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ORIGINAL ARTICLE

The core *FOXG1* syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis

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ABSTRACT

Background Submicroscopic deletions in 14q12 spanning *FOXG1* or intragenic mutations have been reported in patients with a developmental disorder described as a congenital variant of Rett syndrome. This study aimed to further characterise and delineate the phenotype of *FOXG1* mutation positive patients.

Method The study mapped the breakpoints of a 2;14 translocation by fluorescence in situ hybridisation and analysed three chromosome rearrangements in 14q12 by cytogenetic analysis and/or array comparative genomic hybridisation. The *FOXG1* gene was sequenced in 210 patients, including 129 patients with unexplained developmental disorders and 81 *MECP2* mutation negative individuals.

Results One known mutation, seen in two patients, and nine novel mutations of *FOXG1* including two deletions, two chromosome rearrangements disrupting or displacing putative *cis*-regulatory elements from *FOXG1*, and seven sequence changes, are reported. Analysis of 11 patients in this study, and a further 15 patients reported in the literature, demonstrates a complex constellation of features including mild postnatal growth deficiency, severe postnatal microcephaly, severe mental retardation with absent language development, deficient social reciprocity resembling autism, combined stereotypies and frank dyskinesias, epilepsy, poor sleep patterns, irritability in infancy, unexplained episodes of crying, recurrent aspiration, and gastro-oesophageal reflux. Brain imaging studies reveal simplified gyral pattern and reduced white matter volume in the frontal lobes, corpus callosum hypogenesis, and variable mild frontal pachgyria.

Conclusions These findings have significantly expanded the number of *FOXG1* mutations and identified two affecting possible *cis*-regulatory elements. While the phenotype of the patients overlaps both classic and congenital Rett syndrome, extensive clinical evaluation demonstrates a distinctive and clinically recognisable phenotype which the authors suggest designating as the *FOXG1* syndrome.

INTRODUCTION

Recently, a series of reports have implicated deletions or sequence alterations of *FOXG1* as the cause of a developmental disorder described as a congenital variant of Rett syndrome (RTT; MIM 312750). Small de novo interstitial deletions in 14q12 were detected by chromosome microarrays in four children[1–4] and a complex chromosome rearrangement consisting of a translocation and adjacent small inversion in another patient.[5] The common deleted region includes the telomeric breakpoint of the inversion in the latter patient and contains *FOXG1*, a strong candidate gene based on high and specific expression in developing brain and complex malformations of the telencephalon in both homozygous and heterozygous mouse mutants.[6–8]

Subsequently, sequencing of *FOXG1* in five small cohorts of patients with overlapping phenotypes but negative results for *MECP2* testing identified 11 patients with intragenic mutations including five nonsense, four frameshift, and two missense mutations.[9–13] Common clinical features in all these children included decelerating head circumference from 3 months that resulted in severe postnatal microcephaly, severe mental retardation with absent language, apraxia, jerky movements, and generalised seizures. Brain imaging in several patients revealed hypogenesis of the corpus callosum.[9 10 12] The phenotype was interpreted as resembling Rett syndrome except for no early period of normal development, which we view as one of several significant differences. Recently, duplications of *FOXG1* have been associated with developmental epilepsy, mental retardation, and severe speech impairment in eight patients.[14 15]

After mapping a de novo chromosome translocation found in a severely mentally retarded girl to this region, we became interested in the types of mutations involving *FOXG1* and the nature of the associated developmental disorder. Is the phenotype accurately described as a congenital variant of Rett syndrome, or is it a specific and recognisable syndrome in its own right? Here we report two microdeletions, two chromosome rearrangements most likely causing dysregulated *FOXG1* expression, and seven intragenic sequence changes among 210 patients tested. This cohort includes 129

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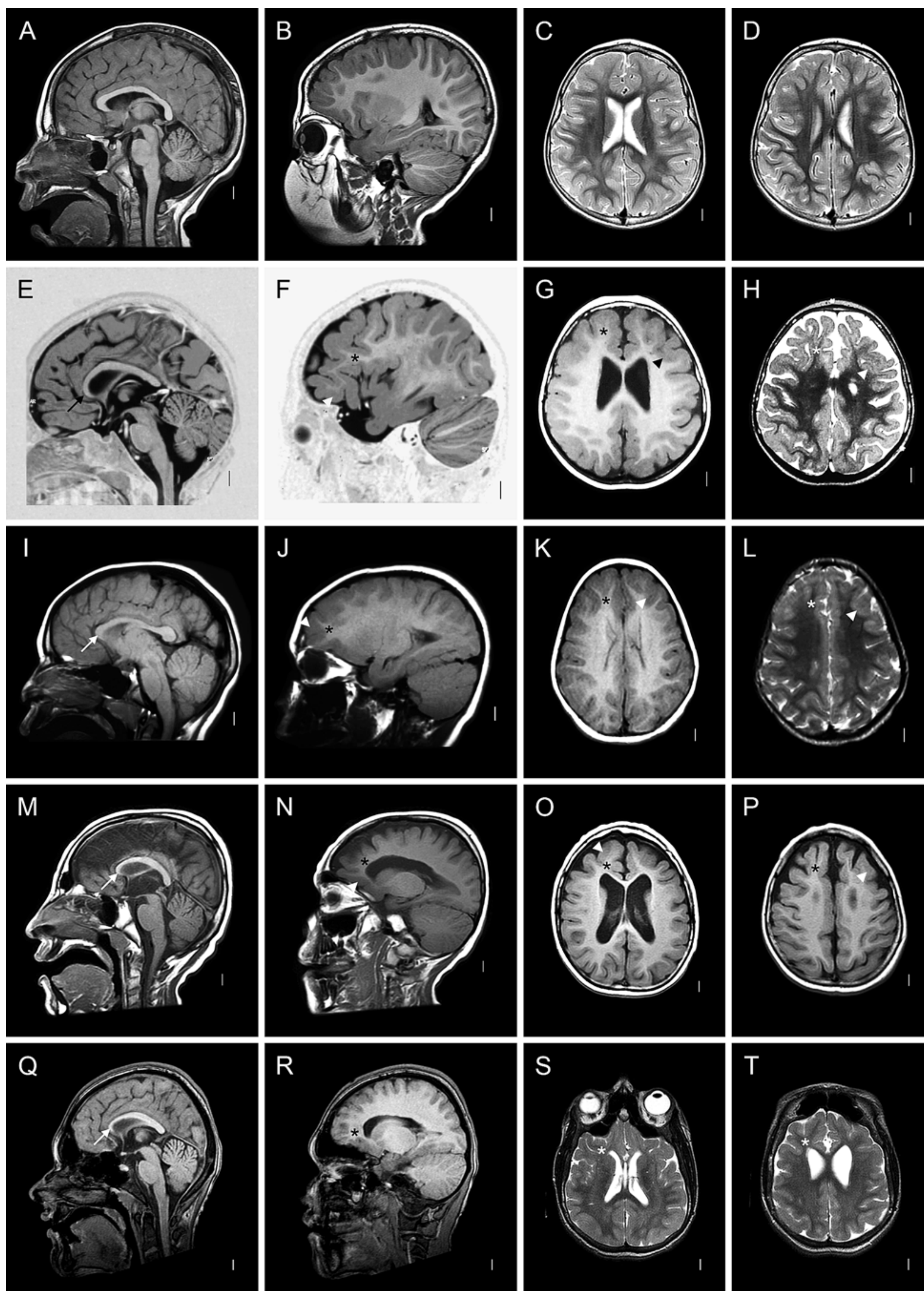

