FOXG1-Related Disorders: From Clinical Description to Molecular Genetics

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Key Words

Chromosome 14 • Clinical features • Congenital variant • Encephalopathy • *FOXG1* • Human • Microcephaly • Molecular basis of disease • Mouse • Rett syndrome

Abstract

Rett syndrome (RTT) is a severe neurodevelopmental disease that affects approximately 1 in 10,000 live female births and is often caused by mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MECP2). Mutations in loci other than *MECP2* have also been found in individuals that have been labeled as atypical RTT. Among them, a mutation in the gene forkhead box G1 (*FOXG1*) has been involved in the molecular aetiology of the congenital variant of RTT. The *FOXG1* gene encodes a winged-helix transcriptional repressor essential for the development of the ventral telencephalon in embryonic forebrain. Later, *FOXG1* continues to be expressed in neurogenetic zones of the postnatal brain. Although RTT affects quasi-exclusively girls, *FOXG1* mutations have also been identified in male patients. As far as we know, about 12 point mutations and 13 cases with *FOXG1* molecular abnormalities (including translocation, duplication and large deletion on the chromosome 14q12) have been described in the literature. Affected individuals with *FOXG1* mutations have shown dysmorphic features and Rett-like clinical course, including normal perinatal period, post-

natal microcephaly, seizures and severe mental retardation. Interestingly, the existing animal models of *FOXG1* deficiency showed similar phenotype, suggesting that animal models may be a fascinating model to understand this human disease. Here, we describe the impacts of *FOXG1* mutations and their associated phenotypes in human and mouse models.

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History of the Syndrome

In 2005, Shoichet et al. reported a 7-year-old girl exhibiting severe cognitive disability associated with a significant asymmetrical enlargement of the lateral ventricles, frontal and parietal myelination defects, complete agenesis of the corpus callosum, cerebral seizures, tetraplegia and microcephaly with a balanced de novo translocation t(2;14)(p22;q12) with a neighboring 720-kb inversion in chromosome 14q12 that disrupts the winged-helix transcription factor forkhead box G1 (*FOXG1*) gene [Shoichet et al., 2005]. Later, three 14q12 interstitial deletions (3.1 Mb, 2.9 Mb, and 3.6 Mb) including *FOXG1* (MIM 164874) were identified and characterized in 2 girls with psychomotor retardation, epilepsy, microcephaly, and unusual facial features, and in a 10-month-old male patient with mental retardation, microcephaly,

and facial dysmorphism [Bisgaard et al., 2006; Papa et al., 2008; Mencarelli et al., 2009]. Finally, the importance of the *FOXG1* gene was reinforced by linking *FOXG1*-null mutations and the congenital variant of Rett syndrome (RTT) in 2 unrelated girls [Ariani et al., 2008]. The congenital variant is 1 of the 5 subgroups of atypical RTT, and although up to 95% of classical RTT and 40–50% of atypical RTT are caused by mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene, only few girls described as congenital variants have been reported as mutated in this gene [Huppke et al., 2000; Monrós et al., 2001; Smeets et al., 2003; Rajaei et al., 2011]. Initially described by Rolando, the affected girls showed several clinical features observed in classic RTT, but in addition they were described as atonic and mentally retarded from the very first months of life [Rolando, 1985]. The most consistent RTT-like features observed in these patients were microcephaly, either of congenital onset or secondary to early postnatal deceleration of head growth, hand stereotypies, neurogenic scoliosis, and some autonomic features including hypotrophic feet, bloating, and impaired nociception. However, because RTT is a neurodevelopmental disorder affecting almost exclusively females, large molecular screening of the *FOXG1* gene were initially carried out in cohorts of female individuals suffering from typical and atypical forms of RTT [Bahi-Buisson et al., 2010; Mencarelli et al., 2010; Philippe et al., 2010], and this bias may explain why only one male patient has been reported to date with *FOXG1* point mutations [Le Guen et al., 2011].

Clinical Features

Microdeletions on Chromosome 14q12

Up to now, interstitial deletions of the long arm of chromosome 14 are a quite rare finding. Reported deletions have ranged from the loss of multiple bands to smaller deletions involving a single band [Kamnasaran et al., 2001; Petek et al., 2003]. The clinical phenotype varies, but some features commonly seen include global developmental delay, hypotonia, delayed myelination, seizures, microcephaly and craniofacial anomalies. Few numbers of interstitial deletions smaller than 3.5 Mb, involving band 14q12 and including only few genes, have been described in the literature (table 1). In 2006, Bisgaard et al. reported an 11-month-old girl with a 14q12 interstitial deletion of 3.1 Mb. This girl showed psychomotor retardation, epilepsy, microcephaly, and unusual facial features [Bisgaard et al., 2006]. Two years later, a de

novo chromosome 14 interstitial deletion of about 3.12 Mb has been revealed using array-based comparative genomic hybridization (CGH) analysis [Papa et al., 2008]. In this last study, the patient showed severe neurological impairment, and a distinctive facial feature very similar to the Bisgaard's case. Together, Bisgaard and Papa's studies have identified 5 genes from the commonly deleted region: *FOXG1*, *PRKD1*, *SCFD1*, *COCH* and *STRN3*.

