapies and **(ii)** to identify the exact neuronal populations that express MCT8. This information would be crucial for drug development because misdirected THs may have devastating consequences due to ectopic TH action. For more detailed information on cerebral MCT8 expression, see the published data (**page 57**).

First described by endocrinologists, children with MCT8 deficiency have recently been diagnosed primarily on the basis of characteristic laboratory findings such as normal TSH despite elevated T3 levels and subsequent panel sequencing. However, with advances in genetic diagnostics (particularly whole-exome sequencing), the number of affected children in child neurology clinics seeking medical attention with the presenting complaint of "developmental delay" has increased. Recent cohort studies have shown that the phenotypic spectrum of MCT8 deficiency is broader than previously expected [92,93]. In our study analyzing patients' movement disorders, we found that dystonia, although present in most patients, was not the predominant symptom [94]. Instead, muscle hypotonia seemed to be the most severe feature [94] raising the question of the pathophysiological involvement of myelination delay or basal ganglia dysfunction in MCT8 deficiency. The natural history of patients with MCT8 deficiency needs to be studied

in detail, not only for topographic neurological diagnosis to better understand the pathophysiology, but also for the development of disease-specific percentiles of motor, verbal, and social milestones, which have recently been lacking as control data in treatment studies [95]. For a detailed discussion of the phenotype, we refer the reader to the published data (**page 67**).

8 Methods and contributions

The detailed methods have been published elsewhere (see **page 45**). In summary, we tested antibodies against MCT8/Mct8 (NBP2-57308, Lot no. 100566; Novus) against established but recently "out of stock" antibodies (HPA003353, Lot no. A61491; Atlas) [13]. To exclude false-negative results, we compared immunosignals in cell lines (MDCK1: Madin-Darby canine kidney cell lines) stably transfected with N-terminal HA (hemagglutinin)-labeled MCT8 [13]. To exclude false-positive results, immunolabeling was performed in control *versus* knockout mice (n=4 each) [13]. For immunohistochemical and -fluorescent studies, 19 brain regions from older body donors (age 78-82 years, *post mortem* delay 20-48 hours) and one cortical postoperative tissue (age 50 years, post explantation delay 0 minutes) were freshly frozen [13]. Just before performing immunostaining, the tissue was fixed with ethanol [13]. Specific immunosignals were distinguished from non-specific autofluorescence using a control channel approach [13]. Tissue preparation in mice was performed in a similar manner [13]. Brain tissue from mice from postnatal day 6-83 was included in semi-quantitative analyses (n=4 each) [13]. The mean fluorescence intensities of the regions of interest were recorded and compared [13]. One-way analysis of variance (ANOVA) with Tukey's multiple comparisons test was performed for statistical analyses [13]. Human cerebral organoids were prepared according to a modified protocol by Lancaster and Knoblich [13,101]. For immunolabeling studies, forebrain-like organoids from culture day 21-50 were used [13].

The author of this dissertation project (NMW) performed antibody validation (in cell lines and tissue) and tissue preparation of murine and human tissues (in addition to mouse killing and human neurosurgery) (**Table 5**) [13]. Human brain organoid preparation was performed by RO (Robert Opitz), DS (David Sebing), PK (Peter Kühnen), PM (Philipp Mergenthaler), and HS (Harald Stachelscheid) [13]. All immunolabeling analyses were performed by NMW, including qualitative analyses, imaging, and semi-quantitative analyses [13]. The figures (except for the supplementary figures of human brain organoids) were prepared by NMW [13]. NMW wrote the first draft of the manuscript, dynamically added comments, and prepared several revisions during the peer review process [13].

For the analysis of movement disorders, a total of twelve centers recorded videos of n=27 children with MCT8 deficiency according to a predefined protocol [94]. Two independent pediatric neurologists who are experts in hereditary white matter disorders analyzed the videos and extracted quantitative data on the occurrence of movement disorders, the predominant movement disorders and applied the BFMDRS [94]. The detailed methods have been published elsewhere (see **page 66**). NMW contributed with video recordings of four German patients with MCT8 deficiency [94]. The first draft of the manuscript was written by DM and DT; NMW edited the manuscript (**Table 6**) [94].

Table 5. Methods and contributions of cerebral MCT8/Mct8 expression analysis. In a first step, antibodies recognizing MCT8/Mct8 were validated. Then, immunohistochemical/-fluorescence studies were performed on human brain tissue from older body donors, postnatal mouse brain tissue, and human forebrain-like organoids. Dynamic changes were analyzed semi-quantitatively. IF: immunofluorescence, IHC: immunohistochemistry, MCT8: monocarboxylate transporter 8, KO: knockout, y: years, d: days, P: postnatal days, F: figure, S: supplementary data, NMW: Nina-Maria Wilpert, SP: Sarah Paisdzior, EW: Eva K. Wirth, JS: Joachim Spranger, MK: Martin Krueger, IB: Ingo Bechmann, HB: Heike Biebermann, PV: Peter Vajkoczy, AS: Angela Schulz, RO: Robert Opitz, HS: Harald Stachelscheid, PK: Peter Kühnen, PM: Philipp Mergenthaler, DS: David Sebinger. [13] additional data. Unpublished table, copyright by Nina-Maria Wilpert.

Methods	Material	Contributions
1 Optimization of IF, IHC protocol		
1.1 Validation of the MCT8 antibodies	MCT8-knock-out mice, -transfected cells	NMW, SP, EW, JS
1.2 Comparison of different tissue preparations	Human brain tissue	NMW (MK, IB, HB)
2 Immunofluorescence, immunohistochemical analysis		
2.1 Autopsies	Body donor brain tissue (78-82 y)	NMW, MK, IB
2.2 Operative tissue collection	Cortical human brain (50 y)	NMW, PV
2.3 Preparation of murine tissue	Murine brain tissue (P6-P154)	AS, EW
2.4 Generation of cerebral organoids	Cerebral organoids (21-50 d)	RO, HS, PK, PM, DS
2.5 Tissue embedding		NMW (MK, IB)
2.6 Tissue cutting		NMW (MK)
2.7 IF and IHC labeling		NMW (MK, IB, HB)
2.8 Semi-quantification of the IF signals		NMW (MK, IB, HB)
2.9 Visual analysis and interpretation		NMW (MK, IB, HB)
3.0 Imaging		NMW (MK, IB)
3 Publication		
3.1 Creating figures and tables	Results of MCT8/Mct8 expression in	NMW, F8/S5/S6: RO
3.2 Writing the first draft of the manuscript	cerebral human, murine tissue,	NMW
3.3 Editing and reviewing the manuscript	and organoids	all authors

Table 6. Methods and contributions to phenotyping of MCT8 deficiency. Videos of movement disorders were recorded in n=27 patients with MCT8 deficiency. The movement disorders were analyzed by two pediatric neurologists. MCT8: monocarboxylate transporter 8, y: years, MDs: movement disorders, BFMD: Burke-Fahn-Marsden Dystonia, NMW: Nina-Maria Wilpert, MS: Markus Schuelke, HK: Heiko Krude, SM: Silvia Masnada, DT: Davide Tonduti. additional data. [94] additional data. Unpublished table, copyright by Nina-Maria Wilpert.

Methods	Material	Contributions
1 Analyzation of movement disorders		
1.1 Recording of the videos	Standardized video of 27 patients	4 cases: NMW, MS, HK
1.2 BFMD Rating Scale	with MCT8 deficiency (0.9-18.5 y)	SM, DT
1.3 Interpretation of results		SM, DT
2 Publication		
2.1 Creating figures and tables	Results of MDs analysis	SM, DT
2.2 Writing the first draft of the manuscript		SM, DT
2.3 Editing and reviewing the manuscript		all authors

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Eidesstattliche Versicherung

„Ich, Nina-Maria Wilpert, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Molekulare und phänotypische Charakterisierung zweier monogener Entwicklungsstörungen des Nervensystems: MCT8 Defizienz & FOXG1 Syndrom“/“Molecular and phenotypic characterization of two monogenetic neurodevelopmental disorders: MCT8 deficiency & FOXG1 syndrome” selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit der Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation als Top-Journal im Rahmen der Promotionsverfahren zum MD/PhD

Publikation 1

Wilpert N-M, Marguet F, Maillard C, Guimiot F, Martinovic J, Drunat S, Attié-Bitach T, Razavi F, Tessier A, Capri Y, Laquerrière A, Bahi-Buisson N. Human neuropathology confirms projection neuron and interneuron defects and delayed oligodendrocyte production and maturation in FOXG1 syndrome. Eur J Med Genet. 2021 Sep;64(9):104282.
Beitrag im Einzelnen:

- Auswertung und Interpretation neuropathologischer Analysen zweier Feten mit FOXG1 Syndrom
- Durchführung einer systematischen Literaturrecherche zu pathophysiologischen Grundlagen des FOXG1 Syndroms in murinen Modellen inklusive:
    - Definition und Anwendung der Such-, Ein- und Ausschlusskriterien
    - Durchführung der systematischen PubMed Suche
    - Datenkollektion und -analyse
- Verfassung des Erstentwurfs eines Manuskriptes in Zusammenarbeit mit Annie Laquerrière
- Bearbeitung des Manuskriptes während des Revisionsprozesses

Publikation 2 (Top-Journal)

Wilpert NM, Krueger M, Opitz R, Sebinger D, Paisdzior S, Mages B, Schulz A, Spranger J, Wirth EK, Stachelscheid H, Mergenthaler P, Vajkoczy P, Krude H, Kuhnen P, Bechmann I, Biebermann H. Spatiotemporal Changes of Cerebral Monocarboxylate Transporter 8 Expression. Thyroid. 2020 Sep;30(9):1366-83.
Beitrag im Einzelnen:

- Validierung der anti-MCT8/Mct8 Antikörper im Zellkultur-, Mausmodell und auf humanem Gewebe
- Protokolloptimierung insbesondere verschiedener Gehirngewebeaufarbeitungen
- Gewebeentnahmen zerebralen, humanen Gewebes von Körperspendern in Zusammenarbeit mit der Anatomie (Ingo Bechmann, Martin Krüger)
- Gewebeentnahmen zerebralen, humanen Gewebes intraoperativ in Zusammenarbeit mit der Neurochirurgie (Peter Vajkoczy)
- Gehirngewebeaufarbeitung (Einbettung, Schneiden)
- systematische Immunfluoreszenz und immunhistochemische Färbemethoden
- visuelle und semi-quantitative Analyse der Gewebeschnitte
- mikroskopische Aufnahmen
- Erstellung der
    - Abbildungen 1-7, anteilig Abbildung 8
    - Tabellen 1, 2
    - Abbildungsanhang 1-4, Tabellenanhang 1, 2
- Verfassung des Erstentwurfs eines Manuskriptes
- Bearbeitung des Manuskriptes während des Revisionsprozesses

Publikation 3

Masnada S, Sarret C, Antonello CE, Fadilah A, Krude H, Mura E, Mordekar S, Francesco N, Olivotto S, Orcesi S, Porta F, Remerand G, Siri B, Wilpert N-M, Amir-Yazdani P, Bertini E, Schuelke M, Bernard G, Boespflug-Tanguy O, Tonduti D. Movement disorders in MCT8 deficiency/Allan-Herndon-Dudley Syndrome. Mol Genet Metab. 2022 Jan;135(1):109–13.