Figure 1 Brain imaging in a normal 3-year-old girl (A–D) and four patients with *FOXG1* mutations (E–T). Here and in figure 2, each row shows four images from the same patient. The columns contain midline sagittal (left column) and parasagittal (second column) images, and axial images through the lateral ventricles (third column) and high convexity (right column). All four patients have a low forehead that reflects underlying microcephaly, foreshortened frontal lobes and reduced white matter volume that appears severe in the frontal lobes (asterisks in 12/16 images) and subtle in posterior

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patients referred to us directly because of unexplained developmental disorders, and 81 ascertained following negative testing for *MECP2*.

Our data and review of prior reports confirm mutations or dysregulation of *FOXG1* as the cause of the developmental phenotype, which differs from classic Rett syndrome and other so-called Rett variants based on a specific and recognisable combination of developmental and brain imaging features. We prefer to designate this as the *FOXG1* syndrome, which has overlapping features with a rapidly growing group of developmental encephalopathies that already includes Angelman (*UBE3A* associated), Rett (*MECP2* associated), Pitt–Hopkins (*TCF4* associated), *CNTNAP2* associated, *NRXN1* associated, and *SLC9A6* associated syndromes.[16–22]

PATIENTS AND METHODS

Patients

We obtained clinical data, brain imaging studies and results of laboratory testing, as well as blood or DNA samples, from 129 patients with mental retardation, microcephaly, frontal pachygyria or hypogenesis of the corpus callosum who were assessed by experienced clinical geneticists or neurologists. Two patients were recruited through the MRNET consortium (http://www.german-mrnet.de). We received 81 DNA samples from patients tested in a diagnostic lab for *MECP2* and found to be negative. All available brain imaging studies from patients with a *FOXG1* mutation were interpreted by one of the authors (WBD) with selected images shown in figures 1 and 2. The clinical data and samples were obtained with informed consent, including consent to use the photographs and videos in this report, under protocols approved by Institutional Review Boards at all participating institutions.

Fluorescence in situ hybridisation

Metaphase spreads from peripheral blood lymphocytes were prepared by standard procedure. Fluorescence in situ hybridisation (FISH) experiments for delineation of the 2q11.2 and 14q12 breakpoints were performed with bacterial artificial chromosome (BAC) and fosmid clones. FISH with BAC clones was also performed to confirm array comparative genomic hybridisation (CGH) and molecular karyotyping data. BACs (RP11 Human BAC Library) were obtained from the Resource Center for Genome Research at the Max-Planck-Institute for Molecular Genetics, Berlin, Germany, or the BACPAC Resource Center, Children's Hospital Oakland, California, USA. Fosmid clones (WIBR-2 Human Fosmid Library (G248P8)) were received from the BACPAC Resource Center, Children's Hospital. BAC and fosmid DNA was prepared using the NucleoBond Xtra Midi kit (Machery-Nagel, Düren, Germany) or the Qiagen Large-Construct kit (Qiagen, Hilden, Germany). DNA was labelled by nick translation using the CGH Nick Translation Kit and Spectrum Green-dUTP (Vysis, Downers Grove, Illinois, USA) according to the protocol provided. Chromosomes were counterstained using 4',6-diamidino-2-phenylindole (DAPI) (Serva Feinbiochemica, Heidelberg, Germany) and mounted in antifading solution (Vector Labs, Burlingame, California, USA). Slides were analysed with a Leica Axioscope fluorescence microscope. Images were merged using a cooled CCD camera (Pieper, Schwerte, Germany) and Cyto Vision software (Applied Imaging, San Jose, California, USA).

Molecular karyotyping and array CGH

Molecular karyotyping using the Affymetrix Mapping GeneChip 250 K Mapping SNP-Array (Nsp) (Affymetrix, Santa Clara, California, USA) was performed in patient 3 according to the supplier's instructions. Data were analysed using Nexus and CNVF2.2 software.[23] Array CGH in patient 4 was performed using a whole genome oligonucleotide array (244K, Agilent Technologies, Santa Clara, California, USA). 244K image data were analysed using Feature Extraction 9.5.3.1 and CGH Analytics 3.4.40 software (Agilent) with the following analysis settings: aberration algorithm ADM-2; threshold: 6.0; window size: 0.2 Mb; filter: 5probes, log2ratio=0.29.

Mutation analysis

We amplified the coding region of the *FOXG1* gene (1 exon; GenBank accession no. NM_005249) from genomic DNA with five primer pairs that yielded overlapping amplicons. Primer sequences are available on request. Amplicons were directly sequenced using the ABI BigDye Terminator Sequencing Kit (Applied Biosystems) and an automated capillary sequencer (ABI 3130; Applied Biosystems). Sequence electropherograms were analysed using Sequence Pilot software (JSI medical systems, Kippenheim, Germany). Where mutations were shown to have arisen de novo, we verified self-reported relationships by genotyping both parents and the patient at 10 microsatellite loci.

RESULTS

Mapping of the chromosomal breakpoint in 14q12 by FISH

Patient 1, a 12-year-old girl, was referred at 7 years because of severe mental retardation and postnatal microcephaly. She is the fourth child of healthy parents and her three older sisters are healthy. She was born at 40 weeks gestation by natural delivery with a birth weight 3350 g (0 SD), length 51 cm (0 SD), and occipitofrontal circumference (OFC) 32.5 cm (−1 SD). At 6 months, she was able to turn, but she has never been able to sit or stand. She did not react to visual and acoustic stimuli in infancy, but this improved at later ages. Ophthalmologic examination revealed convergent strabismus. At 7 months she developed seizures. An electroencephalogram (EEG) revealed spikes and sharp waves over the left centroparietal and both centrotemporal regions. She could speak single words at 1 year, but lost this ability by 2 years. She had gastro-oesophageal reflux and constipation. Her brain MRI demonstrated a strikingly reduced volume of white matter in the anterior frontal lobes with mildly thick cortex, striking hypoplasia and dysplasia of the anterior corpus callosum resembling a sharp hook, and probably dysplastic hippocampus (figure 1E–H).