More recently, a 3.6-Mb de novo deletion has been reported in a 10-month-old Caucasian male [Mencarelli et al., 2009]. This patient showed microcephaly noted before the fifth month of life, severe feeding problems and facial dysmorphisms. EEG abnormalities and epilepsy were not yet present. Importantly, the patient also showed an additional de novo deletion in 10q21.1 of about 4.8 Mb. Interestingly, the case described by Mencarelli et al. showed similarities with the other cases described in Bisgaard and Papa's studies only for few clinical features (probably due to the presence of the additional rearrangement on chromosome 10). Another de novo deletion about 2.6 Mb was identified by array-CGH analysis in a 3-year-old female [Jacob et al., 2009]. The genes localized to this region included *FOXG1* and a putative gene *C23orf14* with unknown function. Developmental delay was noticed at 4 months of age. Brain magnetic resonance imaging (MRI) at 6 months showed microcephaly with appropriate structure and myelination.

In conclusion, the emerging phenotype of microdeletions in 14q12 region is characterized by severe mental retardation with a normal perinatal period followed by a phase of developmental regression at the age of 3–6 months. The phenotype includes postnatal microcephaly, postnatal growth retardation, hypotonia, and stereotypic movements. Comparison of the clinical pictures presented by these patients allowed the definition of a peculiar facial phenotype characterized by mild dysmorphisms such as bulbous nasal tip and prognathism.

Duplications on Chromosome 14q12

Duplication of the chromosomal region encompassing *FOXG1* has been first reported in 1 patient with infantile spasms, severe intellectual impairment, and minor dysmorphisms [Yeung et al., 2009]. More recently, 6 cases with duplications of the 14q12 region containing the *FOXG1* gene were described [Brunetti-Pierri et al., 2011], and a seventh case with developmental impairment and a 14q12 duplication involving the *FOXG1* gene was described in the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER 248559) (table 2). Three cases were de-

Table 1. Clinical summary of the patients with interstitial deletions of the long arm of chromosome 14 including the *FOXG1* gene

	Bisgaard et al. [2006]	Papa et al. [2008]	Mencarelli et al. [2009]	Jacob et al. [2009]
Case number	1 (3.1 Mb)	1 (3.12 Mb)	1 (3.6 Mb)	1 (2.59 Mb)
Sex	female	female	male	female
Age	11 months	7 years	10 months	3 years
Normal OFC at birth	33 cm (–1 SD)	32 cm (–1 SD)	33 cm (–1 SD)	32.5 cm (–1 SD)
Deceleration of head growth from birth (microcephaly)	yes	yes	yes	yes
Regression	no	yes (<6 months)	yes (<3 months)	no
Severe intellectual disability	present	present	present	present
Hypotonia	yes	yes	yes	yes
Poor to absent voluntary hand use	no	yes	no	N/A
Facial abnormalities	prominent metopic suture, apparently large ears, bilateral epicanthal folds, bulbous nasal tip, depressed nasal bridge, tented upper lip, and everted lower lip	prominent metopic suture, large ears, bilateral epicanthal folds, bulbous nasal tip, depressed nasal bridge, thick upper lip, everted lower lip, prognathism, and hypermetropia	apparently large ears, bilateral downsloping palpebral fissures, bulbous nasal tip, depressed nasal bridge, thin upper lip, and lower lip, prognathism	low ears, synophrys, depressed nasal bridge, bulbous nasal tip, thin lips, and pointed chin
Seizures	present	present (6 months)	no	present
Stereotypic movements	dyskinetic movements	constant of hands and tongue	yes	yes (face, limb)
Jerky movement of the upper limbs	no	yes	yes	N/A
Bruxism	no	yes	no	yes
Speech	no	no	no	N/A
Delayed myelination or hypomyelination	N/A	N/A	N/A	no
Hypoplastic corpus callosum	no	agenesis	agenesis	N/A
Frontal and temporal atrophy with gyral simplification	no	no	absence of gyrus anguli	no

N/A = Not available.