Beitrag im Einzelnen:

- standardisierte Videoaufnahme von vier Patienten mit MCT8 Defizienz
- Bearbeitung des Manuskriptes

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Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

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Unterschrift der Doktorandin

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE,SSCI Selected Categories: **"GENETICS and HEREDITY"** Selected Category Scheme: WoS

Gesamtanzahl: 177 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS GENETICS	37,390	33.133	0.070320
2	NATURE GENETICS	97,380	27.603	0.207900
3	TRENDS IN ECOLOGY & EVOLUTION	38,175	14.764	0.032330
4	TRENDS IN GENETICS	12,530	11.333	0.022030
5	Annual Review of Genetics	7,800	11.146	0.009710
6	GENOME RESEARCH	41,755	11.093	0.076940
7	MOLECULAR BIOLOGY AND EVOLUTION	50,486	11.062	0.084810
8	GENOME BIOLOGY	44,221	10.806	0.133970
9	Genome Medicine	6,463	10.675	0.026510
10	AMERICAN JOURNAL OF HUMAN GENETICS	36,785	10.502	0.060140
11	GENES & DEVELOPMENT	55,192	9.527	0.063070
12	MOLECULAR THERAPY	17,977	8.986	0.030980
13	GENETICS IN MEDICINE	13,045	8.904	0.040880
14	ONCOGENE	66,303	7.971	0.068320
15	Annual Review of Genomics and Human Genetics	2,679	7.243	0.005190
16	AMERICAN JOURNAL OF MEDICAL GENETICS PART C-SEMINARS IN MEDICAL GENETICS	2,288	7.101	0.005340
17	GENOMICS PROTEOMICS & BIOINFORMATICS	2,224	7.051	0.005980
18	GENOMICS	9,595	6.205	0.005790

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	Molecular Autism	2,510	5.869	0.007450
20	MUTATION RESEARCH-REVIEWS IN MUTATION RESEARCH	3,621	5.803	0.003120
21	HUMAN GENETICS	8,803	5.743	0.013370
22	npj Genomic Medicine	574	5.631	0.003320
23	CURRENT OPINION IN GENETICS & DEVELOPMENT	7,707	5.512	0.016170
24	Horticulture Research	1,360	5.404	0.003360
25	CRISPR Journal	218	5.343	0.001170
26	PLoS Genetics	45,571	5.174	0.114250
27	HUMAN MOLECULAR GENETICS	39,652	5.100	0.064170
28	Journal of Genetics and Genomics	2,271	5.065	0.004310
29	Clinical Epigenetics	3,787	5.028	0.010640
30	JOURNAL OF MEDICAL GENETICS	12,049	4.943	0.015100
31	Genes & Diseases	1,081	4.803	0.003310
32	Microbial Genomics	1,139	4.632	0.005810
33	CANCER GENE THERAPY	2,914	4.534	0.002860
33	Circulation-Cardiovascular Genetics	3,090	4.534	0.008600
35	THEORETICAL AND APPLIED GENETICS	21,335	4.439	0.014120
36	JOURNAL OF MOLECULAR MEDICINE-JMM	7,543	4.427	0.009210
37	Biotechnology & Genetic Engineering Reviews	590	4.375	0.000380
38	HUMAN GENE THERAPY	5,631	4.273	0.008140
39	Genes and Nutrition	1,585	4.258	0.002000

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
40	Epigenetics	5,512	4.251	0.009770
41	Epigenetics & Chromatin	1,889	4.237	0.007550
42	MOLECULAR GENETICS AND METABOLISM	7,759	4.170	0.010090
43	GENE THERAPY	6,795	4.128	0.005520
44	HUMAN MUTATION	13,747	4.124	0.020800
45	Epigenomics	2,981	4.112	0.007600
46	Circulation-Genomic and Precision Medicine	375	4.063	0.002220
47	JOURNAL OF INHERITED METABOLIC DISEASE	6,306	4.036	0.007330
48	GENETICS	42,739	4.015	0.044500
49	DNA RESEARCH	3,230	4.009	0.004980
50	MITOCHONDRION	3,860	3.992	0.005160
51	GENETICS SELECTION EVOLUTION	3,400	3.950	0.005520
52	Plant Genome	1,787	3.847	0.003920
53	Genes	5,889	3.759	0.017290
54	EVOLUTION	32,140	3.698	0.024360
55	EUROPEAN JOURNAL OF HUMAN GENETICS	10,250	3.657	0.020500
56	BMC GENOMICS	43,220	3.594	0.086430
57	CLINICAL GENETICS	7,723	3.578	0.013950
58	Orphanet Journal of Rare Diseases	7,494	3.523	0.014200
59	Neurology-Genetics	804	3.509	0.003670
60	MOLECULAR PHYLOGENETICS AND EVOLUTION	19,367	3.496	0.024610
61	Genome Biology and Evolution	7,387	3.462	0.024830

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
62	GENES CHROMOSOMES & CANCER	4,930	3.444	0.005510
63	CHROMOSOMA	3,259	3.442	0.004220
64	HEREDITY	9,838	3.436	0.010550
65	CHROMOSOME RESEARCH	2,237	3.413	0.002160
66	AMERICAN JOURNAL OF MEDICAL GENETICS PART B-NEUROPSYCHIATRIC GENETICS	4,033	3.387	0.006040
67	Molecular Diagnosis & Therapy	1,187	3.380	0.002220
68	MUTAGENESIS	3,495	3.379	0.002510
69	Human Genomics	1,345	3.351	0.002840
70	DNA REPAIR	5,644	3.339	0.011860
71	Cancer Genomics & Proteomics	1,033	3.280	0.001490
72	Biology of Sex Differences	1,289	3.267	0.003640
73	Frontiers in Genetics	10,161	3.258	0.026230
73	JOURNAL OF GENE MEDICINE	1,961	3.258	0.001230
75	DNA AND CELL BIOLOGY	3,602	3.191	0.004100
76	Mobile DNA	927	3.161	0.003890
77	ENVIRONMENTAL AND MOLECULAR MUTAGENESIS	3,500	3.131	0.002840
78	Cancer Genetics	1,277	3.105	0.002850
79	FUNGAL GENETICS AND BIOLOGY	5,821	3.071	0.006440
80	BMC EVOLUTIONARY BIOLOGY	12,731	3.058	0.018960
80	FUNCTIONAL & INTEGRATIVE GENOMICS	2,164	3.058	0.002580

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
82	Comparative Biochemistry and Physiology D-Genomics & Proteomics	1,181	3.011	0.001600
83	GENE	27,976	2.984	0.030860
84	Briefings in Functional Genomics	1,786	2.941	0.003300
85	PHARMACOGENOMICS JOURNAL	2,607	2.910	0.004520
86	ANIMAL GENETICS	3,863	2.841	0.004010
87	JOURNAL OF HUMAN GENETICS	4,253	2.831	0.007850
88	JOURNAL OF ASSISTED REPRODUCTION AND GENETICS	5,750	2.829	0.010680
89	JOURNAL OF HEREDITY	6,232	2.809	0.004930
90	PLASMID	1,917	2.805	0.001670
91	MOLECULAR GENETICS AND GENOMICS	4,740	2.797	0.006230
92	G3-Genes Genomes Genetics	6,487	2.781	0.024210
93	NEUROGENETICS	1,235	2.774	0.002200
94	PHYSIOLOGICAL GENOMICS	4,535	2.749	0.004520
95	DISEASE MARKERS	4,094	2.738	0.006650
96	JOURNAL OF EVOLUTIONARY BIOLOGY	10,761	2.720	0.013000
97	CURRENT GENOMICS	2,190	2.630	0.002070
98	Pharmacogenetics and Genomics	3,032	2.628	0.002620
99	IMMUNOGENETICS	3,277	2.621	0.002810
100	BMC Medical Genomics	2,924	2.570	0.006440
101	BMC GENETICS	4,387	2.567	0.007310
102	OMICS-A JOURNAL OF INTEGRATIVE BIOLOGY	2,568	2.507	0.002470

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
103	MUTATION RESEARCH-GENETIC TOXICOLOGY AND ENVIRONMENTAL MUTAGENESIS	6,325	2.506	0.003080
104	MUTATION RESEARCH-FUNDAMENTAL AND MOLECULAR MECHANISMS OF MUTAGENESIS	6,786	2.463	0.002700
105	Human Gene Therapy Methods	523	2.446	0.001520
106	CURRENT GENE THERAPY	1,161	2.431	0.001500
107	PRENATAL DIAGNOSIS	5,618	2.425	0.008650
108	International Journal of Genomics	947	2.414	0.002470
109	HEREDITAS	1,567	2.412	0.000580
110	European Journal of Medical Genetics	2,312	2.368	0.005900
111	MAMMALIAN GENOME	2,693	2.287	0.003490
112	BEHAVIOR GENETICS	3,016	2.231	0.003200
113	CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION	1,025	2.156	0.000810
114	Journal of Genetic Counseling	2,235	2.149	0.005020
114	MOLECULAR BREEDING	5,756	2.149	0.007200
116	AMERICAN JOURNAL OF MEDICAL GENETICS PART A	11,825	2.125	0.020000
116	Journal of Nutrigenetics and Nutrigenomics	359	2.125	0.000500
118	Tree Genetics & Genomes	2,827	2.081	0.004440
119	GENOME	4,431	2.037	0.003130
120	BIOCHEMICAL GENETICS	1,232	2.027	0.000900
120	JOURNAL OF APPLIED GENETICS	1,356	2.027	0.001760
122	Molecular Genetics and Metabolism Reports	665	2.022	0.001990

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Human neuropathology confirms projection neuron and interneuron defects and delayed oligodendrocyte production and maturation in FOXG1 syndrome

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ABSTRACT

The Forkhead transcription factor FOXG1 is a prerequisite for telencephalon development in mammals and is an essential factor controlling expansion of the dorsal telencephalon by promoting neuron and interneuron production. Heterozygous *FOXG1* gene mutations cause FOXG1 syndrome characterized by severe intellectual disability, motor delay, dyskinetic movements and epilepsy. Neuroimaging studies in patients disclose constant features including microcephaly, corpus callosum dysgenesis and delayed myelination. Currently, investigative research on the underlying pathophysiology relies on mouse models only and indicates that de-repression of FOXG1 target genes may cause premature neuronal differentiation at the expense of the progenitor pool, patterning and migration defects with impaired formation of cortico-cortical projections. It remains an open question to which extent this recapitulates the neurodevelopmental pathophysiology in *FOXG1*-haploinsufficient patients. To close this gap, we performed neuropathological analyses in two foetal cases with *FOXG1* premature stop codon mutations interrupted during the third trimester of the pregnancy for microcephaly and corpus callosum dysgenesis. In these foetuses, we observed cortical lamination defects and decreased neuronal density mainly affecting layers II, III and V that normally give rise to cortico-cortical and inter-hemispheric axonal projections. GABAergic interneurons were also reduced in number in the cortical plate and persisting germinative zones. Additionally, we observed more numerous PDGFRα-positive oligodendrocyte precursor cells and fewer Olig2-positive pre-oligodendrocytes compared to age-matched control brains, arguing for delayed production and differentiation of oligodendrocyte lineage leading to delayed myelination. These findings provide key insights into the human pathophysiology of FOXG1 syndrome.

1. Introduction

Mammalian brain development critically depends on the spatio-temporal expression and abundance (Hou et al., 2019; Toma et al., 2014) of the winged helix transcription factor Forkhead box G1 (FOXG1) which is mostly expressed in telencephalic structures (Tao and Lai, 1992) across species (Kumamoto and Hanashima, 2017). In rodents, Foxg1 has been shown to tightly coordinate progenitor fate (Hanashima

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et al., 2004; Shen et al., 2006b) and migration (Miyoshi and Fishell, 2012; Yang et al., 2017), cortical layering (Cargnin et al., 2018) and patterning of the neuroaxis (Danesin et al., 2009; Du et al., 2019; Muzio and Mallamaci, 2005). In human, its importance is underscored by the existence of pathogenic variants on a single *FOXG1* allele, first identified in 2005 in a patient presenting severe intellectual disability, corpus callosum (CC) agenesis and microcephaly (Shoichet et al., 2005). Since then, up to 100 *de novo* and mosaic germline variants in *FOXG1* located on chromosome 14q12 have been identified (Wong et al., 2019), and genotype-phenotype correlations have revealed that the most devastating mutations are located in the Forkhead-binding and N-terminal domains of the FOXG1 protein (Mitter et al., 2018; Pringsheim et al., 2019; Vegas et al., 2018). Formerly accounted as the "congenital variant of Rett-syndrome" (Neul et al., 2010), distinct phenotypic descriptions and advances in molecular diagnosis have led to the delineation of "FOXG1 syndrome" as an independent clinical entity [OMIM #613454]. FOXG1 syndrome develops soon after birth, and its key features include severe microcephaly, developmental delay, dyskinetic movement disorders, epilepsy, stereotypies and abnormal sleeping patterns (Mitter et al., 2018; Vegas et al., 2018; Wong et al., 2019).

To date, the pathophysiological mechanisms underlying FOXG1 syndrome remain partly unknown as they are limited to neuroimaging analyses in patients and to neuropathological studies in other species. Human cerebral features associate simplified gyration or pachygyria, hypoplasia/agenesis of the corpus callosum, hippocampus abnormalities, and myelination delay (Harada et al., 2018; Mitter et al., 2018; Pringsheim et al., 2019; Vegas et al., 2018). Histological analyses of different knockout mouse models have revealed an expansion of early born neurons at the expense of the cortical overall thickness (Cargnin et al., 2018; Dou et al., 1999; Eagleson et al., 2007; Hanashima et al., 2004; Shen et al., 2006a; Siegenthaler et al., 2008; Xuan et al., 1995) as well as corpus callosum and hippocampus abnormalities (Cargnin et al., 2018; Eagleson et al., 2007; Pringsheim et al., 2019; Tian et al., 2012). Additionally, hypoplasia of the ganglionic eminences (GE) and basal ganglia (Dou et al., 1999; Du et al., 2019; Hanashima et al., 2002; Pringsheim et al., 2019; Xuan et al., 1995), an imbalance of exhibitory/inhibitory neurons (Mariani et al., 2015; Patriarchi et al., 2016; Shen et al., 2019), along with an enlargement of dorsal telencephalic structures (Hanashima et al., 2007; Muzio and Mallamaci, 2005; Xuan et al., 1995) have been reported.

However, it remains an open question to which extent these findings recapitulate the neurodevelopmental pathophysiology in *FOXG1*-haploinsufficient patients. In the present study, we report for the first time the characteristics of two molecularly proven *FOXG1*-haploinsufficient foetuses from two unrelated families and provide a comprehensive neuropathological study of this rare syndrome.

2. Patients and methods

2.1. Patients

2.1.1. Family 1

In a Para 2 Gravida 3 31-year-old pregnant woman without any previous medical family history or consanguinity, routine ultrasound examination (US) at 22 weeks of gestation (WG) revealed isolated agenesis of the corpus callosum. Magnetic resonance imaging (MRI) performed at 30 WG confirmed the complete corpus callosum agenesis associated with bilateral fronto-parietal pachygyria. Due to the poor prognosis, the parents opted for a medical termination of the pregnancy which was achieved at 33 WG after approval of the local ethic committee and with the informed written consent of the parents in accordance with the French law. The karyotype was normal, 46, XX.