[Continued]
regions. All four have hypogenesis of the anterior corpus callosum with a 'pointed hook' appearance in three of them (arrows in E, M, Q) that consists of striking narrowing of the anterior body, genu and rostrum with the tiny rostrum forming a pointed tip, and relatively normal posterior callosum. In the remaining patient (arrow in I), the entire body of the corpus callosum is narrow and the genu small but less so than the others, leaving it dysmorphic but different from the 'pointed hook' appearance. Three patients have subtle pachygyria over the frontal lobes only that consists of mildly short and wide gyri and mildly thick cortex (arrowheads in F–H, J–L, N–P), a subtle abnormality that may be accentuated by the reduced volume of the white matter. The increased cortical thickness was not seen in the remaining patients (R–T and figure 2). Also, three patients had mildly enlarged lateral ventricles, with one having an abnormally narrow anterior body and frontal horns (S). These images come from patients 1 (E–H), 5 (I–L), 7 (M–P) and 9 (Q–T), and a normal control (A–D).

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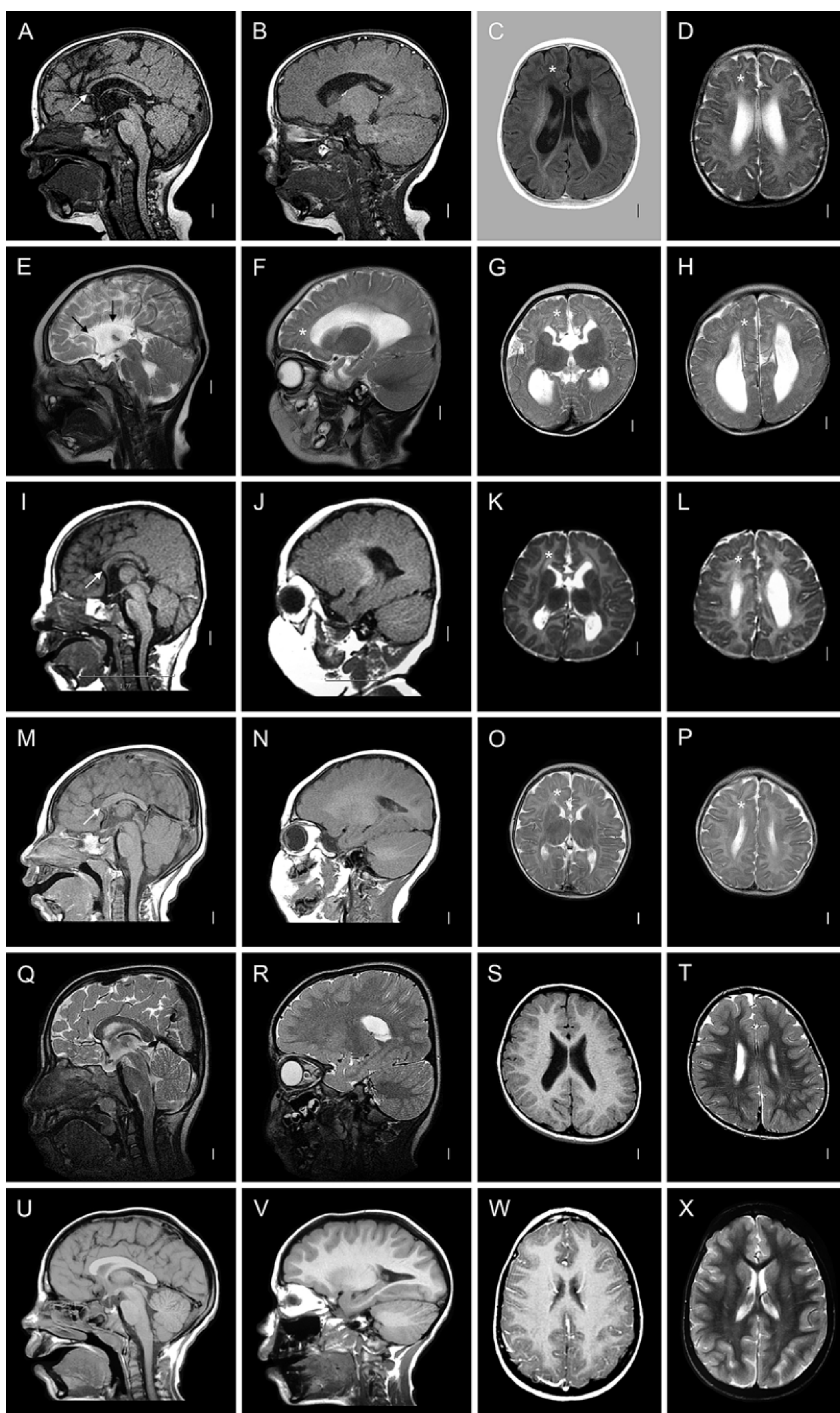

Figure 2 Brain imaging in another six patients with *FOXG1* mutations. Five have mildly enlarged lateral ventricles. The patients in the top four rows have changes similar to those seen in figure 1, including microcephaly (E, I, M: not obvious in A, Q, U), short frontal lobes and reduced volume of frontal white matter (asterisks in 9 images). Hypogenesis of the corpus callosum was seen in 4/6 (arrows in A, E, I, M), but with different patterns. The first patient (A) has a thin and dysmorphic corpus callosum similar to figure 1I, the next total agenesis of the corpus callosum (E), and the third and