Three other cases have been described, but clinical data were insufficient to be included in this table (a de novo 0.64-Mb deletion [unpublished data] and two 0.14–1.8-Mb deletions (DECIPHER database) [Mencarelli et al., 2009]).

scribed by using array CGH among over 11,000 patients (0.027%), and 3 cases among 3,752 patients (0.08%). The emerging phenotype of duplications is characterized by a severe developmental and intellectual impairment associated with an absence or a delay of speech. The majority of the patients with duplications on 14q12 showed developmental epilepsies and infantile spasms (4/8). Five of them were affected with body dysmorphic disorders, but did not share any facial dysmorphisms. The differences in the phenotype may be explained in part by the size of the duplications on 14q12 varying between 3.1 and 18.4 Mb. It has been proposed that the genes *SUPT16H* and *CHD8* may account for the varying degrees of developmental delay/mental retardation in patients with 14q11.2 deletions and may also be relevant for patients with duplications involving this region. The minimal duplicated region on 14q included only the following 3 genes: *FOXG1*, *MAPK1IP1L* and *PRKDI* [Brunetti-Pierri et al., 2011].

Point Mutations in the *FOXG1* Gene

Only 11 different point mutations (including the p.Gln46X) [Mari et al., 2010; F. Mari, personal communication] have been identified in the *FOXG1* gene. Combining the clinical data from the literature (tables 3 and 4), we have listed the most consistent features observed on the 10 published cases with *FOXG1* point mutations: (i) normal pregnancy and normal delivery, (ii) normal auxological parameters at birth, followed by severe presentation excluding the classic period of regression of typical RTT patients after a period of normal development, (iii) very limited motor development, (iv) generalized hypotonia, (v) congenital microcephaly (or early-onset deceleration of head growth progressively resulting in absolute microcephaly before 4 months of age) and (vi) relative preservation of eye contact though not as intense eye gaze as the eye pointing of classical RTT and no language (if any, limited to babbling). No girl with a mutation could either walk with support, although 2 cases can stand up

Table 2. Clinical summary of the patients with *FOXG1* duplications

	Yeung et al. [2009]	Brunetti-Pierri et al. [2011] ^a
Case number	1	7
Sex	female	6 males, 1 female
Age range	9	19 months–35 years
Normal OFC at birth	yes	1 normal; 6 N/A
Deceleration of head growth from birth (microcephaly)	no	2/7
Regression	yes (3–6 months)	1/6, 1N/A
Developmental delay/mental retardation	yes	7/7
Hypotonia	yes	1/7
Absence/delayed speech	no	7/7
Walk	yes	5/7
Ophthalmological abnormalities	no	Keratoconus 1/7
Seizures	yes (3 months)	4/7 (1 generalized tonic-clonic seizures, 3 infantile spasms)
Dysmorphic features	N/A	4/7
Cleft palate	no	1/7
Postaxial polydactyly	no	1/7
Syndactyly	yes	1/7
Deletion size	4.45 Mb	3.1–18.4 Mb

N/A = Not available. ^a Including the DECIPHER 248559 patient.

with assistance [Mencarelli et al., 2010]. They also demonstrated feeding difficulties and features of autonomic origin, such as cold and hypotrophic extremities and abdominal bloating, but no breathing disturbances.

More specifically, the 10 patients with *FOXG1*-point mutations showed intense hyperkinetic movement disorders with polymorphic midline stereotypies and jerklike movements mainly consisting of axial and limb myoclonia. The pattern of these stereotypies differs from those of classic RTT with no hair-pulling, rare hand-washing and a predominance of hand-pulling and pill-rolling. Moreover, they had bruxism and repetitive protrusive tongue movements. Another striking feature in *FOXG1*-related encephalopathy is the high prevalence of strabismus in these patients, which is usually not observed in other RTT variants. Epilepsy is also a frequent feature with generalized tonic and myoclonic seizures, with a highly variable age of onset ranging from 4 months to 14 years of age [Ariani et al., 2008]. The EEG pattern does not suggest any specific epilepsy syndrome. In the great majority of cases and in contrast with *CDKL5*-related disorders, seizures were easily controlled by antiepileptic drugs.

Fine analysis of brain MRI data showed significantly delayed myelination in 2 *FOXG1* mutation patients investigated at 22 months of age [Bahi-Buisson et al., 2010]. These effects range from delayed myelination to global hypomyelination, combined with frontal and temporal

Table 3. Major clinical signs that characterize patients with *FOXG1* point mutations (in bold in the table)

	Girl (n = 11) ^{a-d}	Boy (n = 1) ^e
Head circumference at birth	2/11	1
Postnatal microcephaly <−3 SD	10/10 (1 N/A)	1
Eye contact and pursuit	4/7 (4 N/A)	1
Ability to walk	1/11	0
Hand stereotypies	11/11	1
Jerky-like movement	8/10 (1 N/A)	1
Bruxism	10/11	1
Seizure/epilepsy	7/10	0
Sleep disorders	5/10	1

N/A = Not available.