2.1.2. Family 2

In Para 0, gravida 2, 34-year-old woman with no previous medical family history or consanguinity, routine US performed at 22 WG revealed microcephaly with delayed gyration. The foetal MRI performed at 32 WG, showed pachygyria more prominent in frontal and temporal regions associated with a dysmorphic CC. These malformations were confirmed on a second MRI performed at 35 WG. The karyotype was normal, 46 XX, and no structural rearrangement was visualized on array CGH. Due to the poor prognosis, the parents opted for a medical termination of the pregnancy which was achieved at 36 WG after approval of the local ethic committee and with the informed written

Table 1
Antibodies used for the study.

Neuronal stem cells and progenitors				
Antisera	Cells	Company (Cat,-Numb.)	Dilution	Target
Nestin	Neuroepithelium vRGC	Millipore (ABD69)	1:500	Intermediate filament protein
PAX6	Neuroepithelium vRGC, oRGC	Protein Tech group (12323-1-AP)	1:50	Stem cell transcription factor
SOX2	vRGC, oRGC	Abcam (ab97959)	1:150	Stem cell self-renewal transcription factor
Post-mitotic neurons and layer markers				
Reelin	Layer I (Cajal Retzius cells)	Gift from A. Goffinet	1:500	Secreted extracellular matrix protein
MAP2	Migrating neurons and Layers III and V	Sigma Aldrich (M4403)	1:100	Brain microtubule-associated protein
HES1	Differentiating cells	Abcam (ab108937)	1:50	Target of NOTCH signalling
SATB2	Layers II-IV Callosal projections Subcortical connections	Abcam (ab51502)	1:50	Special AT-rich sequence-binding protein
CTIP2	Layers V-VI Motor neuron projections	Abcam (ab18465)	1:100	COUP-TF-interacting protein 2C2H2 zinc finger
TBR1	Layers I-III and VI Cortico-cortical projections	Abcam (ab31940)	1:25	T-box homeobox gene family member
CULT-1	Layers II-V, predominant in upper layers	Antib.-online GmbH (AA521-620)	1:100	Member of the homeodomain family of DNA binding proteins
NF	Axono-dendritic network	Agilent (GA60761-2)	1:200	Phosphorylated intermediate filament protein
Cortical interneurons				
GABA	Interneurons	Invitrogen (PA5-32241)	1:100	Neurotransmitter
Calretinin	Cortical interneurons	Life technology (18-0211)	1:100	Calcium binding protein
Glial and microglial markers				
Vimentin	Radial glia and glia limitans, immature astrocytes	Agilent (M072501-2)	1:1000	Intermediate filament protein
GFAP	Astrocytes	Diagomics (RBK037)	1:200	Intermediate filament protein
PDGFR-α	Oligodendrocyte precursor cell	MMFrance (RB-1691)	1:100	Platelet derived growth factor subunit α
Olig2	Pre-oligodendrocytes	Epitomics (AF2418)	1:200	Oligodendrocyte lineage transcription factor 2
CD68	Microglia/ macrophages	Agilent (MOB094)	1:300	Cluster of differentiation 68

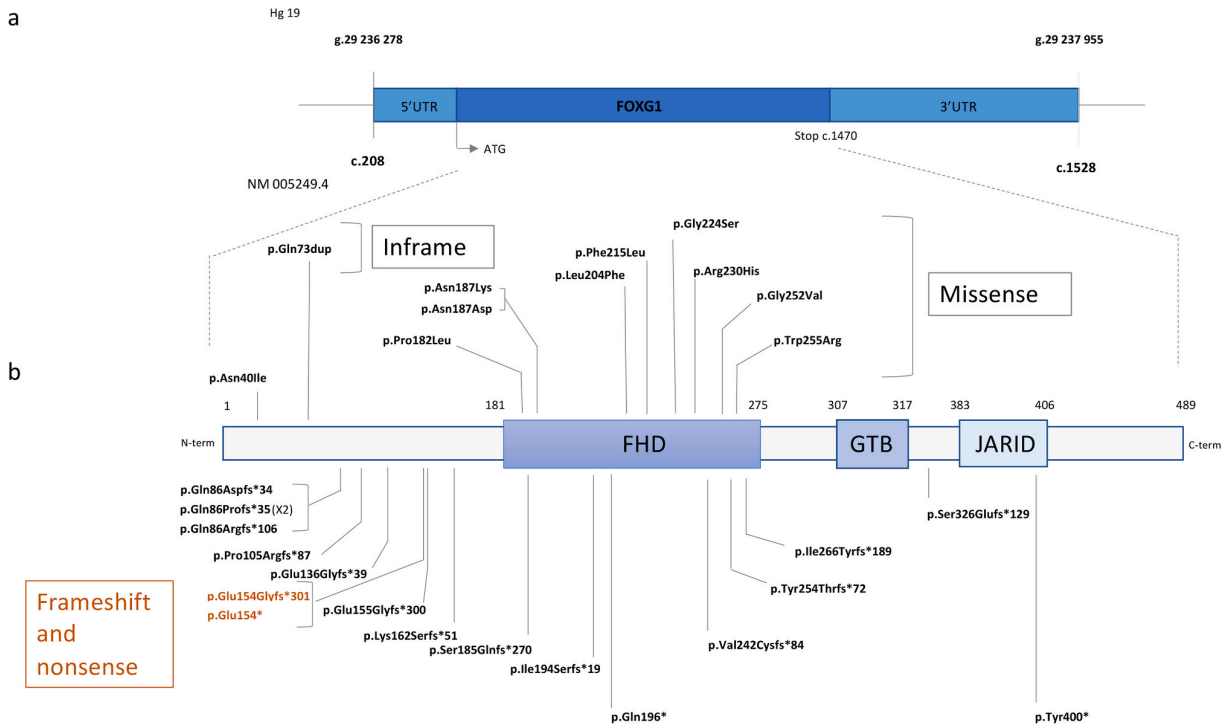

Fig. 1. Schematic representation of *FOXG1* gene and protein domain structure (adapted from (Vegas et al., 2018)).
The position of the variations previously identified are depicted in black colour and the variations identified in the two foetuses in orange colour. FHD domain: forkhead DNA binding domain (amino acids 181–275); GTB domain: Groucho binding domain (amino acids 307–317); JBD domain: JARID1B binding domain (amino acids 383–406).

consent of the parents in accordance with the French law.

2.2. Methods

2.2.1. Molecular analyses

In both foetal cases, molecular studies were performed in a trio-based panel of the index patient and of both parents. The first one on a panel dedicated to microcephaly syndrome, and the second one, dedicated to CC anomalies. For each panel, the list of genes included is presented in **Supplementary data 1**.

2.2.2. Morphological studies

A complete autopsy was carried out in the two cases with the informed written consent of the parents and following standardized protocols including X-rays, photographs, macroscopic and histological examination of all viscera. Foetal biometric data were evaluated according to Guihard–Costa et al. (Guihard-Costa et al., 2002). The brains were fixed in a 10% formalin-zinc buffer solution for one month. Brain growth and macroscopic assessment of brain maturation including gyration were evaluated according to the criteria of Guihard-Costa and Larroche and the atlas of Feess-Higgins and Larroche (Guihard-Costa and Larroche, 1990). Seven-micrometre sections obtained from paraffin-embedded tissues were stained using Haematoxylin-Eosin (HE). Luxol-phloxin stains were performed on infratentorial sections since myelination starts only around birth in the cerebral hemispheres. Immunohistochemical studies were carried out on the frontal cortical plate (CP), germinative zone of the dorsal telencephalon and ganglionic eminences (GE). Immunohistochemical procedures included a microwave pre-treatment protocol to aid antigen retrieval (pre-treatment CC1 kit, Ventana Medical Systems Inc, Tucson AZ). Incubations with the primary antibodies listed in Table 1 were performed for 32 or 44 min at room temperature using the Ventana Benchmark XT system. After incubation, slides were processed by means of the Ultraview Universal 3, 3′-diaminobenzidine detection kit (Ventana). All immunolabelings were compared with two age-matched control brains aged 33 and 36 WG respectively, interrupted for cardiomyopathy and whose brains were free of macroscopical and histological lesions.

2.2.3. Quantitative analysis of SOX2, CTIP2, SATB2, MAP2 and PDGFR-α positive cell numbers

Quantitative analyses were carried out in the inner and outer subventricular zones for SOX2 and in the frontal CP for, CTIP2, SATB2, MAP2 and PDGFRα. For measurements of positive cell numbers and densities, images were acquired and saved in TIFF format using a Leica DMI 6000B microscope. Images were subsequently opened in Mercator software and regions of interest (ROIs) were drawn. A counting frame was defined within the ROI and a threshold was set in order to differentiate immunoreactive cells from the background. By a segmentation process, the computer calculated the number of objects corresponding to immunoreactive cell somata within the ROI, yielding cell number per 10^4 µm^2.

2.2.4. Statistical analyses

Statistical analyses were performed using the GraphPad Prism software. Chi square test was used to compare the intrinsic distribution of CTIP2, SATB2, MAP2 and PDGFRα cells in the cortical plate and Student test for SOX2 in inner and outer subventricular zones between the first patient's and control brains.

3. Results

3.1. Molecular results

Both foetuses carried previously reported mutations (Fig. 1) affecting

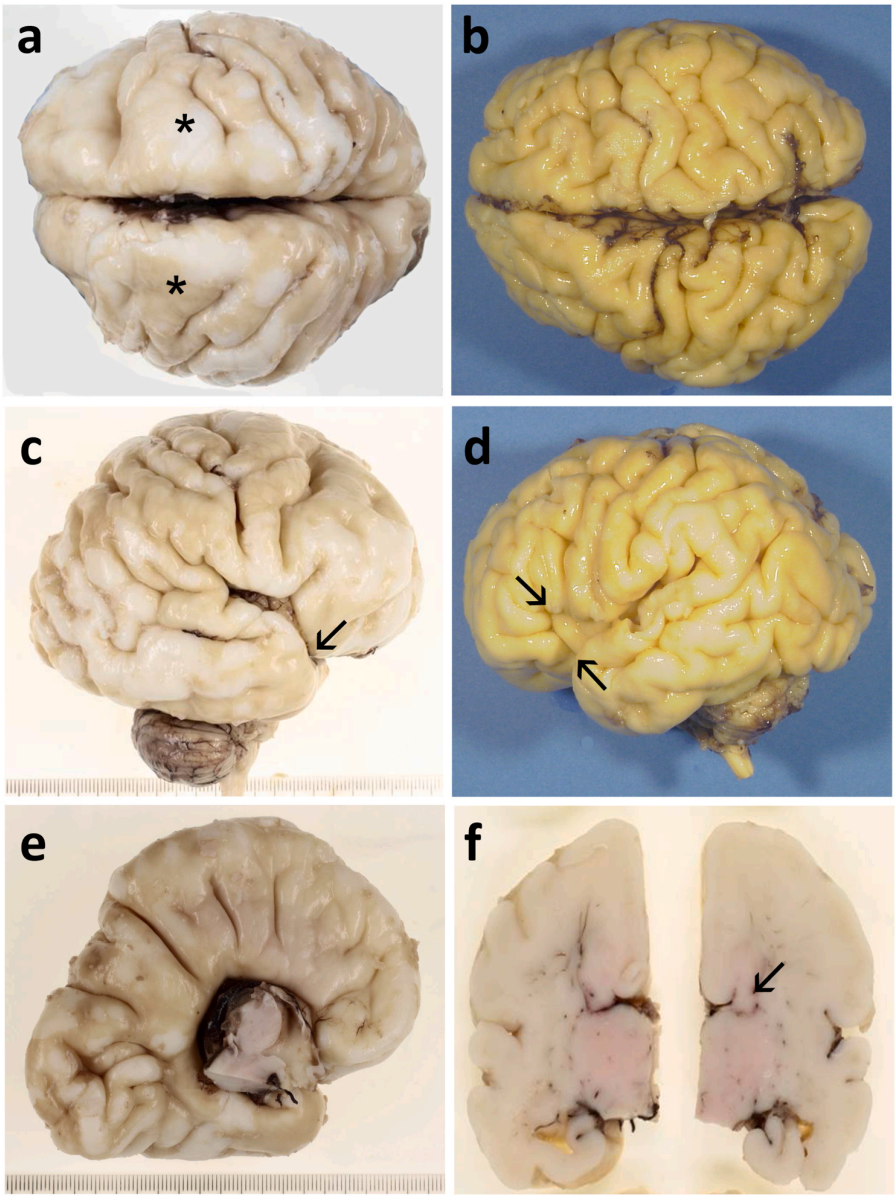

Fig. 2. Brain macroscopic findings in case 1
(a) Superior view of the brain displaying bi-frontal parasagittal pachygyria (asterisks), **(b)** compared with an age-matched control brain in which tertiary sulci have already appeared. **(c)** Macroscopic view of the left profile showing underdeveloped frontal lobes and almost closed and dysmorphic Sylvian fissure (arrow), **(d)** in contrast to the control brain in which the frontal lobes are adequately developed for a term of 33 WG, with a Sylvain fissure which remains open in its anterior part (arrows). **(e)** On the median sagittal section, corpus callosum agenesis and abnormal radiating sulci toward the midline, **(f)** with, on coronal sections Probst bundles (arrows).

the same residue G at the position 460, c.460dupG leading to a frame-shift mutation and a premature stop codon (p.Glu 154Glyfs*301) in case 1, and c.460G>T leading to a premature stop codon (p.Glu154*) in case 2 respectively.