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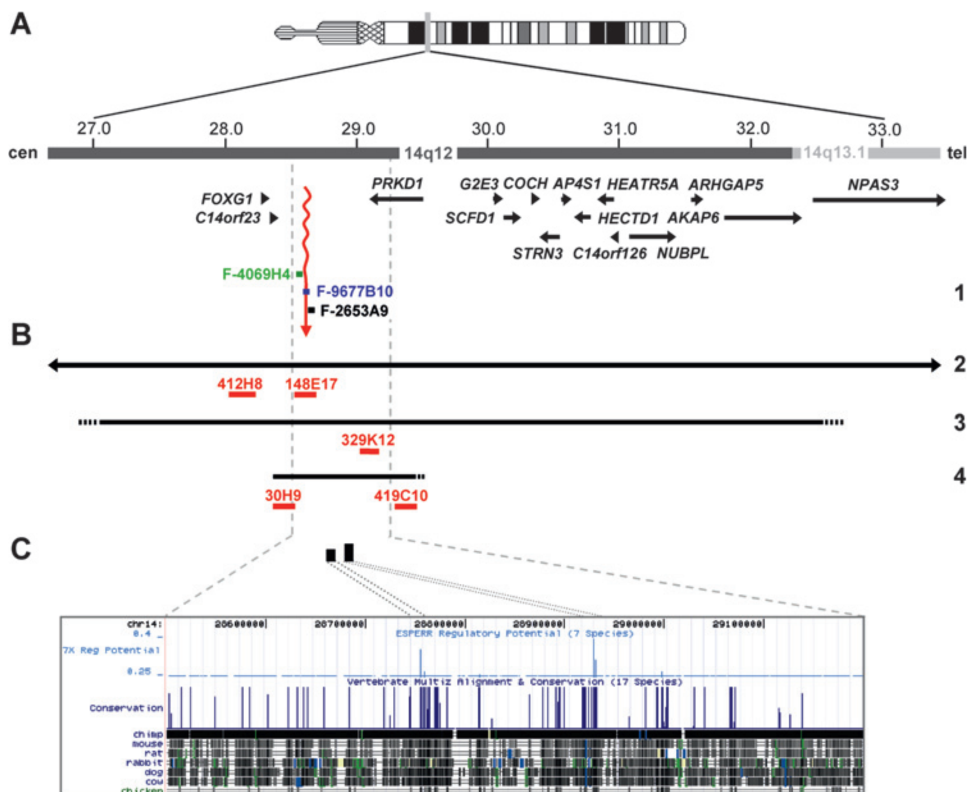

Figure 3 Deletions including *FOXG1* and regulatory mutations. (A) Physical map of the 14q12-q13.1 region. Genes in this region are represented by arrows indicating the 5′→3′ orientation. Fosmid clones (F- (G248P8); WIBR-2 Human Fosmid Library) used for mapping the 14q12 breakpoint of the 2;14 translocation in patient 1 (1) are indicated by coloured bars and names are given. Colour code of fosmids; black: mapped distal to the translocation breakpoint; blue: spanned the breakpoint; green: mapped proximal to breakpoint. The breakpoint region is indicated by a wavy vertical arrow in red. (B) Deletions in 14q12. Horizontal black lines depict the deletions identified in patients 2–4 (2, 3, 4). Arrowheads at the left and right side of the deletion in patient 2 show that this deletion extends to either side. Dotted lines indicate that the respective deletion breakpoints have not been fine-mapped. Bacterial artificial chromosome (BAC) clones (RP11 Human BAC Library) used for fluorescence in situ hybridisation (FISH) analysis to confirm the presence of the deletions in the patients are indicated by red bars and names are given. (C) A detailed view of the region containing putative long range *cis*-regulatory elements of *FOXG1*. In the upper part, the two black vertical bars represent potential regulatory elements (genomic positions chr14:28,754,647–28,756,495 bp and 28,930,280–28,932,099 bp) that have been identified with the ESPERR (evolutionary and sequence pattern extraction through reduced representations) computational method. In the lower part, a more detailed view of the region of high regulatory potential (RP) values, with the UCSC genome browser map of seven-way (human, chimpanzee, macaque, mouse, rat, dog, and cow; March 2006 assembly) RP analysis of the candidate *cis*-regulatory elements distal to *FOXG1*.

Prenatal chromosome analysis revealed an apparently balanced chromosome translocation: 46,XX,t(2;14)(q13;q13). Chromosome analysis was normal in both parents, indicating that it occurred de novo (paternity confirmed). FISH analysis with fosmid G248P81425A7 from chromosome 2 identified signals on 2q11.2 as well as the der(2) and der(14), indicating that this clone spanned the breakpoint (data not shown). No gene was directly disrupted by the breakpoint, although *INPP4A* is located 5–10 kb telomeric to the breakpoint (data not shown). A 1-bp deletion in *Inpp4a* encoding inositol polyphosphate 4-phosphatase type I occurred in the spontaneous weeble mouse mutant, which has severe locomotor instability and significant neuronal loss in the cerebellum and hippocampal CA1 sector.[24] Patient 1 is heterozygous for the breakpoint close to *INPP4A*, and further the weeble phenotype is a recessive condition that differs significantly from the phenotype in this girl.[24]

We therefore fine-mapped the 14q breakpoint, finding fosmid probes that hybridised proximal (F-4069H4) and distal (F-2653A9) to the breakpoint, as well as a single fosmid clone that spanned the breakpoint (F-9677B10, figure 3A). We narrowed the breakpoint to a ~10 kb gene-poor region in 14q12 located ~265 kb downstream of *FOXG1* (figure 3A), suggesting that a position effect could cause transcriptional misregulation of this gene. In silico analysis using the Regulatory Potential score identified several candidate *cis*-regulatory elements that are evolutionarily conserved throughout a 1 Mb region downstream of *FOXG1* (figure 3C). Two of these non-coding elements located at genomic positions chr14:28,930,280-28,932,099 and chr14:28,754,647-28,756,495 (NCBI Build 36.1; figure 3C) have been analysed for gene enhancer activity as assessed in transgenic mice. Both DNA sequence elements are evolutionarily highly conserved and were found to drive expression of a reporter gene (*lacZ*) in mouse forebrain (http://enhancer.lbl.gov/frnt_page.shtml). These data suggest that translocation of either or both of these putative *cis*-regulatory elements to chromosome 2 may have caused dysregulated expression of *FOXG1* in the translocation patient.

Identification of deletions in 14q12 by cytogenetic and array CGH analysis

Patient 2 presented with developmental delay, slow head growth, and severe feeding problems. Brain MRI showed a short corpus callosum (figure 2M–P). Routine chromosome analysis revealed a de novo deletion in chromosome 14 (46,XX,del(14)(q13.1q13.2)). We confirmed the deletion by FISH with two BAC clones, RP11-412H8 and RP11-148E7, flanking *FOXG1* as well as BAC RP11-330O19 hybridising proximal and RP11-908D14 and RP11-116N8 hybridising distal to the deletion, respectively (data not shown and figure 3B). We estimate the maximum size of the deletion as ~8.4 Mb in 14q12-q13.1 including *FOXG1*.