^a Mencarelli et al. [2010]. ^b Ariani et al. [2008]. ^c Bahi-Buisson et al. [2010]. ^d Philippe et al. [2010]. ^e Le Guen et al. [2011].

atrophy with gyral simplification and a hypoplastic corpus callosum (fig. 1). Previous studies also described that *FOXG1* mutations are associated with corpus callosum abnormalities [Ariani et al., 2008; Philippe et al., 2010] or, in few cases, with poor development of frontal and parietal lobes [Shoichet et al., 2005]. This severe myelination delay may suggest a link between *FOXG1* and oligodendrocyte maturation. Whether *FOXG1* loss of function di-

Table 4. Clinical summary of female and male patients with *FOXG1* mutations

	Mencarelli et al. [2010], Ariani et al. [2008]	Bahi-Buisson et al. [2010]	Philippe et al. [2010]	Le Guen et al. [2011]
Case number	5	3	2	1
Sex	female (5/5)	female	female	male
Age range, years	2.6–22	3–5.8	10–22	3
Normal OFC at birth, cm	33.5–34 (one N/A)	31.7–34 (–1 to 2 SD)	34 (–1 SD)	33 cm (10th p.)
Deceleration of head growth from birth	4/5; 1 N/A	2/3	2/2	yes
Current OFC centile	42–49 cm (–2 to –2.6 SD)	42–45 cm (–3 to –4 SD)	48.5 cm (–2 SD), 1 N/A	43 cm (<3rd p.)
Regression	5/5 (3–6 months)	0/3	2/2 (4–6 months)	no
Severe intellectual disability	5/5	3/2	2/2	yes
Relative preservation of eye contact	1 yes; 1 no; 3 N/A	2/3	No	yes
Hypotonia	3/4; 1 N/A	3/3	1/2	yes
Scoliosis	3/5; 1 N/A	2/3	0/2	no
Ability to walk	0/5	0/3	1/2	no
Poor to absent voluntary hand use	4/5 (17 months–14 years); 1 N/A	3/3	1/2	yes
Ophthalmological abnormalities	2 strabismus; 3 N/A	3/3 convergent strabismus	2/2 strabismus	yes, convergent strabismus
Seizures (age of onset)	2/5; 1 N/A	2/3 (4 and 18 months)	1/2 (2 years)	no
Hand stereotypies	4/5; 1 N/A	3/3 complex intermixed with wringing movements of fingers and mouthing	2/2	yes hand mouthing
Jerky movement of the upper limbs	4/5; 1 N/A	3/3	1/2	yes
Bruxism	4/5; 1 N/A	3/3	1/2	yes
Mood lability inconsolable crying	2/5; 3 N/A	2/3	2/2	yes
Sleep disturbance	1/5; 1 N/A	1/3	1/3	yes
Delayed myelination or hypomyelination	5 N/A	3/3 mild to severe	1/2 severe, with reduced white matter volume	yes, severe
Hypoplastic corpus callosum	3/5; 1 N/A	2/3	1/2	hypoplastic
Frontal and temporal atrophy with gyral simplification	N/A	2/3	1/2	yes, severe

N/A = Not available.

rectly or indirectly affects myelination via alterations of myelin-axon interactions or both remains to be addressed by further experiments.

Altogether, association of postnatal microcephaly, dyskinetic movement disorders, stereotypic hand movements, absence of purposeful hand movement and feeding difficulties combined with some relatively preserved nonverbal communication skills and frontal gyral simplification and severe myelination delay suggest a *FOXG1* deficiency.

Consensus Criteria

The large majority of *FOXG1*-mutation patients demonstrate a phenotype reminiscent of congenital RTT variant except one presenting a classical form of RTT [Philippe et al., 2010]. Only few girls described as congenital variants have been reported as mutated in the *MECP2* gene.

Subsequently, efforts have been concentrated to define clinical criteria of *FOXG1* related encephalopathy [Neul et al., 2010]. According to these consensus criteria, patients with *FOXG1* mutation meet criteria for atypical RTT and present with the following specific features: (i) grossly abnormal initial development, (ii) severe psychomotor delay; (iii) inability to walk; (iv) severe postnatal microcephaly before 4 months; (v) regression in first 5 months; (vi) lack of typical intense ‘RTT’ eye gaze; (vii) typical RTT autonomic abnormalities including small cold hands and feet and peripheral vasomotor disturbances.

In addition to these clinical criteria, the MRI pattern, showing the combination of frontal gyral simplification with severe myelination delay most prominent in both frontal region and thin corpus callosum, constitutes a key feature of *FOXG1*-related encephalopathy in females as in male [Bahi-Buisson et al., 2010; Le Guen et al., 2011].