3.2. Morphological studies

The first female foetus (case 1) was eutrophic (biometric data measured at the 95th percentile) for the term according to Guilhard-Costa et al. (Guihard-Costa et al., 2002), except for the cranial perimeter which was measured at 29 cm (corresponding to the 50th percentile for the term) with no cranio-facial dysmorphism. Neither macroscopic nor histological visceral anomalies were identified. The brain weighed 274 g, corresponding to the 50th percentile for the term, but <3rd percentile in relation to body weight, similarly to the infratentorial structures (17.9 g with a transverse cerebellar diameter at 46.5 mm), indicative of microcephaly. External examination revealed parasagittal pachygyria of the underdeveloped frontal lobes (Fig. 2a and b). The primary fissures were identified, but the Sylvian fissure was dysmorphic and almost already closed (normally closed around 38 WG according to Feess-Higgins and Larroche) (Fig. 2c and d). The secondary convolutions were thin with deep sulci. On median sagittal section, the CC was absent with abnormal sulci radiating toward the midline (Fig. 2e), but with the presence of short Probst bundles on coronal sections and of a thick fornix with a hardly discernible cingular sulcus (Fig. 2f). The other supra- and infratentorial neuroanatomical structures appeared macroscopically normal. Histologically, no lesions were observed in the brainstem and cerebellum using H&E stains, but Luxol-phloxin stains were entirely negative along the brainstem and in the cerebellum where myelination starts from 27 WG (Fig. 3a and b). At the supra-tentorial level, neuronal depletion predominated in layer III with absent lamination and neuronal immaturity (Fig. 3c and d) and sometimes micro-columnar dysplasia was observed, mainly in the frontal areas which were the most affected structures (Fig. 3e). Strikingly, numerous neurons were calcified in layer V, associated to multiple foci of calcified, Von Kossa-positive neurons in layer II and III (Fig. 3f). The IZ intermediate zone contained numerous

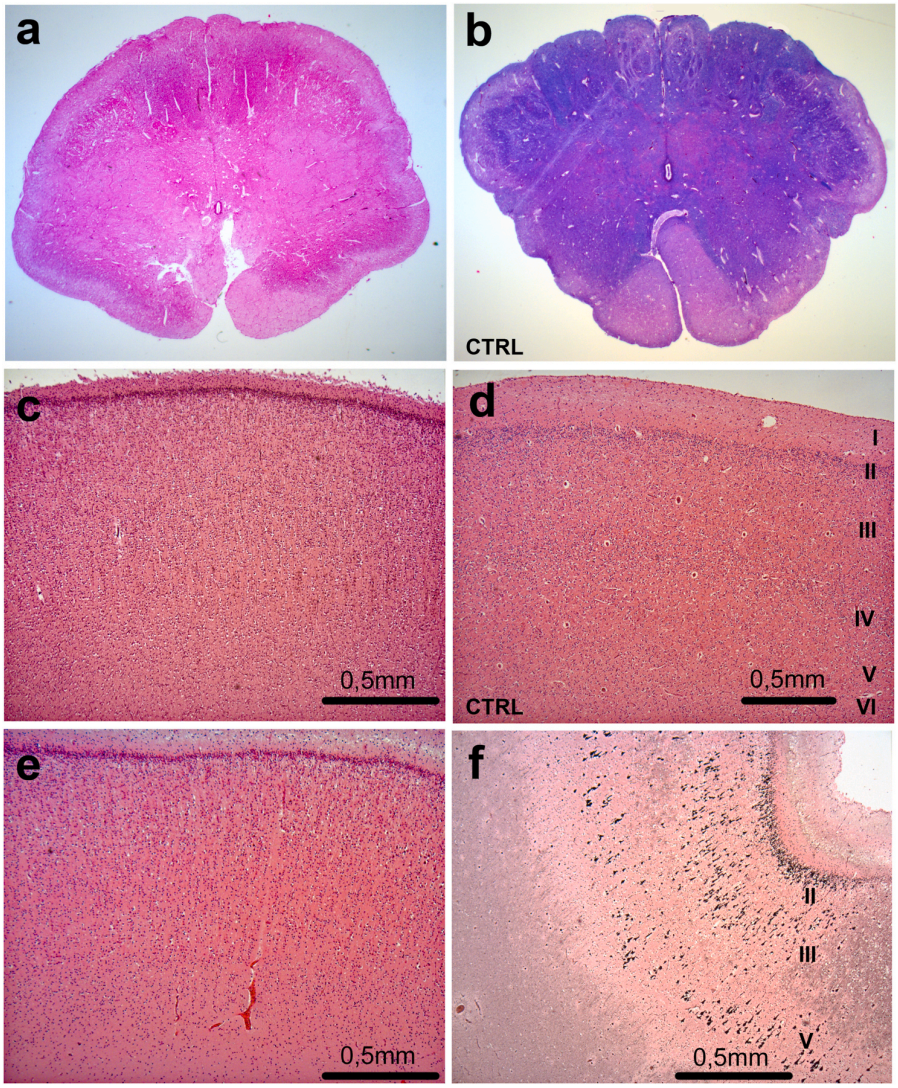

Fig. 3. Main histological findings in case 1
(a) Phloxin-luxol stained section passing through the medulla at the level of the decussation of the pyramids displaying no myelin [OM x 16]. **(b)** By comparison with the control brain where ascending and descending pathways are myelinated, except for the pyramidal tracts [OM x 16]. **(c)** Absent lamination and immaturity of the frontal cortical plate (H&E staining) [OM x 50]. **(d)** Compared with a normal cortical plate in which all layers are discernible [OM x 50]. **(e)** Micro columnar dysplasia in some frontal cortical areas [OM x 50]. **(f)** And multiple calcified neurons in layers II, III and V (Von Kossa staining) [OM x 50].

astrocytes.

The second female foetus (case 2) was also eutrophic (biometric data measured at the 95th percentile for the term) and neither macroscopic nor microscopic visceral anomalies were detected. The brain weighed 281g (<5th percentile) whereas infratentorial structures were at the 50th percentile (brainstem and cerebellar weight: 23g, cerebellar transverse diameter: 45 mm). As in the first case, the frontal lobes were hypoplastic, with no tertiary sulci due to delayed gyrification (Fig. 4a and b). On supratentorial median sagittal section, the CC was short (35 mm, <10th percentile) and thick (5 mm in width and thickness, >95th percentile). The fornix was also thick (Fig. 4c and d). As in the former case, histological examination displayed decreased neuronal density in the frontal CP and scattered foci of microcolumnar dysplasia. The intermediate zone was gliotic. Similar to case 1, Luxol-phloxin stains performed on infratentorial structures were also negative.

3.3. Immunohistochemical studies

Semi-quantitative immunohistochemical analyses revealed similar abnormalities in the two cases which are detailed in Table 2. GFAP immunohistochemistry confirmed gliosis in the deep and superficial intermediate zone (Fig. 4e and f) but CD68 was entirely negative arguing against hypoxic/ischemic lesions. Since the germinative zones had physiologically disappeared in the second case, SOX2 and PAX6 immunolabelings were performed in case 1, and no major differences were observed in the persistent GE with PAX6 and nestin antibodies. Conversely, only a few SOX2-positive cells were observed in the ventricular zone (VZ) and outer subventricular zone (SVZ) contrary to the control brain in which almost all progenitors were still observed close to the ventricular wall in the VZ and inner SVZ (Fig. 5a and b and Supplementary data 2A). In the CP, the density of reelin-positive Cajal cells in the molecular layer of the cerebral cortex and hippocampus was similar, apart from very few scattered and mislocalized reelin-positive neurons in layers III and V in both cases. Cult1 was diffusely positive in all layers of the cortical plate confirming absent lamination in both affected foetuses. The most striking features were observed with the other layer markers. CTIP2 immunoreactivity was observed in layers II, V-VI in which they were more numerous than in the control case (Fig. 5c and d and Supplementary data 2B) suggesting that in the two patients early born neurons were at their final place with probably no further enrichment of these layers whereas in controls, neurons intended to populate CP were likely still migrating from the germinative zones. Moreover, SATB2, a marker of upper layer neurons was observed only in layer II and III where they were less numerous in both cases, whereas in

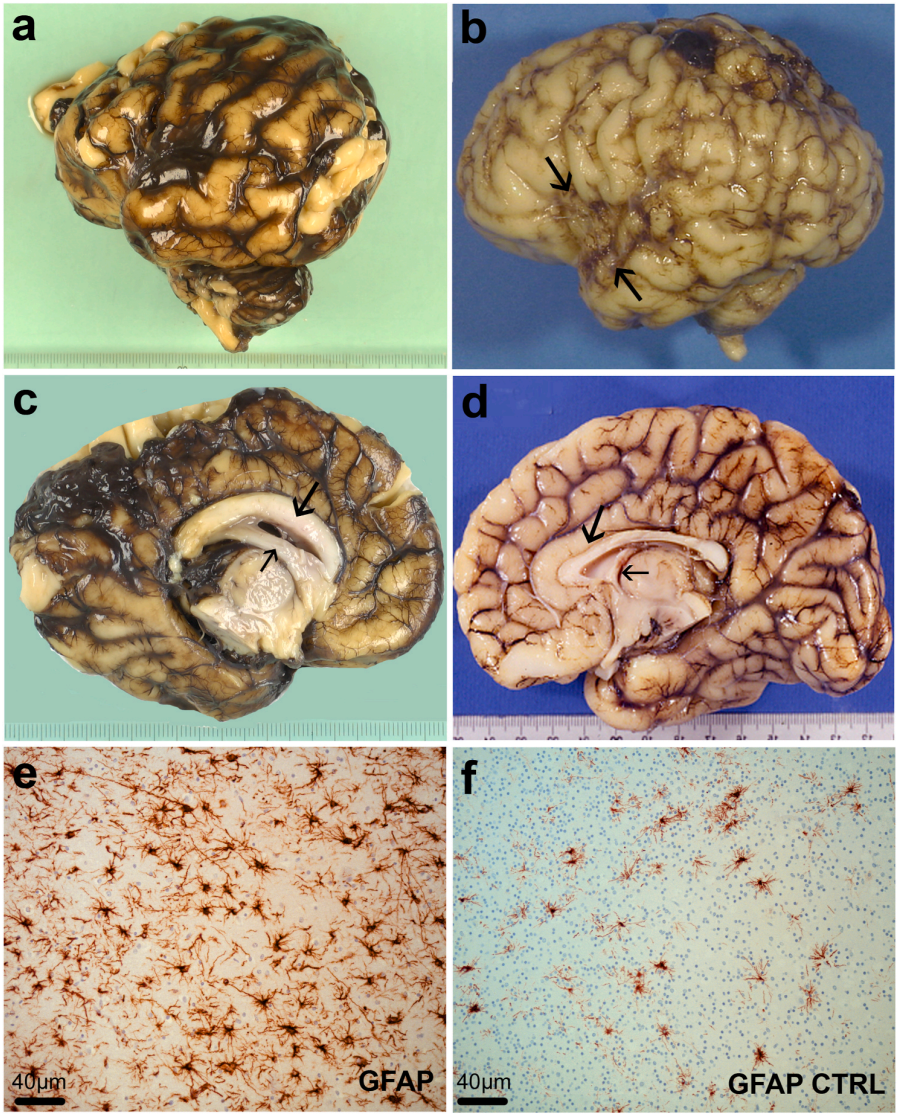

Fig. 4. Brain lesions in case 2
(a) Poorly developed frontal lobes, simplified gyral pattern and prematurely closed sylvian fissure (arrow). **(b)** By comparison with an age-matched control brain (36 WG) in which the tertiary sulci are well-formed and Sylvain fissure is still open in its anterior part (arrows). **(c)** On median sagittal section, the corpus callosum is short and thick (thick arrow), and the fornix thick and dysmorphic (thin arrow). **(d)** Conversely to the control brain in which the corpus callosum and fornix are normal in shape and size (thick and thin arrows respectively). **(e)** Diffuse astrogliosis in the IZ as revealed by GFAP immunohistochemistry [OM x 50]. **(f)** Conversely to the control brain in which astrocytes are less numerous [OM x 50].

control brains numerous neurons were identified in layers II-IV as well as in the layer VI, which suggests a defect of later born neuron production in the two mutated foetuses (Fig. 5e and f and Supplementary data 2C). MAP2-positive immature neurons were dispersed in all layers, instead of being abundantly located in layers II, III and V, reflecting severe dyslamination (Fig. 5g and h and Supplementary data 2D). Similar abnormalities were observed with TBR1 antibody which immunolabeled all layers whereas its expression is normally observed in layers II- III and V. In case 1, GABAergic interneurons were virtually absent in the GE whereas they still represented more than 50% of the cells in the control brain, likely due to either a production defect or delay (Fig. 6a and b). They were also reduced in number and were disseminated in all layers of the CP contrary to the controls in which GABAergic interneurons were more numerous and located mainly in layers II, III and V (Fig. 6c and d). Cortical calretinin-positive interneurons were reduced in number, but their location (layers II and III) was similar. Oligodendrocyte (OL) lineage was also impaired in the CP with more abundant PDGFRα-positive oligodendrocyte precursors (OPCs) (Fig. 6e and f and Supplementary data 2E) and fewer Olig2-positive pre-oligodendrocytes (pre-OLs) than in controls (Fig. 6g and h). These observations along with absent myelin in the infratentorial structures as demonstrated by Luxol-phloxin stains argue for delayed oligodendrocyte production and maturation and consequently delayed myelination as previously observed in post-natal supratentorial structures. Detailed results obtained from quantitative analyses are presented in **Supplementary data 2**.