[Continued]
fourth partial agenesis with a short and thin corpus callosum (I, M). No patients in this group have pachygyria. The last two patients have normal brain imaging except for subtle reduced volume of the frontal white matter and mildly simplified gyral pattern. These images come from patients 6 (A–D), 3 (E–H), 2 (I–L), 10 (M–P), 4 (Q–T), and 11 (U–X).

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Genome-wide array CGH was performed on a clinical basis on two patients with postnatal microcephaly and severe mental retardation. We detected a ~5.4 Mb heterozygous deletion in 14q12-q13.1 in patient 3 that encompasses at least 13 genes including *FOXG1*, and confirmed the deletion by FISH with BAC clone RP11-329K12 (figure 3B and data not shown). Neither parent carried the deletion (data not shown; paternity confirmed). We identified a ~1.09 Mb microdeletion downstream of *FOXG1* in patient 4 that removes a large part of the next gene, *PRKD1*. *PRKD1* encodes protein kinase D1 (also known as PKD or PKD1), a serine/threonine kinase that regulates a variety of cellular functions, including membrane receptor signalling, transport processes, protection from oxidative stress, transcriptional regulation, and F-actin reorganisation.[25 26] FISH with BAC clones RP11-30H9 and RP11-419C10 yielded only one signal on metaphase spreads, whereas two signals were obtained on metaphase spreads of his parents (figure 3B and data not shown; paternity confirmed). By quantitative PCR we confirmed the presence of two copies of the *FOXG1* gene in patient 4 (data not shown), suggesting that similar to patient 1 a position effect might have caused altered expression of *FOXG1*. In line with this finding, the deletion spans the two putative long range *cis*-regulatory elements for *FOXG1* expression (figure 3C).

Sequence analysis of *FOXG1*

We next selected 125 patients with phenotypes overlapping patients 1–4, including mental retardation, postnatal microcephaly, mild frontal pachygyria, and callosal abnormalities. We sequenced *FOXG1* in this cohort, and detected four intragenic mutations in the heterozygous state, including the transitions c.757A→G (p.N253D) in patient 5 and c.700T→C (p.S234P) in patient 11, the frameshift mutation c.460dupG (p.E154GfsX301) in patient 6, and the nonsense mutation c.256C→T (p.R86X) in patient 9. The missense mutations affect invariant amino acids, asparagine at position 253 and serine at position 234. Both residues are located in the DNA binding (forkhead) domain of FOXG1, suggesting that these amino acid exchanges may alter DNA binding properties of FOXG1. The c.757A→G mutation was not detected in the parents of patient 5 or in 204 control chromosomes. Similarly, the c.700T→C mutation was not found in the parents of patient 11. The 1 bp duplication was not identified in the parents of patient 6 or in 200 alleles, and the nonsense mutation was absent from the DNA sample of the mother of patient 9 (the father was deceased). Thus, three of four intragenic *FOXG1* mutations occurred de novo (data not shown; all parental identities confirmed).

We also sequenced *FOXG1* in a cohort of 81 patients (55 females and 26 males) tested for *MECP2* mutations in a diagnostic laboratory with negative results. We detected the intragenic insertion–deletion mutation c.505_506delGGinsT (p.G168SfsX23) in patient 7 and the frameshift mutation c.263_278del16 (p.R88PfsX99) in patient 10, both in the heterozygous state. The parents of patients 7 and 10 did not carry the respective mutation (paternity confirmed), which was not detected in 200 control chromosomes. We also identified the same c.460dupG mutation in patient 8 as detected in patient 6. Sequencing of *FOXG1* in patients 1–4 was negative.

Phenotype of the *FOXG1* mutation positive patients

We reviewed clinical (table 1) and brain imaging (table 2) data in all 11 patients, and videotapes in four of the 11 patients (supplementary videos 1–4). Detailed results are listed in supplementary table 1 for all patients, and comparable information is collated for 16 previously reported patients in supplementary table 2. All of our patients had normal body measurements at birth with mildly slow growth thereafter leading to low weight (−1.5 to −2.5 SD) and low normal stature (0 to −2 SD) by 1–2 years. Birth head size was low normal (0 to −2 SD) in 5/7 and borderline small (−2 to −3 SD) in 2/7 children. Severe postnatal microcephaly (MIC) was apparent by 2 years (−4 to −6 SD) in 6/8 patients.

All 11 patients had early global developmental delay and later severe mental retardation. Only 3/10 learned to sit independently and only 1/11 learned to walk. None developed speech. All had deficient social interactions, especially poor eye contact. Several improved enough to allow use of pointing and assistive communication devices (but not speech), and limited social interaction. Two children had a history of possible regression, but this was subtle and difficult to document. The remainder had no history suggesting regression.

Exams reported muscular hypotonia in 10/10 and spasticity in 7/9 patients. We found stereotypies especially of the hands in 8/11, and dyskinesias in 8/10 with features of chorea, athetosis and dystonia. However, we observed dyskinesia in 6/6 patients reviewed during the course of this study with videos available of four patients (see supplementary videos 1–4), which suggests that this may be seen in all patients.

Dysfunction in several vegetative functions was apparent in all children. Sleep was disrupted from infancy in at least 8/11 children, with frequent night-time waking. This usually improved with age, or after gastrostomy placement in one child. Prominent irritability or crying was reported in 6/10 patients, especially in infancy. Gastro-oesophageal reflux was diagnosed in 9/10 children, and was often severe, becoming a prominent part of the overall phenotype. Aspiration was documented in 6/10. A gastrostomy tube was recommended for feeding in 2/7 children but only placed in one.

Seizures were documented in 8/10 patients with onset between 3 months and 6 years. They consisted of tonic, generalised tonic-clonic, and partial complex seizures. None had infantile spasms. EEG findings were variable from reports, but the original studies were not reviewed. Several other features are noted in supplementary table 1.

Brain MRI studies were reviewed in all 11 patients (figures 1 and 2). The forehead was usually low, although this was subjective. All 11 had a simplified gyral pattern defined as a reduced number of gyri separated by shallow sulci, and significantly reduced volume of white matter that appears most severe—by far—in the frontal lobes. We observed mild frontal pachygyria in 3/11 patients; our recognition of subtle frontal pachygyria in patient 1 led directly to testing and detection of an intragenic mutation in patient 5. We found hypogenesis of the corpus callosum in 9/11 patients including three with a novel defect in which the frontal portion of the corpus callosum narrows to a sharp point or hook, with an absent rostrum and very small genu (figure 1E,M,Q). One child with a large 14q12 deletion had complete agenesis of the corpus callosum (figure 2I). The remaining patients had a short or thin corpus callosum with dysmorphic or absent rostrum and narrow or absent splenium. The two patients with a normal corpus callosum were those with a 14q12 deletion 35 kb distant from *FOXG1* (figure 2Q) and the patient with the missense mutation p.S234P (figure 2U).