Fig. 1. Axial section of brain MRI of a 2.8-year-old patient with *FOXG1* point mutation (**A, B**) compared with a control individual at the same age (**C, D**). A significant myelination defect on T2-weighted axial section (**A**), and gyral simplification most prominent in frontal region on T1-weighted axial section (**B**).

Structure and Functions of the *FOXG1* Gene

The *FOXG1* Gene

The mammalian forkhead family includes 43 genes and belongs to the large family of 100 known forkhead genes (*FOX* genes) in animals [Solomon et al., 2003]. *FOX* genes have been identified in species ranging from worm to human. They have been described in *Caenorhabditis elegans* [Miller et al., 1993], *Drosophila melanogaster* [Weigel and Jäckle, 1989], zebrafish [Strähle et al., 1993], *Xenopus* [Knöchel et al., 1992], mouse [Sasaki and Hogan, 1993] and human [Hromas et al., 1993]. *FOX* genes are known to encode a subgroup of the helix-turn-helix class of proteins [Clark et al., 1993]. Currently, they are divided into 17 subclasses (A to Q), according to the amino acid sequence of their conserved forkhead domains [Kaestner et al., 1993]. Since the discovery of the *Drosophila* transcription factor forkhead, many studies have investigated the role of the forkhead box genes in organogenesis, including patterning and morphogenesis, through the regulation of proliferation and the cell fate specification [Solomon et al., 2003].

One of the *FOX* family, the winged-helix transcription factor forkhead box G1, *FOXG1* (formerly named forebrain-restricted transcription factor BF-1), has been de-

scribed to play an important role in the development of the telencephalon [Tao and Lai, 1992; Murphy et al., 1994]. Human *FOXG1* gene (previously *FOXG1B*) is located in chromosome 14q12 and contains only 1 coding exon (exon 1 in fig. 2) [Wiese et al., 1995; Bredenkamp et al., 2007]. Four alternative transcripts for *FOXG1* (exon 2 to 5) have been identified in fetal brain [Shoichet et al., 2005].

Functions of the *FOXG1* Protein

Domains of the *FOXG1* Protein. The *FOXG1* protein consists of a 100-residue forkhead DNA-binding domain (FHD), highly conserved across all members of the *FOX* family. *FOXG1* recruits transcriptional corepressor proteins, a histone demethylase and Groucho (Gro), via 2 further protein-binding domains, the 10-residue KDM5B (previously JARID1B)-binding domain (JBD) and the about 20-residue Gro-binding domain (GBD), respectively (fig. 2). Structurally, the FHD consists of 3 alpha helices and 1 beta hairpin (2 beta strands and 1 loop), whereas the GBD and JBD are random coiled. Mutations of one of these binding domains disrupt the *FOXG1* protein at different sites (fig. 2). Ariani et al. have described the first *FOXG1*-truncating mutations in 2 patients affected by the congenital variant of RTT [Ariani et al., 2008]. In this first patient, a stop codon mutation (named p.Trp255X) impaired the DNA binding properties, while the second patient presented a 1-bp deletion (named p.Ser323ArgfsX325) causing the loss of JBD interaction domain and the misfolding of the motif responsible for GBD. More recently, Mencarelli et al. have described a new frameshift mutation (named p.Ser185-GlnfsX454), a stop mutation (named p.Tyr208X) and 2 missense mutations (named p.Phe215Leu and p.Asn227Lys) in female patients [Mencarelli et al., 2010]. The same year, 3 de novo nonsense mutations and 1 frameshift mutation (named p.Trp308X, p.Tyr400X, p.Tyr416X, and p.Glu154GlyfsX300) have been described in female patients [Bahi-Buisson et al., 2010; Philippe et al., 2010], and a mutation with a cytosine duplication between the nucleosides 256 and 257 (named c.256_257dupC) generating a truncated protein (p.Gln86ProfsX34) lacking the FHD in a male patient [Le Guen et al., 2011].

The *FOXG1* Transcription Factor is a Master Gene of Telencephalic Development. The vertebrate telencephalon exhibits one of the most heterogeneous collections of neurons in the entire nervous system in terms of morphology, structure, function and genetic specification. Regional specification, growth and differentiation of telencephalic divisions and subdivisions, such as the cere-

Fig. 2. Schematic representation of human *FOXG1* gene and its deleterious mutations. The 489-amino-acid-long *FOXG1* transcription factor (ARN NM_005249) is encoded by the intronless *FOXG1* coding region (exon 1). Shaded regions indicate the 3 functional domains of the protein, i.e. the DNA-binding fork-head domain (FHD) (amino acids 181–275), the Gro-binding do-

main (GBD) (amino acids 307–317) and the KDM5B (formerly JARID1B) binding domain (JBD) (amino acids 383–406). Three different mutations reported in *FOXG1* exon 1 are represented: frameshift mutations (red), stop codon mutations (green) and missense mutations (black). Amino acid numbers are indicated below the protein representation.