4. Discussion

The transcription factor FOXG1 is a critical regulator that acts dynamically during human brain development. Loss of function mutations of the *FOXG1* gene are responsible for the rare neurodevelopmental FOXG1 syndrome for which hypotheses on underlying pathophysiological mechanisms are limited to MRI descriptions and mouse models. The present neuropathological findings on two foetuses carrying recurrent, already described FOXG1 mutations bring new insights into the pathophysiology of this rare disorder.

The point mutation c.460G>T (p-Glu154*) occurs in 17% of FOXG1 syndrome patients (Mitter et al., 2018). Remarkably, this substitution c.460G>T leads to an immediate stop codon (p-Glu154*) whereas duplications (c.460dup.G) at the same position causes frameshift with a downstream transcriptional stop (p.Glu154Glyfs*301). Recent

Table 2
Immunohistochemical results. VZ: ventricular zone, SVZ: subventricular zone, DT: dorsal telencephalon, GE: ganglionic eminence, oSVZ: outer subventricular zone, iSVZ: inner subventricular zone, IZ: intermediate zone, SP: subplate, CP: cortical plate.

Antibodies	Case 1 (33 WG)	Control 1 (33 WG)	Case 2 (36 WG)	Control 2 (36WG)
Neuronal progenitor markers				
Nestin	0 in VZ and SVZ of the DT <10% in GE	0 in VZ and SVZ of the DT 20% in GE	0	0 in VZ and SVZ of the DT 5% in the remaining GE
PAX6	Few neuroblasts in VZ of the DT Scattered in GE	Numerous neuroblasts in VZ and oSVZ of the DT 0 in GE	Scattered in the iSVZ of the DT 0 in GE	Scattered in the iSVZ of the DT 0 in GE
SOX2	Few neuroblasts in VZ and SVZ of the DT 60% in GE (radial migration delay of progenitors)	Few cells in VZ and SVZ of the DT 40% in GE with accumulation in SVZ	0 in VZ and SVZ of the DT Disappearence of GE	Few neuroblasts in the remaining GE with accumulation in the SVZ
Post-mitotic neurons and layer markers				
Reelin	Cajal Retzius cells in layer I Scarce neurons in layers II and III	Cajal Retzius cells in layer I	Cajal Retzius cells in Layer I Scarce neurons in layers II and III	Cajal Retzius cells in layer I
TBR1	Diffuse in all cortical layers Dispersed in IZ 0 in VZ and SVZ of the DT 50% in GE	Layers II, III and V Dispersed in IZ 20% in VZ and SVZ of the DT 60% in GE	Diffuse in all cortical layers Dispersed in IZ 0 in VZ and SVZ of the DT 50% in GE	Diffuse in all cortical layers Slight predominance in layers V and VI Dispersed in IZ 0 in VZ and SVZ of the DT 10% in GE
MAP2	Layer III, absent in layer V Dispersed in unlayered areas 80% in VZ and SVZ of the GE	Almost all neurons in layers III and V Abundant in VZ of the DT 80% in SVZ of the GE 40% in OSVZ of the GE	Neuron depletion in layer V and immaturity	Almost all neurons in layer V 80% in VZ and SVZ of the DT and GE 40% in oSVZ of the GE
HES1	Diffuse in CP 80% in VZ and SVZ of the DT and GE	Diffuse in CP 80% in VZ and SVZ of the DT and GE	Diffuse in CP	Diffuse expression in cortex Numerous in remaining VZ/SVZ of the DT 80% in GE
SATB2	Layer II (No more enrichment)	Layers II and IV Dispersed in layer III Migrating neurons in SP	Absent	Mainly layers II and IV Dispersed in layer III Migrating neurons in SP
CTIP2	Layers V and VI Almost absent in GE (no more enrichment in the deepest layers)	Layers V and VI scattered in layer I, II and III 10% in VZ and SVZ of the DT >50% in GE	Absent in layers II and IV, scarce in layer V	Layers V and VI Rare in layers I, II and III
CULT1 (CUX1)	Diffuse in all layers	Diffuse all layers	Diffuse in all layers	Diffuse in all layers
OTX1	Neurons of layers II-V	Neurons of layers II-V	Neurons of layers II-V	Neurons layers II-V
PH-NF	Fibre network in layer I	Fibre network in layer I	Fibre network in layer I	Fibre network in layer I
Interneurons				
GABA	Diffuse but fewer predominating in layer III Almost no neurons in the germinative zones	Diffuse, predominating in layer III and V (40%) 50% in GE	Diffuse Unlayered	Diffuse predominating in layers III and V (40%)
Calretinin	Few in layers II and III <5% in germinative zones	Layers II and III 50% in SVZ of the DT 10% in the GE	Few in layers II and III	20% in the layers II and III Scarce in SVZ of the DT 0 in the remaining GE
Glial markers				
Vimentin	Decreased density of radial glia (premature migration termination) Numerous immature astrocytes migrating in IZ	Persistence of radial glia Rare immature astrocytes in the CP	Decreased density of radial glia Numerous migrating immature astrocytes in IZ	Persistence of radial glia Rare immature astrocytes in the CP
GFAP	Diffuse gliosis in IZ and VZ	Scattered astrocytes in IZ	Diffuse gliosis in VZ and IZ	Scattered astrocytes in IZ
PDGFR-α	Still 50% in GE Dispersed oligodendrocyte precursors in IZ Numerous in the CP	Dispersed in the IZ Moderate in the CP	Abundant oligodendrocyte precursors in the IZ and CP	Dispersed in the IZ Moderate in the CP
Olig2	Dispersed in GE and oSVZ Rare in IZ and CP	Numerous in IZ Moderate in the CP	0 (more severe than case 1)	Numerous in IZ Moderate in the CP

genotype-phenotype studies have suggested that N-terminally truncating mutations were associated with the most severe FOXG1 syndrome (Mitter et al., 2018). Nevertheless, the six patients reported by Vegas et al. carrying the same c.460dup.G (p.Glu154Glyfs*301) mutation presented clinical and imaging features of variable severity suggesting that additional factors such as epigenetic and environmental could be involved (Vegas et al., 2018). In line with this, the two foetuses reported here showed distinct neuropathological findings at the level of the cortical plate, with abnormal cortical layering in one case, and calcified neurons in layers II, III and V in the other. However, both cases showed the same significant alterations of oligodendrocyte production and differentiation with diffuse gliosis.

Our analyses uncovered pronounced lamination defects of cortico-cortical, callosal and subcortical projection neurons. Pathophysiological mechanisms may be related to a dysregulation of neurogenesis, neuronal migration and differentiation, midline patterning and axonal guidance (Edwards et al., 2014). Interestingly, analyses of *Foxg1*-mutant mice have revealed similar lesions to those observed in human foetuses (Cargnin et al., 2018; Eagleson et al., 2007; Hanashima et al., 2004; Miyoshi and Fishell, 2012; Pringsheim et al., 2019; Siegenthaler et al., 2008; Toma et al., 2014). During murine corticogenesis, Foxg1 maintains progenitor fate within the VZ (Hanashima et al., 2004), its downregulation allows the migration of post-mitotic neurons through the intermediate zone. Its reexpression triggers neuronal entry into the cortical plate (Miyoshi and Fishell, 2012) and thereafter, Foxg1 remains expressed in layers II/III and V which project to homotypic contralateral

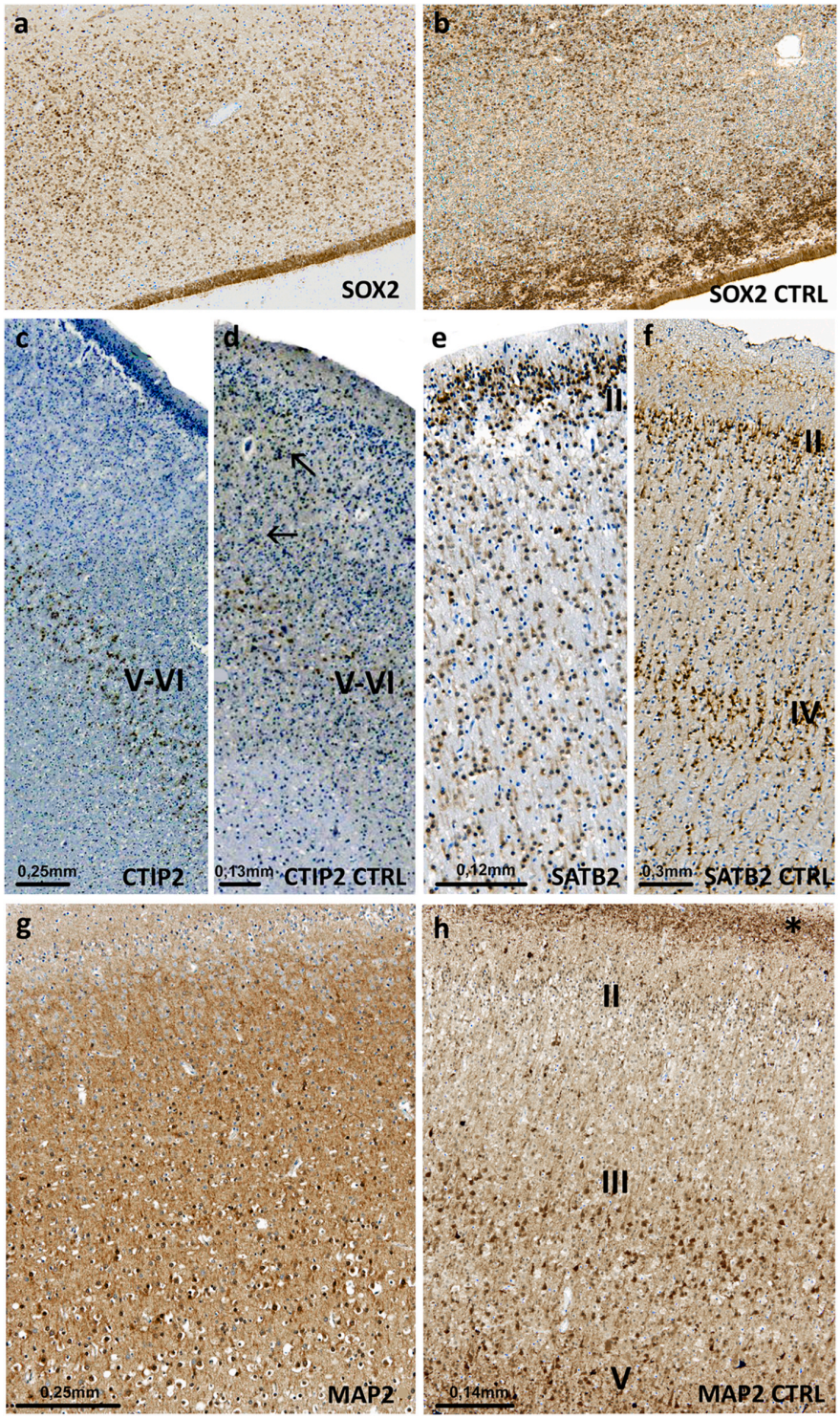

Fig. 5. Immunohistochemical hallmarks of *FOXG1*-mutated brains

(a) SOX2 immunolabeling showing a reduced number of neuron progenitors located close to the VZ of the GE in case1 [OM x 100]. **(b)** By comparison with the control brain in which numerous progenitors are observed in the VZ of the GE [OM x 100]. **(c)** CTIP2 immunolabelings revealing predominant location of immunoreactive neurons in layers V and VI and to a lesser extent in layer II in the CP of case1 [OM x 25]. **(d)** Contrary to the control brain where some CTIP2-positive neurons are still observed in all upper layers (arrow) [OM x 25]. **(e)** SATB2-positive neurons mainly located in layer II [OM x 100]. **(f)** Contrary to the control brain where a certain number of SATB2-positive neurons are observed in layers II and IV (arrows) [OM x 100]. **(g)** MAP2 immunolabelings in the CP of case 2 revealing dispersed neurons in all layers [OM x 100], **(h)** instead of being numerous and located in layers II, III and V and associated to a MAP2 positive fibre network in layer I (asterisk) in the control CP [OM x 100].

cortical areas via the CC (Hou et al., 2019). Furthermore, derepression of Foxg1 target genes, namely family zinc finger 2 (Fezf2), Tbr1 and chicken ovalbumin upstream promoter transcription factor 1 (COUP-TFI) results in an altered layer-specific cell fate with prolonged deep-layer competence at the expense of upper layer neurons and in a decrease of these neurons in postnatal cortices of *Foxg1*-mutant mice (Hou et al., 2019; Toma et al., 2014).