The two children with large deletions (patients 2 and 3) had mild dysmorphic facial features in addition to the MIC, including wide and round face, flat midface, large ears and small jaw. The remaining children had obvious MIC with subtle and non-specific dysmorphic features (figure 4).

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Table 1 Clinical data for patients with deletion 14q12 or *FOXG1* mutations

	This report N=11	Literature[1–5 9–13] N=15
FOXG1 mechanism	4 CYTO, 7 intragenic	5 CYTO, 10 intragenic
Subject demographics		
Sex	5 female:6 male	14 female:1 male
Age last follow-up	2 years to 31 years	10 months to 22 years
Growth		
Weight birth (%)	10/10 normal (10–90%)	15/15 (10–90%)
Length birth (%)	9/9 normal (10–75%)	14/14 (25–90%)
OFC birth (SD)	5/7 (0 to −2 SD); 2/7 (−2.5 SD)	4/14 (+1 to 0 SD); 10/13 (0 to −2)
Weight age 1–2 years (SD), age	5/6 (−1.5 to −2.6 SD); 1/6 25%	Insufficient data
Length age 1–2 years (SD), age	5/6 (0 to −2 SD); 1/6 (−3.5 SD)	Insufficient data
OFC age 1–2 years (SD), age	8/8 (−2.5 to −6 SD)	Insufficient data
Weight most recent (SD), age	4/10 (−1 to −2 SD); 6/10 (−2 to −5.5 SD)	6/9 (−1 to −2 SD); 3/9 (−3 SD)
Length most recent (SD), age	2/8 (−1 to −2 SD); 5/8 (−2 to −5 SD)	6/9 (−0 to −2 SD); 2/9 (−3.5 to −4)
OFC most recent (SD), age	9/9 (−2.5 to −5.5 SD)	12/12 (−2 to −5 SD)
Development		
Developmental delay (DD)	11/11 DD	
Mental retardation (MR)	11/11 MR	15/15 MR
Mental retardation (severity)	11/11 severe	5/5 severe
Speech–language development	11/11 no language	13/14 no language
Social interaction (eye contact)	10/10 poor	7/9 poor
Sitting (age)	3/10 sit, all late	3/13 sit
Walking (age)	1/11 walk, late	1/15 walk
Loss of psychomotor skills (age)	2/11 vague history loss skills	8–11 regression
Behaviour, sleep, autonomic		
Sleep pattern	8/11 poor sleep pattern	4/8 poor sleep pattern
Irritability	5/10 excess irritability	Insufficient data
Crying/weeping (inconsolable)	6/10 excess crying	3/6 excess crying
Laughing (inappropriate)	0/11 excess laughing	Insufficient data
Motor and dyskinesias		
Hypotonia	10/10 hypotonia	6/6 hypotonia
Spasticity	7/9 spasticity	1/2 insufficient data
Functional hand use	8/11 no hand use	8/10 no hand use
Stereotypic movements	8/11 stereotypies	10/10 stereotypies
Dyskinesias (chorea, dystonia)	8/10 dyskinesia (or all?)	10/10 dyskinesia
Strabismus	insufficient data	9/9 strabismus
Bruxism	5/8 bruxism	10/13 bruxism
Drooling (sialorrhea)	No data	7/9 drooling
Epilepsy		
Seizures (age onset)	8/10 seizures	10/15 seizures (6 months to 14 years)
Seizure types (specify)	CPS, FTCS, GTCS	CPS, GTCS, myoclonic
Gastrointestinal and respiratory systems		
Feeding difficulties	9/11 poor feeding	5/6 poor feeding
Aspiration	6/10 aspiration	Insufficient data
Gastro-oesophageal reflux (GER)	9/10 GER often severe	5/5 GER
Constipation	Insufficient data	6/6 constipation
Breathing abnormalities	Non-specific	3/5 abnormal respirations
Other abnormalities		
Facial dysmorphism	2/3 with deletions	4/4 with deletions
Scoliosis	Insufficient data	4/11 scoliosis

CPS, complex partial seizures; CYTO, cytogenetic abnormality; FTCS, focal tonic-clonic seizures; GER, gastro-oesophageal reflux; GTCS, generalised tonic-clonic seizures; OFC, occipitofrontal circumference.

DISCUSSION

Foxg1 is a transcription factor that regulates development of the telencephalon from early embryonic to adult stages by multiple diverse mechanisms.[6 7 27] Not surprisingly, it was recognised as a strong candidate gene to explain the developmental disorder associated with deletion 14q12 and as a single gene cause of human developmental disorders.[5 9] Our study extends several previous reports, demonstrating that heterozygous loss of FOXG1 results in a consistent and severe developmental phenotype with emerging genotype–phenotype correlations.

Foxg1 function

Foxg1 is a conserved transcriptional repressor that is strongly expressed in progenitors of the ventricular zone and early post-mitotic neurons in the developing neuroepithelium of the telencephalon and visual structures.[28–31] It is involved in the timing of neuronal differentiation and in the specification of subdomain identity, regulating dorsal–ventral and subsequently rostral–lateral regional differentiation and later neural progenitor versus Cajal-Retzius cell fate, expansion of the neural progenitor pool, and progenitor cell cycle length.[8 30 32–35]

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Table 2 Brain imaging data for patients with deletion 14q12 or *FOXG1* mutations

	This report N=11	Literature[1–5 9–13] N=15
Simplified gyral pattern	11/11 SIMP	01/01 SIMP
Pachygyria, mild frontal	03/11 frontal pachygyria	00/02 frontal pachygyria
Reduced volume white matter (frontal)	11/11 reduced WM	04/04 reduced WM
Hypogenesis corpus callosum (frontal)	09/11 hypogenesis CC	09/09 hypogenesis CC
Agenesis corpus callosum (severe)	01/11 ACC with deletion	02/13 ACC

ACC, agenesis of corpus callosum; CC, corpus callosum; SIMP, simplified gyral pattern; WM, white matter.

Homozygous *Foxg1*$^{-/-}$ mutants die at birth with a dramatic reduction in the size of the cerebral hemispheres affecting ventral more severely than dorsal structures, and depletion of neural progenitor pools.[8 30 32–35] The cortical plate is poorly organised with loss of layer-specific markers, and appears relatively thick in lateral cortical regions as a result of accelerated neuronal differentiation (see figure 1 in Hanashima *et al*[33]).