bral cortex, are regulated by the interplay of secreted proteins produced by patterning centers and signal transduction systems deployed in the surrounding neuroepithelium. Three different signaling centers are required for correct specification of the telencephalon, and to regulate the expression of region-specific genes such as bone morphogenetic protein (BMP), wingless/int protein (WNT), extracellular signal fibroblast growth factor 8 (FGF8), and sonic hedgehog (SHH) [Ericson et al., 1995; Furuta et al., 1997; Lee et al., 2000; Walshe and Mason, 2003].

Previous studies have shown that *FOXG1* is an important regulator of the progenitor-to-neuron transition in the mammal telencephalon. In the absence of *FOXG1*, telencephalic progenitor cells differentiate prematurely, leading to early depletion of the progenitor population, suggesting that *FOXG1* promotes cell proliferation in the telencephalon [Xuan et al., 1995]. Disruption of *FOXG1* function showed an ectopic expression of *BMP4* in the telencephalic neuroepithelium indicating that *FOXG1* facilitates proliferation by inhibiting *BMP4* expression [Xuan et al., 1995; Dou et al., 1999]. Unlike *FOXG1*, *BMP4*

was shown to inhibit telencephalic progenitor cell proliferation [Furuta et al., 1997]. Furthermore, *FOXG1* has been proposed to play a role in ventral telencephalon development, by inducing the expression of *FGF8* [Hébert and Fishell, 2008]. *FOXG1* is required for the *FGF8* expression and, conversely, *FOXG1* expression is itself regulated by FGF signaling [Martynoga et al., 2005]. Initially, *FOXG1* expression was restricted to the most rostral region of the neural tube. By embryonic day 9 (E9), the *FOXG1* expression domain is composed of the telencephalic neuroepithelium, including the progenitor cells of the cerebral cortex, the basal ganglia and the olfactory bulb [Shimamura et al., 1995; Dou et al., 1999]. After E9.5, expression of *FOXG1* declines in the dorsomedial telencephalon and the dorsal midline, showing a shallow dorsal-medial gradient and giving a high level of *FOXG1* in the ventral telencephalon. At E12.5, *FOXG1* is present in the neural progenitors of the telencephalon and absent from the rest of the neural tube. Finally, *FOXG1* expression remains restricted to cells derived from the telencephalic neuroepithelium, including cerebral cortex and the hippocampus [Dou et al., 1999].

Moreover, *FOXG1* interacts with the members of the Gro/transducin-like enhancer of split family of transcription factors, which are involved in a number of developmental pathways [Tao and Lai, 1992; Yao et al., 2001; Hanashima et al., 2002, 2004; Marçal et al., 2005] and may regulate different processes such as proliferation rate, differentiation rate, and apoptosis. *FOXG1* is nuclear in progenitor cells but cytoplasmic in differentiating cells, suggesting that *FOXG1* may be having a distinct function in the cytosol [Regad et al., 2007]. While *FOXG1* continues to be expressed in neurons postnatally and through adulthood, its role in differentiated neurons is still not well known. Nevertheless, a recent study showed that *FOXG1* promotes survival of postmitotic neurons [Dastidar et al., 2011]. The authors concluded that the survival promoting activity of *FOXG1* is mediated by the PI3 kinase-Akt signaling pathway, and also that *FOXG1* is a downstream target of IGF1-mediated signal transduction.

Genetics of *FOXG1* Disorders

Mode of Inheritance

FOXG1-related disorder is an autosomal dominant disorder. Up to now, all described cases are simplex cases (i.e., a single occurrence in a family), resulting from a de novo mutation. Because of the possibility of germline mosaicism, it is appropriate to offer prenatal diagnosis to couples who had a child with a *FOXG1*-related disorder regardless of whether the disease-causing mutation has been detected in a parent.

Frequency of FOXG1 Mutations and Molecular Diagnosis

The prevalence of these *FOXG1*-related disorders has not been estimated, but these disorders appear to be rare, but not exceptional. The diagnosis of all *FOXG1*-related disorders relies on molecular genetic and cytogenetic testing. Sequence analysis and deletion/duplication testing for exonic, and whole-gene deletions/duplications are available on a clinical basis. Point mutations in the *FOXG1* coding region (alias exon 1) are detected by bidirectional sequencing and/or mutation scanning (e.g. DHPLC). Nevertheless, supplemental investigations on the non-coding exons (exon 2 to 5) of *FOXG1* gene would be helpful to update the molecular etiology of Rett syndrome or Rett syndrome-like phenotypes.