Besides cortical layering defects, CC dysgenesis with aberrant fibre bundles and enlarged fornices were striking in the two foetuses. Accordingly, postnatal axonal tracing experiments in *Foxg1* heterozygous mice have revealed a failure of callosal axons to cross the midline with Probst bundles formation as observed in the human foetuses (Cargnin et al., 2018). Semi-quantitative immunostainings have also revealed enlarged fornices, similarly to our cases (Pringsheim et al.,

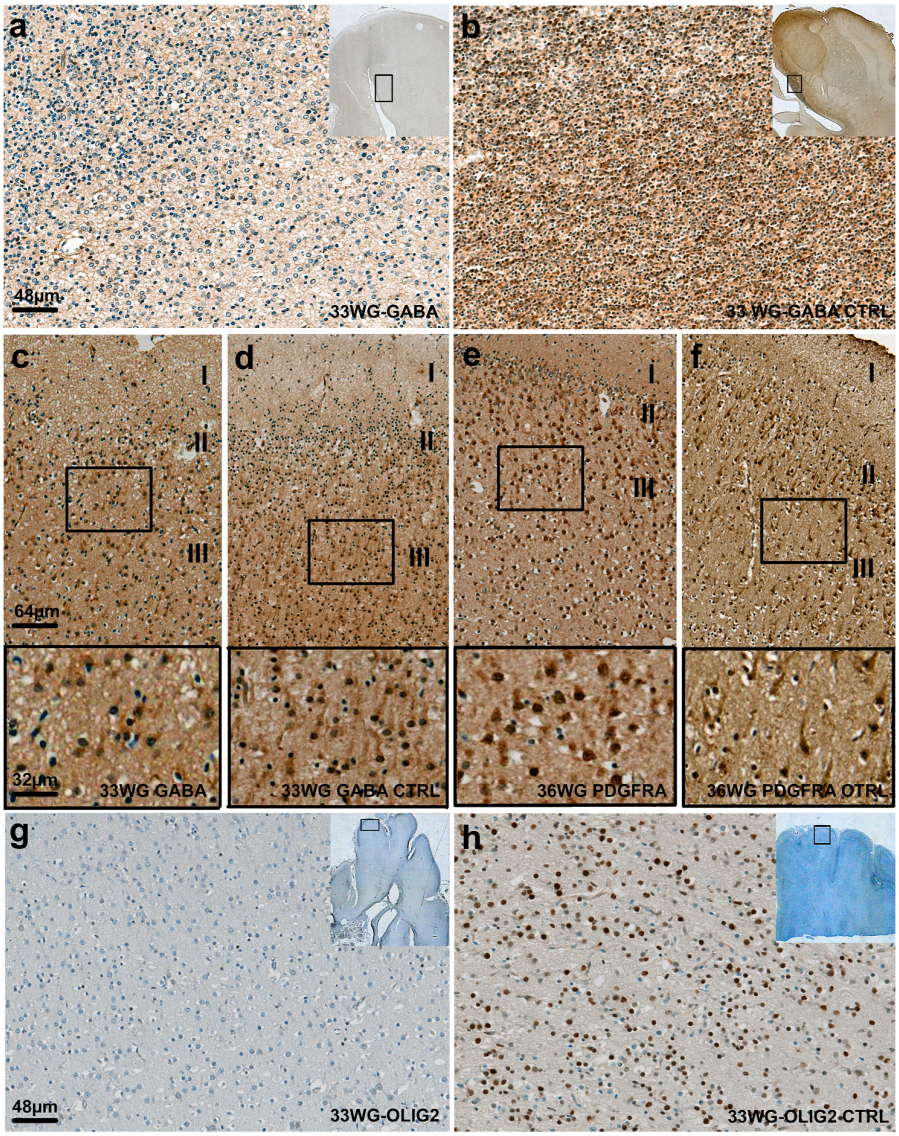

Fig. 6. Immunohistochemical hallmarks of *FOXG1*-mutated brains (continued)
(a) GABA immunohistochemistry displaying reduced density of GABAergic interneurons within the GE in case 1 [OM x 200; inset: low power picture marking the location (rectangular frame) of the mid-power picture], **(b)** compared with the control brain in which GABAergic interneurons represent at least 50% of the progenitors [OM x 200; inset: low power picture marking the location (rectangular frame) of the mid-power picture]. **(c)** Associated to reduced density in the CP [OM x 100; insert: layer III at OM x 400], **(d)** by comparison with the control CP in which GABAergic interneurons of various morphologies are observed in all layers with a predominance in upper layers II and III [OM x 100; inset: layer III at OM x 400]. **(e)** Increased PDGFRα-positive OPCs in the in the superficial layers of CP in case 2 [OM x 100; inset: layer III at OM x 400], **(f)** compared to the control brain in which PDGFRα-positive OPCs are dispersed in the upper layers of the CP [OM x 100; inset: layer III at OM x 400], **(g)** Along with almost no Olig2-positive pre-OLs in the cortical plate [OM x 400; inset: low power picture marking the location (rectangular frame) of the mid-power picture]. **(h)** By comparison with the control CP which contains numerous Olig2-positive pre-OLs [OM x 400; inset: low power picture marking the location (rectangular frame) of the mid-power picture]. Scale bars **(a, b, g, h)** 48 µm, **(c, d, e, f)** 64 µm, **(insets c, d, e, f)** 32 µm. OM: original magnification.

2019). Critical for axonal guidance, underdeveloped midline indusium griseum glia and disrupted FOXG1-repressor protein 58 (Rp58) repressive complex formation have been reported (Cargnin et al., 2018).

After birth, patients also present CC anomalies in 82% of the cases on MRI and fornix enlargement in 74% of the cases (Pringsheim et al., 2019). These findings strongly suggest that *FOXG1* haploinsufficiency alters combinatorial regulation of neuronal transcription profiles resulting in projection neuron identity disruption, insight-out migration and axonal guidance.

The two foetuses also presented haphazardly dispersed cortical GABAergic in all layers instead of predominating in layers III and V, but calretininergic interneuron alterations appeared globally normal in position though reduced in number. Interestingly, conditional *Foxg1*-deficient mice show abnormal distribution of these cells with an impaired laminar interneuron distribution and an increased ratio of exhibitory/inhibitory synapses persisting into adulthood (Chen et al., 2019; Eagleson et al., 2007; Shen et al., 2019; Yang et al., 2017). These findings could explain an increased susceptibility to epilepsy observed in 57–86% of FOXG1 deficient patients (Mitter et al., 2018; Vegas et al., 2018). Taken together, the present neuropathological report along with animal studies suggest that impaired lamination of cortical interneurons and consequently connectivity defects may play a central role in the pathophysiology underlying patients' epilepsy.

In third trimester FOXG1-deficient foetuses we detected more abundant astroglial cells of normal morphology in the IZ, in the absence of infectious or hypoxic-ischemic disruptive lesions. Interestingly, Falcone et al. showed in a recent work that Foxg1 overexpression within neocortical stem cells commits these cells to neuronogenesis rather than astrogenesis and that Foxg1 levels decline while neocortical stem cells move from neuronogenesis to gliogenesis (Falcone et al., 2019), pointing out on a pivotal role of Foxg1 in temporal regulation of astrogenesis. From their results and our observations, the excess of astrocytes in the IZ is very likely related to *FOXG1* haplosufficiency.

We also detected more abundant PDGFRα+ OPCs and fewer Olig2+ pre-OLs arguing for delayed production of OPCs, delayed oligodendrocyte differentiation and consequently delayed myelination. Myelination is an energy-demanding process which starts at the beginning of the third trimester in humans. OPCs originate from the periventricular germinative zones in multiple waves along a ventral-dorsal gradient (Fogarty et al., 2005; Kessaris et al., 2006; Tripathi et al., 2011; Vallstedt

et al., 2005). Fate mapping studies in Cre-lox transgenic mice have revealed that the first wave of OPCs is produced at embryonic day (E) 11.5 (Kessaris et al., 2006) under the early influence of ventral signalling centres (Lu et al., 2002). A second wave of OPCs is generated in the lateral GE and caudal GE at E15, followed by a last wave originating from the postnatal cortex (Kessaris et al., 2006). Whereas the first wave-derived OPCs are eliminated, the other wave-derived OPCs migrate and differentiate into pre- and mature OLs (Kessaris et al., 2006). In *Foxg*1-deficient mice, severe patterning defects with loss of ventral Shh specification and expanded dorsal markers have been repeatedly demonstrated (Huh et al., 1999; Manuel et al., 2010; Martynoga et al., 2005). At the time of first OPC production (E12.5), only a flattened residue of the GE has developed and cells rarely express Olig2 (Du et al., 2019) suggesting a lack of Shh-dependent Olig2-induction.

Knowing that forebrain OPCs express high levels of FOXG1, FOXG1-deficiency could also lead to cell-autonomous proliferation and differentiation defects of oligodendrocyte lineage (Marques et al., 2018). In a recent study using a conditional *Foxg1*-knockout mouse model Dong et al. described accelerated OPC differentiation and remyelination after cuprizone-induced demyelination in these mice (Dong et al., 2021) arguing against a cell-autonomous defect of the FOXG1-deficient oligodendrocyte lineage. These conflicting results could be explained by the fact that cuprizone is used to study demyelinating diseases of adulthood and is a model of toxic demyelination rather than of dysmyelination. One could hypothesize that myelin defects which are transiently observed in *FOXG1*-haploinsufficient humans could result from impaired specification of OPCs that requires activation of the Shh pathway which controls transcription factors Nkx2, Gsh2, Olig1/2 and Ascl1 while dorsalizing signals (BMPs) induce astrocyte specification. Myelin defects could also result from impaired proliferation and differentiation of OPCs which are regulated by several neuronal signals, positively by Olig1/2, SOX10 and Ascl1, and negatively by Lingo1 and Gpr17. Furthermore, in order to ensure an equivalent number of oligodendrocytes to that of axons which must be myelinated, OPCs are produced in excess under the influence of growth factors Platelet Derived Growth Factor-α (PDGF-A), FGF-2, Insulin Growth Factor 1 (IGF-1), neurotrophin 3 (NT-3) and Ciliary Neurotrophic factor (CNTF) then eliminated by apoptosis (reviewed by Simons and Nave, 2015) (Simons and Nave, 2015); Jiang and Nardelli, 2016 (Jiang and Nardelli, 2016)). These signaling pathways differ from the Wnt pathway which are involved in remyelination (Dong et al., 2021). It should also be kept in mind that in adult *Foxg1*-deficient mice no myelination defect has been reported up to now indicating that the second and third OPC production waves may compensate the embryonic failure of OPC generation. Pre-OLs expressing low levels of Foxg1 (Marques et al., 2018) may efficiently mature into myelinating OLs in rodents.

These findings may explain that the majority of FOXG1 syndrome patients (64%) present mild to severe reduction of myelin during infancy. Gradual improvement and normalization by the age of five years are in line with delayed oligodendrocyte maturation rather than oligodendrocyte lineage production alone (Vegas et al., 2018).

In conclusion, we describe for the first time the neuropathological hallmarks of antenatal FOXG1 syndrome in two foetuses which harboured premature stop codon mutations located at the same residue. Overall, human neuropathological findings recapitulate previous observations reported in animal models, i.e., severe layering defects of upper-layer projection neurons, GABAergic inhibitory interneuron alterations and delayed maturation of oligodendrocyte lineage with gliosis. These findings provide additional clues on the pathophysiological mechanisms underlying the symptomatology of *FOXG1*-haploinsufficient children including microcephaly, developmental delay, epilepsy and dyskinetic-epileptic symptoms.

CRediT authorship contribution statement

Nina-Maria Wilpert: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Florent Marguet:** Formal analysis, Investigation, Visualization. **Camille Maillard:** Formal analysis, Writing – review & editing. **Fabien Guimiot:** Investigation. **Jelena Martinovic:** Investigation. **Séverine Drunat:** Formal analysis. **Tania Attié-Bitach:** Formal analysis. **Ferechté Razavi:** Formal analysis. **Aude Tessier:** Investigation. **Yline Capri:** Investigation. **Annie Laquerrière:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision. **Nadia Bahi-Buisson:** Conceptualization, Formal analysis, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors have no competing interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2021.104282.

Abbreviations

CC	corpus callosum
FOXG1	Forkhead box G 1
GE	ganglionic eminences
H&E	Haematoxylin-Eosin
MRI	magnetic resonance imaging
OLs	oligodendrocytes
OM	original magnification
OPCs	oligodendrocyte precursor cells
Pre-OLs	pre-oligodendrocytes
Shh	Sonic hedgehog
SP	subplate
SVZ	subventricular zone
iSVZ	inner subventricular zone
oSVZ	outer subventricular zone
US	ultrasound
VZ	ventricular zone
WG	weeks of gestation

Availability of data and materials

Most data generated or analysed during this study are included in this article. Additional datasets are available from the corresponding author on request.

Ethics approval and consent to participate

Autopsies and genetic analyses were performed after appropriate written informed consent from the parents and in accordance with the French law.