Heterozygous *Foxg1*$^{+/-}$ (especially *Foxg1*$^{+/cre}$) mutants have less severe developmental defects including reduced volumes of the cerebral cortex, striatum and hippocampus, and thin cortex due to reduced thickness of the superficial layers (II–III) of the cortex. The latter results from loss of neuron generating intermediate progenitor cells during mid and late corticogenesis and, to a lesser extent, from a prolonged cell cycle in late corticogenesis.[6 7] These data predict that humans with *FOXG1* haploinsufficiency should have microcephaly, thin cortex with abnormal cortical cytoarchitecture (but with a thicker cortex possible in lateral cortical regions), and cognitive plus behavioural defects.

FOXG1 mutations

Combining our series and prior reports, 18 intragenic sequence changes of *FOXG1* have been reported including 14 null—six nonsense and eight frameshift—and four missense mutations (supplementary tables 1 and 2). The missense mutations (p.F215L, p.N227K, p.S234P, and p.N253D) all affect evolutionarily highly conserved amino acid residues in the forkhead domain involved in DNA binding. One group hypothesised that amino acid substitutions in functional domains of FOXG1 and late truncating mutations may lead to a milder phenotype including typical and atypical Rett syndrome because the resulting FOXG1 proteins may retain some functions, especially their ability to bind corepressors.[13] However, the p.Y400X and p.S323fsX325 mutations, identified in patients with a severe phenotype, leave one FOXG1 domain intact which interacts with the Groucho corepressor family.[36] Thus, missense as well as clear loss-of-function mutations can have a severe impact on FOXG1 function, suggesting that other factors may modulate the phenotypic outcome.

The recurrent c.460dupG mutation causing duplication of a guanine after seven subsequent guanines in *FOXG1* was identified twice in our patient cohort and in one reported patient.[10] These findings suggest that this guanine stretch may be prone to replication errors and represent a mutational hot spot in *FOXG1*.

We identified the 14q12 breakpoint in patient 1 about 265 kb downstream of the *FOXG1* gene. The finding of de novo *FOXG1* mutations in patients with a developmental encephalopathy overlapping Rett syndrome strongly suggests that altered

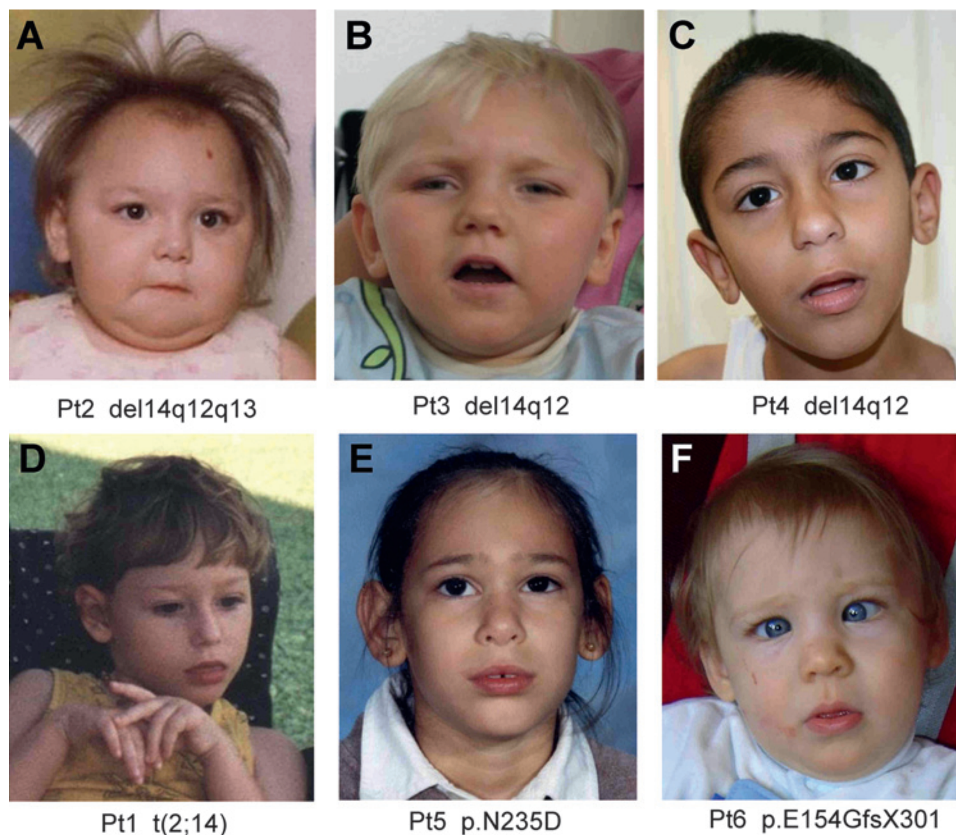

Figure 4 Patients with *FOXG1* mutations. Two patients with 14q12 deletions (top row, A, B) demonstrate mild facial dysmorphism consisting of round face with flat midface, low nasal bridge, bulbous nasal tip, thin upper lip and prominent ears. Four children with regulatory (top row, C and bottom row, D) or intragenic mutations (bottom row, E, F) have normal facial appearance except for mildly prominent ears. One photo shows hand stereotypy (D), and another shows striking esotropia (F). The patient numbers and mutations are shown at the bottom of each photograph.

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expression of *FOXG1* due to displacement of *cis*-regulatory elements important for its spatial and temporal expression caused the disease phenotype in patient 1. The 14q12 breakpoint of a different de novo 2;14 translocation was mapped ∼5 kb downstream of the *FOXG1* gene.[5] The authors postulated that the breakpoint disrupted novel *FOXG1* splice variants between exons 3 and 4 with a brain specific expression pattern, represented by the EST (expressed sequence tag) sequence BX248251. However, the non-coding RNA gene *C14orf23* maps distal to *FOXG1* (figure 3A), and the reference sequence of this gene was derived from BX248251, which suggests that the putative *FOXG1* exons 2−5 more likely represent exons of *C14orf23*. In line with this, no mutations in these exons have yet been reported.[13] Thus, we suggest that both 2;14 translocations resulted in removal of long range regulatory elements of *FOXG1*, located in the gene desert between *FOXG1* and *PRKD1*.