Deletion and duplication analysis are carried out by a variety of methods including real-time quantitative PCR, quantitative multiplex fluorescent PCR and/or CGH-mi-

croarray. Once a putative pathogenic mutation has been identified in a proband, it is appropriate to offer testing to all first-degree relatives regardless of their clinical status.

Genotype-Phenotype Correlation

Although clinical features are quite homogeneous, *FOXG1*-related encephalopathy demonstrates variable degree of severity. Indeed, the more severely affected patients have congenital microcephaly, virtually no visual contact and poor head control combined with severe congenital microcephaly, simplified gyral pattern and hypomyelination. At the other end of the spectrum, the less severely affected patients had a significantly better eye contact and babbling, no epilepsy, developed some purposeful hand function and were able to take some steps with support. Consistent with this, myelination was mildly delayed in the centrum semi-ovale, and no gyral defect was observed. Recently, Philippe et al. have reported a patient with an RTT presentation carrying the late truncating mutation p.Tyr400X [Philippe et al., 2010]. This patient, considered to have classical RTT according to the revised diagnostic criteria for classical and variant RTT, is a 10-year-old girl, considered to be a normal child until the age of 6 months, when developmental delay was noticed. However, the same mutation has recently been identified in a patient with a milder RTT phenotype according with 'forme frustre' and sharing strikingly similar facial features resembling the Kleefstra syndrome due to *EHMT1* gene [Mari et al., 2010; personal communication]. Although genotype-phenotype correlation is difficult to establish with the few number of *FOXG1* mutated cases, all the recent literatures suggest that the mutation does not predict the severity of the phenotype, suggesting that additional factors might contribute to the severity of the *FOXG1*-related disorders.

Management and Treatment

Unfortunately, there are currently no specific treatments that halt or reverse the progression of the disease, and so management is mainly symptomatic and individualized, focusing on aiming to optimize each patient's abilities. A dynamic multidisciplinary approach is most effective, with specialist input from dietitians, physiotherapists, and occupational therapists.

Attention needs to be paid to nutritional problems and the development of spasticity, both of which can have a major impact on quality of life in disabled patients. Psy-

chosocial support for the families is an integral part of the management. Pharmacological approaches to managing problems associated with *FOXG1*-related disorders include melatonin for sleep disturbances, and anti-epileptic drugs for seizures.

State of Research and Mouse Models

Consistent with the clinical human observations described above, previous studies have shown that a null mutation in the *Foxg1* gene in a mouse model causes severe defects in the development of telencephalic structures (e.g. the cerebral cortex and basal ganglia) and mice die at birth [Xuan et al., 1995; Martynoga et al., 2005]. From E10.5 to the perinatal death, the *Foxg1* homozygote null telencephalon is remarkably reduced in size. Mice lacking *Foxg1* display an expansion of dorsal telencephalic markers while ventral cell fates are not specified, leading to morphological defects of telencephalic structures [Xuan et al., 1995; Dou et al., 1999; Hanashima et al., 2002, 2004, 2007; Ahlgren et al., 2003; Hébert and Fishell, 2008]. These defects are accompanied by a perturbation of signaling centers, such as *Wnt* and *Bmp* expression [Hanashima et al., 2007], correlating with an increased *Bmp* activity within the telencephalon [Dou et al., 1999], as well as a loss of *Shh* expression within the ventral telencephalon [Huh et al., 1999]. Moreover, the *Foxg1*^{-/-} knockout mouse has no recognizable olfactory structures, such as epithelium, bulb, or vomeronasal organs [Xuan et al., 1995; Duggan et al., 2008]. This is attributed to a reduction of progenitor cell proliferation (as neurogenesis begins at E10.5 in the rostral telencephalon) in both the dorsal and ventral structures, an acceleration of differentiation of telencephalic progenitors in the dorsal telencephalon, and a reduction of apoptosis in the rostral telencephalon [Hanashima et al., 2004; Martynoga et al., 2005]. At E12.5, the expression domain of the dorsal marker *Emx2* was also extended more ventrally in the *Foxg1* mutant, suggesting that the *Foxg1* mutation causes a transformation of the dorsal telencephalon to a more ventral fate [Xuan et al., 1995].