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Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"ENDOCRINOLOGY and METABOLISM"**
Selected Category Scheme: WoS
Gesamtanzahl: 145 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	Nature Reviews Endocrinology	8,908	24.646	0.026300
2	Lancet Diabetes & Endocrinology	7,961	24.540	0.038680
3	Cell Metabolism	34,829	22.415	0.099550
4	DIABETES CARE	71,305	15.270	0.096210
5	JOURNAL OF PINEAL RESEARCH	10,695	15.221	0.010560
6	ENDOCRINE REVIEWS	13,381	15.167	0.008900
7	TRENDS IN ENDOCRINOLOGY AND METABOLISM	8,968	9.777	0.016630
8	Obesity Reviews	11,567	8.192	0.023730
9	FRONTIERS IN NEUROENDOCRINOLOGY	4,196	7.852	0.005490
10	THYROID	11,972	7.786	0.022810
11	DIABETES	53,532	7.199	0.064540
12	DIABETOLOGIA	30,692	7.113	0.041920
13	NEUROENDOCRINOLOGY	5,046	6.804	0.005690
14	METABOLISM-CLINICAL AND EXPERIMENTAL	14,379	6.513	0.016360
15	Molecular Metabolism	3,415	6.181	0.015290
16	DIABETES OBESITY & METABOLISM	9,982	6.133	0.021570
17	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	19,766	6.040	0.028050
18	Cardiovascular Diabetology	5,392	5.948	0.011550
19	ANTIOXIDANTS & REDOX SIGNALING	20,275	5.828	0.029700
20	JOURNAL OF BONE AND MINERAL RESEARCH	26,818	5.711	0.032070
21	FREE RADICAL BIOLOGY AND MEDICINE	40,820	5.657	0.040300

Publication 2

Wilpert NM, Krueger M, Opitz R, Sebinger D, Paisdzior S, Mages B, Schulz A, Spranger J, Wirth EK, Stachelscheid H, Mergenthaler P, Vajkoczy P, Krude H, Kuhnen P, Bechmann I, Biebermann H. Spatiotemporal Changes of Cerebral Monocarboxylate Transporter 8 Expression. Thyroid. 2020 Sep;30(9):1366–83
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Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI Selected Categories: **"GENETICS and HEREDITY"** Selected Category Scheme: WoS

Gesamtanzahl: 175 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS GENETICS	42,803	53.242	0.058930
2	NATURE GENETICS	113,066	38.330	0.186810
3	TRENDS IN ECOLOGY & EVOLUTION	44,127	17.712	0.028180
4	Annual Review of Genetics	9,053	16.830	0.009270
5	MOLECULAR BIOLOGY AND EVOLUTION	61,557	16.240	0.082270
6	GENOME BIOLOGY	54,758	13.583	0.098990
7	TRENDS IN GENETICS	14,465	11.639	0.018800
8	MOLECULAR THERAPY	24,333	11.454	0.030250
9	GENES & DEVELOPMENT	61,885	11.361	0.048660
10	Genome Medicine	8,115	11.117	0.023450
11	AMERICAN JOURNAL OF HUMAN GENETICS	43,477	11.025	0.054200
12	ONCOGENE	77,576	9.867	0.059180
13	GENOME RESEARCH	47,141	9.043	0.064690
14	Annual Review of Genomics and Human Genetics	3,238	8.929	0.004800
15	GENETICS IN MEDICINE	17,957	8.822	0.041550
16	npj Genomic Medicine	971	8.617	0.003910
17	GENOMICS PROTEOMICS & BIOINFORMATICS	3,241	7.691	0.006360
18	Molecular Autism	3,579	7.509	0.007400
19	Genes & Diseases	1,850	7.103	0.003170
20	Horticulture Research	2,607	6.793	0.004610

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	Clinical Epigenetics	5,526	6.551	0.011550
22	JOURNAL OF MEDICAL GENETICS	15,071	6.318	0.013500
23	HUMAN MOLECULAR GENETICS	47,192	6.150	0.047520
24	CRISPR Journal	453	6.071	0.002240
25	Circulation-Genomic and Precision Medicine	858	6.054	0.003910
26	CANCER GENE THERAPY	3,768	5.987	0.002720
27	PLoS Genetics	52,461	5.917	0.085820
28	GENOMICS	11,771	5.736	0.006800
29	THEORETICAL AND APPLIED GENETICS	25,124	5.699	0.012580
30	HUMAN GENE THERAPY	7,074	5.695	0.006860
31	MUTATION RESEARCH-REVIEWS IN MUTATION RESEARCH	4,185	5.657	0.003170
32	CURRENT OPINION IN GENETICS & DEVELOPMENT	8,648	5.578	0.012100
33	Genes and Nutrition	2,090	5.523	0.001740
34	Environmental Microbiome	56	5.286	0.000100
35	GENE THERAPY	8,112	5.250	0.004130
36	CHROMOSOME RESEARCH	2,752	5.239	0.002250
37	Microbial Genomics	1,939	5.237	0.006440
38	Biology of Sex Differences	2,153	5.027	0.004070
39	GENES CHROMOSOMES & CANCER	6,108	5.006	0.004810
40	JOURNAL OF INHERITED METABOLIC DISEASE	8,207	4.982	0.006970
41	Epigenetics & Chromatin	2,461	4.954	0.007240

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
42	DNA REPAIR	7,382	4.913	0.010500
43	Forensic Science International-Genetics	6,013	4.882	0.006510
44	HUMAN MUTATION	16,381	4.878	0.019060
45	MOLECULAR GENETICS AND METABOLISM	9,612	4.797	0.008610
46	Epigenomics	3,848	4.778	0.006970
47	Human Genomics	2,039	4.639	0.003030
48	Frontiers in Genetics	18,705	4.599	0.034820
48	JOURNAL OF MOLECULAR MEDICINE-JMM	9,445	4.599	0.008480
50	JOURNAL OF GENE MEDICINE	2,294	4.565	0.001380
51	GENETICS	46,408	4.562	0.034850
52	Epigenetics	6,347	4.528	0.006530
53	DNA RESEARCH	3,726	4.458	0.003800
54	CLINICAL GENETICS	9,278	4.438	0.012790
55	CURRENT GENE THERAPY	1,576	4.391	0.001330
56	CHROMOSOMA	3,633	4.316	0.003660
57	GENETICS SELECTION EVOLUTION	4,473	4.297	0.004770
58	MOLECULAR PHYLOGENETICS AND EVOLUTION	22,497	4.286	0.022160
59	Journal of Genetics and Genomics	2,754	4.275	0.003760
60	EUROPEAN JOURNAL OF HUMAN GENETICS	12,623	4.246	0.017880
61	Briefings in Functional Genomics	2,186	4.241	0.002850
62	MITOCHONDRION	4,982	4.160	0.004690
63	HUMAN GENETICS	10,191	4.132	0.009650

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Movement disorders in MCT8 deficiency/ Allan-Herndon-Dudley Syndrome

Silvia Masnada [a,b,*], Catherine Sarret [c], Clara Eleonora Antonello [b,d], Ala Fadilah [e], Heiko Krude [f], Eleonora Mura [a,b], Santosh Mordekar [e], Nicita Francesco [g], Sara Olivotto [a,b], Simona Orcesi [h,i], Francesco Porta [j], Ganaelle Remerand [k], Barbara Siri [j,l], Nina-Maria Wilpert [m], Pouneh Amir-Yazdani [n,o], Enrico Bertini [g], Markus Schuelke [m], Geneviève Bernard [n,p,q], Odile Boespflug-Tanguy [r,s], Davide Tonduti [a,b,*]

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ABSTRACT

Background and objectives: MCT8 deficiency is a rare genetic leukoencephalopathy caused by a defect of thyroid hormone transport across cell membranes, particularly through blood brain barrier and into neural cells. It is characterized by a complex neurological presentation, signs of peripheral thyrotoxicosis and cerebral hypothyroidism. Movement disorders (MDs) have been frequently mentioned in this condition, but not systematically studied.

Methods: Each patient recruited was video-recorded during a routine outpatient visit according to a predefined protocol. The presence and the type of MDs were evaluated. The type of MD was blindly scored by two child neurologists experts in inherited white matter diseases and in MD. Dystonia was scored according to Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). When more than one MD was present, the predominant one was scored.

Results: 27 patients were included through a multicenter collaboration. In many cases we saw a combination of different MDs. Hypokinesia was present in 25/27 patients and was the predominant MD in 19. It was often associated with hypomimia and global hypotonia. Dystonia was observed in 25/27 patients, however, in a minority of cases (5) it was deemed the predominant MD. In eleven patients, exaggerated startle reactions and/or other paroxysmal non-epileptic events were observed.

Abbreviations: Movement disorders, (MDs); Burke-Fahn-Marsden Dystonia Rating Scale, (BFMDRS); Allan-Herndon-Dudley Syndrome, (AHDS); Monocarboxylate Transporter 8, (MCT8); Free triiodothyronine, (FT3); Free Thyroxine, (FT4); Institutional Review Boards, (IRBs).

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Conclusion: MDs are frequent clinical features of MCT8 deficiency, possibly related to the important role of thyroid hormones in brain development and functioning of normal dopaminergic circuits of the basal ganglia. Dystonia is common, but usually mild to moderate in severity, while hypokinesia was the predominant MD in the majority of patients.

1. Introduction

Allan-Herndon-Dudley Syndrome or MCT8 deficiency (AHDS/MCT8) is a rare X-linked neurodevelopmental disorder due to an impairment of the normal transport of thyroid hormones across cell membranes, particularly across the blood brain barrier and into specific neurons. The hallmark of the disease is a striking abnormal plasma thyroid hormones profile with high free triiodothyronine (FT3), low free thyroxine (FT4), and normal thyroid stimulating hormone (TSH) concentrations [1,2]. The clinical picture is characterized by signs of peripheral thyrotoxicosis due to elevated FT3 (e.g. tachycardia at rest) but it is by far dominated by neurological signs that are thought to be related to "cerebral hypothyroidism" although the exact mechanism of Central Nervous System (CNS) deficiency is yet unsolved. Onset is usually during the first year of life with neurodevelopmental delay progressing to intellectual disability of various severity, global hypotonia often associated with pyramidal signs and movement disorders (MD). Epileptic seizures can be observed, more often in advanced disease stages and, in some patients, paroxysmal MDs have been reported [3–10]. Magnetic Resonance Imaging (MRI) usually shows a pattern of severe myelination delay which can be mistaken for hypomyelination during the first 3–4 years of life [11,12]. In fact, even if pathology demonstrated white matter structural alterations in patients older than 4 years of age [13,14] the myelination progression typically seen on MRI does not fulfill neuroradiological criteria of hypomyelination [15].

Although the disease has been first described in 1944 [16], there are still some clinical features which have not been precisely defined. Notably, MDs have been frequently reported but they were variably described as "dystonia", "choreo-athetosis", "rigidity", or "abnormal hand posturing" [3–5,7,17,18]. Paroxysmal MDs have been also reported [7–10,19]. The severity of the MDs and their impact on patients' global disability have not been studied systematically thus far. As specific pharmacologic interventions for AHDS are emerging, it has become urgent to clearly define the neurological features of the disease, and its natural history in order to select the most likely group of patients to benefit from a therapy, and to define clinical endpoints to assess treatment efficacy [19,20]

With the present study, we analyzed MDs in a series of 27 AHDS patients, collected through a multicenter collaboration, aiming at improving the definition of the extrapyramidal features of the disease.

2. Material and methods

We recruited patients with genetically proven AHDS through an international multicenter collaboration from seven centers. The study adheres to the principles of the Code of Ethics of the World Medical Association- Helsinki Declaration. It was approved by the local Institutional Review Boards (IRBs). Written informed consent was obtained from the patients' parents or legal representatives. The parents/legal representatives of patients recorded in the videos signed the consent for videotape authorization, in compliance with any laws regarding patient authorizations related to the use or disclosure of protected health information within the jurisdiction of the participating centers.

A video-recording session was performed locally for each patient following a predetermined video-protocol. It was designed to include elements of commonly used protocols for video-assessment of MD (Supplementary material) [21,22]. All videos were collected and evaluated centrally at C.O.A.L.A. (Center for diagnosis and treatment of leukodystrophies) in Milan, Italy. Videos were blindly scored by two child neurologist experts in inherited white matter diseases and in MD (D.T. and S.M).

Each patient was evaluated for the (i) presence or absence of a MD and (ii) the type of MD (either hypokinetic or hyperkinetic, namely dystonia, chorea, athetosis, ballism, myoclonus, tremor and tics). When more than one type of MD was present we scored each but we noted which was the predominant one. Dystonia was scored using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) [24]. This scale is composed of a Dystonia Severity Score (which is the product of two factors: the Provoking Factor and the Severity Factor) and a Global Disability Score. It is to note that AHDS is a complex disease that comprises a number of different neurological signs and symptoms; e.g. it was not possible to decide whether swallowing problems, which were present in the majority of patients, were specifically due to dystonia or to another etiology. It was the authors' impression that in most cases, dystonia was not the cause. For this reason, the items in connection with swallowing function were excluded from the dystonia severity scoring. After this modification, the severity score ranged from a minimum of 0 to a maximum of 104. The global disability score was not modified and ranged from 0 to 30. Interrater reliability was tested by kappa statistic (kappa with linear weighting [k_w]). Videos scored differently by the raters were jointly re-evaluated and discussed with whole C. O. A. L. A. team (D.T., S.M., E.M, S.O., and C.A.). The final "Dystonia Provoking factor" was decided by consensus and a final agreement has been reached in all cases; the "Dystonia Severity Factor" was the average of the two evaluations. The final Dystonia Severity Score was the product of the two factors.