Further evidence supporting the existence of sequences regulating *FOXG1* expression comes from our identification of a ∼1 Mb microdeletion not covering *FOXG1* in patient 4. The phenotypes of both patients 1 and 4 are very similar to *FOXG1* mutation positive individuals, suggesting that dysregulated *FOXG1* expression may be responsible for their clinical features. In addition, two more patients with small overlapping microdeletions of 0.14−1.8 Mb that do not seem to include *FOXG1* have been reported and are associated with a phenotype fitting with that of *FOXG1* mutation positive patients.[3] Our in silico analysis revealed two highly conserved non-coding elements of 1819 bp and 1848 bp between *FOXG1* and *PRKD1* that drive expression of a reporter gene specifically in the forebrain of transgenic mice (http://enhancer.lbl.gov/frnt_page.shtml). Thus, we propose that regulatory mutations—that is, displacement and deletion of the two putative *cis*-regulatory elements by the translocation and the ∼1-Mb microdeletion, respectively—cause a phenotype similar to that caused by mutations directly affecting *FOXG1*. Nonetheless, the phenotype of patient 4 is less severe than our other patients. This suggests disrupted function of a spatiotemporally specific subset of the normal expression pattern.[37]

The *FOXG1* syndrome

We report the largest series of patients with *FOXG1* mutations to date. Analysis of our 11 patients and 15 patients from the literature[1−5 9−13] reveals a complex and consistent developmental phenotype that affects many areas of neurologic and behavioural function (thus classified as a developmental encephalopathy). By recognising classic dyskinesias and a novel and specific pattern of brain malformations in our cohort of patients we also expand the phenotype.

The characteristic features of the FOXG1 syndrome include: (1) moderate postnatal growth deficiency; (2) severe postnatal microcephaly; (3) severe mental retardation with (4) absent or minimal language development; (5) deficient social interactions including poor eye contact denoting a syndromic form of autism; (6) combined stereotypies and frank dyskinesias with mixed features of athetosis, chorea and dystonia; (7) epilepsy; (8) poor sleep patterns; (9) irritability especially in infancy; (10) excessive episodes of crying; (11) recurrent aspiration; and (12) frequent gastro-oesophageal reflux. While a few prior reports described developmental regression in some children, the history was vague as it was in two of our patients, leading us to exclude this as a diagnostic feature. Several other clinical problems were reported in a few patients, such as clubfeet, scoliosis, bruxism, and constipation.

Brain imaging studies reveal frontal predominant simplified gyral pattern, reduced white matter volume and callosal hypogenesis, with variable appearance of mild frontal pachygyria. Complete agenesis of the corpus callosum was observed in only 3/24 patients overall, but in 2/7 patients with deletion 14q12, which suggests modifying genes in the region. Considering the thin cortex observed in the *Foxg1*$^{+/-}$ mouse, it seems possible that the mild pachygyria seen in a few patients is an artefact resulting from image averaging of the cortical ribbon due to the very thin frontal white matter. However, the *Foxg1*$^{-/-}$ mouse has a dysplastic cortex, so we prefer to reserve judgement on this issue until higher resolution brain scans or human brain tissue become available.

FOXG1 genotype−phenotype analysis

The number of reported mutations is now large enough to begin genotype−phenotype correlation. Combining our data and several literature reports, the core phenotype is seen in individuals with mutations causing protein truncation and in some with missense and other mutations. Patients with large deletions of 14q12 that include *FOXG1* and other genes may have more severe phenotypes, adding complete agenesis of the corpus callosum and mild facial dysmorphism to the core phenotype.

Also, some patients with missense or putative regulatory mutations appear to have less severe phenotypes. Combining our series and literature reports, only 6/23 patients were able to sit, and four of the six had less severe mutations including a late truncation (p.S323fsX325), a regulatory mutation (deletion 34 kb downstream of *FOXG1* in patient 4), and two missense mutations (p.F215L, and p.N253D in patient 5). Only 2/26 patients learned to walk and both had less severe mutations including one late truncation (p.Y400X) and the same missense mutation (patient 5 with p.N253D).

The association between *FOXG1* and developmental abnormalities in humans is further supported by recent reports of duplication 14q12 including the *FOXG1* in eight patients.[14 15] The phenotype resembles the FOXG1 haploinsufficiency syndrome described above, including severe developmental delay, mental retardation and absent or minimal language in 8/8, seizures in 5/8, hypotonia in 2/8, stereotyped behaviour especially perseverative hand movements in at least 4/8, and inappropriate laughing and sleep disturbance in at least 1/8 patients. However, the seizures were more severe, with typical infantile spasms reported in 4/8 patients. Other differentiating features include normal head circumference by age 1−3 years in 7/8 patients, and walking in at least 3/8 patients. Based on limited data, brain imaging features appear to be similar but less severe including subtle hypogenesis of the corpus callosum in at least three patients, and reduced white matter volume in at least two patients (this interpretation is based partly on our interpretation of figure 2 in Brunetti-Pierri *et al*[14]).

The *FOXG1* syndrome or congenital Rett syndrome variant

This disorder was first described as a congenital variant of Rett syndrome. While many features do overlap with Rett syndrome, several features beyond the congenital onset differ as well. For example, the presence of true dyskinesias and brain imaging abnormalities, as well as the lack of regression and lack of respiratory arrhythmia, differ from classic Rett syndrome. We believe that the combination of developmental and brain imaging features observed in individuals with *FOXG1* mutations are sufficiently distinct to allow clinical recognition of this disorder, which we therefore prefer to designate simply as the *FOXG1* syndrome.

Further, the phenotypic overlap with other complex developmental syndromes extends far beyond similarity to Rett

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syndrome to include at least nine different syndromes and genes: Angelman syndrome, classic Rett and other *MECP2* associated syndromes, the *ARX*, *CDKL5*, *CNTNAP2*, *NRXN1*, *SLC9A6*, and *TCF4* associated syndromes, and maternal isodicentric and duplication 15q11.2q13 syndromes.[16 18 21 22 38–42] Most are single gene disorders, and all present with a wide spectrum of cognitive, social, affective, autonomic and motor deficits, as well as epilepsy. Considering the increasing number and phenotypic heterogeneity of these disorders, we have begun to use the term complex or mixed 'developmental encephalopathies' to refer to the group as a whole.

In conclusion, we present the first evidence for mutations of *cis*-regulatory elements required for spatially, temporally, and quantitatively correct activity of *FOXG1* in patients with the same phenotype as individuals with intragenic *FOXG1* lesions, as well as several novel intragenic mutations. The specific pattern of developmental features and brain malformations observed in individuals with *FOXG1* mutations should allow clinical recognition of the *FOXG1* syndrome and prompt genetic testing of the gene.

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The core *FOXG1* syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis

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