As the homozygote mice remained cyanotic and died within minutes after birth [Xuan et al., 1995], new genetic models have been proposed for postnatal studies. Hébert and McConnell generated the *Foxg1* heterozygote null mice by replacing the intronless *Foxg1* coding region with *Cre* (named *Foxg1*^{+/*Cre*}, C57/BL6 background) [Hébert and McConnell, 2000]. The authors showed that *Foxg1*^{+/*Cre*} mice confer a deletion of the *Foxg1* gene spe-

cifically from the telencephalon and from other head structures, including the developing lens, retina, ear, olfactory epithelium, mid-hindbrain junction, facial and head ectoderm. Interestingly, the same phenotype was observed on multiple strains of adult *Foxg1*^{+/-} mice, in which the *Foxg1* coding region was replaced either with the tetracycline transactivation (*Foxg1*^{+/*tTA*}, C57/BL6 background) [Hanashima et al., 2002] or with *lacZ* (*Foxg1*^{+/*lacZ*}, Swiss Webster background) [Xuan et al., 1995]. Indeed, *Foxg1*^{+/*Cre*} and *Foxg1*^{+/*lacZ*} mice showed the same reduction of the dentate gyrus (DG) size, correlated with a loss of postnatal DG neurogenesis, suggesting that the effect of *Foxg1* haploinsufficiency on DG size and postnatal hippocampal neurogenesis is not specific to a mouse strain [Shen et al., 2006]. It is well accepted that the subventricular zone (SZ) plays an important role during the period of neocortical neurogenesis, by containing stem and progenitor cells that generate neuroblasts throughout life. Interestingly, a large proportion of the cortical neurons (from the layer II/III) are born in the SZ [Miller, 1989; Tarabykin et al., 2001; Nieto et al., 2004; Noctor et al., 2004; Zimmer et al., 2004; Englund et al., 2005; Ferrere et al., 2006; Martinez-Cerdeno et al., 2006]. *Foxg1*^{+/*Cre*} mice also display a specific reduction in the thickness of cortical layer II/III [Shen et al., 2006; Eagleson et al., 2007], suggesting the population of the progenitor cells in the SZ is affected in *Foxg1*^{+/*Cre*} mice [Siegenthaler et al., 2008]. Thus, microcephaly observed in *Foxg1*^{+/-} mice may result from specific defects in progenitor cells. Finally, *Foxg1*^{+/*tTA*} mice showed hyperlocomotion and impaired habits in the open field, and a severe deficit in contextual fear-conditioning, which are suggestive of an impaired amygdala and/or hippocampal function [Shen et al., 2006]. Hence, microcephaly and cognitive function deficits are observed in both mice with haploinsufficiency of *Foxg1* [Shen et al., 2006] and humans with *FOXG1* mutations [Shoichet et al., 2005].

Although the first study reported that cortical development appears to be normal in *Foxg1* heterozygous null mice [Xuan et al., 1995; Hébert and McConnell, 2000; Hanashima et al., 2002, 2004], other studies have described the disruption of the telencephalon development to *Foxg1* haploinsufficiency. The first one reported a telencephalic hypoplasia in both hypomorphic and null-*Fgf8* mice, which is likely due, at least partially, to an alteration of *Foxg1* expression [Storm et al., 2006]. In the second report, cerebral microcephaly and impaired postnatal hippocampal neurogenesis were demonstrated in adult *Foxg1* haploinsufficient mice [Shen et al., 2006]. Finally, the third study revealed a reduction of the volume of the prosen-

cephalon, including the cerebral cortex, hippocampus and striatum in the *Foxg1* heterozygous mice [Eagleson et al., 2007]. These last 3 studies are all consistent with the phenotype associated with *Foxg1* haploinsufficiency in humans, suggesting that this knockout model may be a fascinating model to understand this human disease.

Conclusion

Point mutations, deletions and duplications spanning *FOXG1* have been reported in patients with developmental disorders. Although the phenotype overlaps both classical and congenital forms of RTT, the large majority of patients with point mutations and deletions present specific features including severe psychomotor delay, severe postnatal microcephaly, stereotypic movements, and dyskinetic movement disorders. In addition to these clinical criteria, the brain MRI pattern, showing the combination of frontal gyrus simplification with severe myelin-

ation delay and thin corpus callosum, constitutes a key feature of *FOXG1*-related disorders. Although classical RTT has been described quasi-exclusively in girls, *FOXG1*-related mutations have been identified in both female and male patients, showing the importance of *FOXG1* screening in both female and male patients with an emerging developmental profile suggestive of congenital variant of RTT. As a rare disease, congenital variant of RTT presents a small number of reported cases making difficult the relationship between the genotype and the phenotype. As for the *FOXG1* in this atypical form of RTT, several studies have shown a crucial role in earlier developing forebrain, in promoting neural precursor proliferation and cerebral cortex expansion. Finally, investigations that are based on several *Foxg1* haploinsufficient mouse models and on human deficient cells (such as *FOXG1*-deficient induced pluripotent stem cells) should improve our understanding of the consequences of *FOXG1* dysfunction and propose new advances in the development of therapeutic strategies.

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