3. Results

Twenty-seven male patients were included in the study. Mean age at evaluation was 9.3 years (range 0.9–18.5). Molecular genetic data and main clinical findings are reported in Table 1. The types of MD described in this series were dystonia, hypokinesia, and paroxysmal MD. Dystonia was observed in 25/27 patients; however, it was the predominant MD in only a minority of cases (5/27) (video #2). Hypokinesia was present in 25/27 patients, and it was deemed to be the predominant MD in 19/27 patients (video #1). It was usually associated with hypomimia and global hypotonia. No one child exhibited rigidity or tremor. In 3/27 patients Dystonia and hypokinesia were both present but none of the two was deemed to be predominant compared to the other.

Besides hypokinesia and/or dystonia, 11 patients also exhibited paroxysmal phenomena, e.g. 10/11 patients suffered from exaggerated "startle reaction" in response to even mild sudden sensory stimuli. Two of these 10 patients also presented with paroxysmal episodes triggered by diaper change and characterized by sudden blush, tonic asymmetric posture, and chin tremor without loss of consciousness. Ictal electroencephalographic (EEG) did not show any concomitant epileptiform activity. Parents were able to provoke this type of episodes. In one child, there was a certain degree of apparent pleasure derived from it: when parents prepared the child for diaper changing, he showed signs of happiness and he was clearly disappointed if they interrupted the process. One patient suffered from paroxysmal generalized dystonia usually occurring after meals (video #3).

Different MDs existed simultaneously in the majority of patients, e.g. dystonia and hypokinesia were associated in 23 patients, one patient

Table 1
Basic demographic features, *SLCA16A2* pathogenic variants annotated according to genome build GRCh37/hg19 and *SLC16A2* transcript NM_006517, MD types and BFMDRS scores.

Pt number	Age (years)	*SLCA16A2* pathogenic variants	Dystonia	Dystonia severity(range 0–104)	Paroxismal MD	Hypokinesia	Disability score (range 0–30)
1	8.6	c.590G > A	+	26.5	+	+	26
2	8.8	c.1469G > A	+	18	+	+	28
3	12.8	c.1184 T > C	+	3.5	−	+	14
4	18.5	c.795 T > G	+	21	−	+	30
5	12.8	c.1333C > T	+	9.5	+	+	23
6	14.8	c.352A > G	+	12	+	+	24
7	9.8	c.352A > G	+	2.5	+	+	22
8	8.4	c.511C > T	+	63.3	+	−	30
9	1.9	c.623G > A	+	26	−	+	28
10	1.2	c.407_408insA	+	12	−	+	27
11	10.9	c.467_469delTCT	+	33	+	+	29
12	7.9	c.608 T > C	−	0	−	+	30
13	9.6	c.1171-1G > C	+	1.5	−	+	30
14	13.5	c.980G > A	+	3	−	+	2
15	15.9	c.1111C > T	+	22.5	−	+	12
16	15.3	c.1399 + 2 T > C	+	18	−	+	17
17	10.8	c.623G > A	+	14	−	+	30
18	6.0	c.575A > G	+	27	−	+	30
19	15.8	c.439G > A	+	31.5	−	+	29
20	2.5	c.740C > T	+	27.5	+	+	30
21	17.5	c.150_151insCT	+	1.5	+	+	28
22	8.2	c.575A > G	+	44	−	+	29
23	11.8	c.979G > A	−	0	+	+	28
24	1.3	c.435G > A	+	12	−	+	27
25	1.4	c.39_45delGCCCTGG	+	24	−	+	28
26	0.9	c.1190 T > C	+	21.75	−	−	26
27	5.5	c.1190 T > C	+	28.5	−	+	28

suffered from dystonia and paroxysmal MD, one from hypokinesia and paroxysmal MD. In one patient dystonia was the only type MD, while in another hypokinesia was seen in isolation.

As stated above, dystonia was scored using the BFMDRS [23]. A substantial agreement between raters was achieved (linear k_w0.7388; standard error 0.0337; 95% confidence interval 0.6727–0.8049). The mean dystonia severity score was 18.7/104.0 (range 0.0–63.3) (Fig. 1). None suffered from focal dystonia, it was generalized in 5 patients while it was multifocal in all others. In all cases, the type was action dystonia, and none suffered from dystonic posturing at rest. Considering the body distribution of dystonia, according with BFMDRS items: upper limbs were involved in 21 patients, lower limbs in 17, facial distribution (including mouth or eyes) in 20, neck in 10, and trunk in 4.

The mean disability score was 25.4/30.0 (range 2.0–30.0) (Fig. 1). All but one areas were severely affected in most patients with a mean score of 3.63/4.0 in the speech subscale, 3.41/4.0 in handwriting, 3.52/4.0 in feeding, 3.70/4.0 in hygiene, 3.52/4.0 in dressing, 5.5/6.0 in walking. Eating was relatively less affected with a mean score of 2.1/4.0.

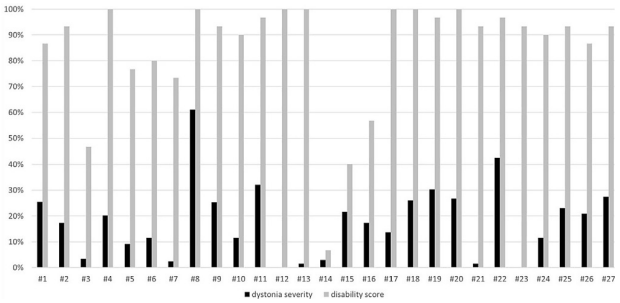

Fig. 1. BFMDRS results.
The graphs show dystonia severity and global disability scores obtained by BFMDRS for each patient. Scores are expressed in percentage of the total to allow for comparison between both sub-scores. The global disability level was generally more severe as compared to dystonia severity.

4. Discussion

We report here on a series of 27 patients affected with AHDS. The global neurological picture was usually complex including cognitive impairment, pyramidal signs often predominant at the lower limbs, MDs and in some cases epileptic seizures. In this study, we focused on MDs. Our study is the so far largest one on the topic. According to literature [4,5], in our cohort, MD was a common feature and particularly dystonia, which was present in a large number of patients. It was usually multifocal, and the body segments that were most frequently involved were the facial district and upper limbs. In all patients, it was present during voluntary movements or during stressful situations, while it was absent at rest. If on one hand our series confirms literature data, namely that dystonia represents a common feature of AHDS, on the other hand, our series reveals that dystonia was rarely severe. In our study we scored the severity of dystonia by BFMDRS, which is designed as a composite score: section one rates dystonia severity, section two rates the disability level. In the whole group, mean global disability level was much more severe (average 25.4/30) as compared to the mean dystonia severity score (average 18.7/104.0) (Fig. 1). This observation, as well as our general clinical impression, suggests that dystonia in AHDS-patients only mildly contributes to their functional disability.

Dystonia was not the only type of MD observed in our cohort. Most patients presented with hypokinesia and hypomimia, severe trunk hypotonia, and derangement of postural reactions. These were usually much more prominent than dystonia and appeared to contribute much more to the overall functional disability burden of our AHDS patients, in addition to pyramidal signs and severe cognitive impairment.

A group of patients also presented with a paroxysmal MD, that was stimulus dependent in all cases. Some patients showed exaggerated startle reactions in response to sudden sensorial stimuli. In two patients, a complex MD mimicking a tonic asymmetric epileptic seizure (excluded by ictal EEG recording), was triggered by diaper change. Similar findings have been already reported in literature in other AHDS patients [9,10,18].

Thyroid hormones play a central role during brain development, particularly during neuronal and glial cell maturation, cyto-architectural organization, and in synaptogenesis. They are also important for normal

metabolism and function of the brain and particularly in dopaminergic circuits [24]. Indeed, some studies have shown that thyroid hormones are involved in dopamine regulation; e.g. dopamine degradation is enhanced and dopamine synthesis reduced in hypothyroid states through inhibition of the rate-limiting enzyme tyrosine hydroxylase [25]. We could argue that both mechanisms might contribute to the occurrence of MDs in AHDS patients. However, in patients with untreated congenital hypothyroidism severe muscular hypotonia and severe motor developmental delay is usually present but MD as observed in our AHDS patients is absent [26]. The exact pathophysiological mechanism underlying MDs in AHDS patients is still to be elucidated and further studies on that topic are needed.

The study has some limitations. This is an international cohort and the MD evaluation was based on video recordings. This allowed collecting a larger number of patients to be scored by the same team but may have the intrinsic limit of not having evaluated patients in a "live" clinical setting. Moreover, this work represents only a first step towards a better definition of the neurological phenotype of AHDS. We focused here on a cross-sectional analysis of MD, and did not systematically and prospectively collect data. Further studies will be needed to define the natural history of the disease and particularly the evolution of the extrapyramidal signs.

5. Conclusion

In conclusion, we confirmed that MDs are a frequent feature of AHDS. This might be explained through the important role of thyroid hormones on brain development and normal dopaminergic circuits functioning. However, the exact mechanism underlying MDs in AHDS patients remains to be uncovered. Dystonia is common, but moderate or mild, while hypokinetic MD seems to be more common and severe. Paroxysmal movement disorders may also be present and in some cases may mimic epileptic seizures.

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Documentation of author roles

Davide Tonduti: involved in the care of the patients, in the preparation of patients' videos, conceptualization of the study, data acquisition and interpretation, scoring of patients' videos, manuscript drafting and revision.

Silvia Masnada: involved in the preparation of patients' videos, conceptualization of the study, data acquisition and interpretation, scoring of patients' videos, manuscript revision.

Eleonora Mura, Sara Olivotto, Clara Eleonora Antonello: scoring of patients' videos, manuscript revision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2021.12.003.

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Curriculum vitae

No curriculum vitae are to be included in electronic dissertations for reasons of confidentiality.

List of Publications

Original articles

1 Wilpert N-M, Marguet F, Maillard C, Guimiot F, Martinovic J, Drunat S, Attié-Bitach T, Razavi F, Tessier A, Capri Y, Laquerrière A, Bahi-Buisson N. Human neuropathology confirms projection neuron and interneuron defects and delayed oligodendrocyte production and maturation in FOXG1 syndrome. Eur J Med Genet. 2021 Sep;64(9):104282.

2 Wilpert NM, Krueger M, Opitz R, Sebinger D, Paisdzior S, Mages B, Schulz A, Spranger J, Wirth EK, Stachelscheid H, Mergenthaler P, Vajkoczy P, Krude H, Kuhnen P, Bechmann I, Biebermann H. Spatiotemporal Changes of Cerebral Monocarboxylate Transporter 8 Expression. Thyroid. 2020 Sep;30(9):1366–83.

3 Masnada S, Sarret C, Antonello CE, Fadilah A, Krude H, Mura E, Mordekar S, Francesco N, Olivotto S, Orcesi S, Porta F, Remerand G, Siri B, Wilpert N-M, Amir-Yazdani P, Bertini E, Schuelke M, Bernard G, Boespflug-Tanguy O, Tonduti D. Movement disorders in MCT8 deficiency/Allan-Herndon-Dudley Syndrome. Mol Genet Metab. 2022 Jan;135(1):109–13.

Conference contributions

1 Poster presentations

Gordon Research Conference, Barriers of the CNS. June 2018, New London, NH, US. Highway to the Human Brain: How do Thyroid Hormones reach the Central Nervous System?

2 Prize presentations

63. Deutscher Kongress für Endokrinologie. March 2020, Gießen. Von Basedow-Preis: Spatiotemporal Changes of Cerebral MCT8 Expression.

3 Oral presentations

Thyroid Trans Act meeting (SPP 1629). June 2017, Bremen. Development of T3-peptide ligands to treat MCT8 deficiency via a Trojan horse like mechanism.

33. Arbeitstagung Experimentelle Schilddrüsenforschung (AESF). January 2018, Berlin. Thyroid hormones: highway to the human brain.

61. Deutscher Kongress für Endokrinologie. March 2018, Bonn. Distribution of Monocarboxylate Transporter 8 in the Human Neurovascular Unit.

21st Barrier and Transporter Meeting. May 2019, Bad Herrenalb. Monocarboxylate Transporter 8 Expression Profile: Constant Protein Abundance in Barriers of the CNS versus Developmental Decline of Neuronal Expression.

30ème congrès de la société française de neurologie pédiatrique. January 2020, Toulouse. Aspects neuropathologiques de formes extrêmes du syndrome FOXG1: Défaut de prolifération et de lamination corticale associée à un défaut de différenciation oligodendrocytaire.

30ème congrès de la société française de neurologie pédiatrique. January 2020, Toulouse. Cerebral MCT8 Expression Profile.

European Pediatric Neurology Society Virtual Research Meeting (EPNS). November 2021, virtual. Extreme Phenotype of FOXG1 Syndrome: a Neuropathological Study.

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