The distinct and overlapping phenotypic spectra of \textit{FOXP1} and \textit{FOXP2} in cognitive disorders

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Abstract  Rare disruptions of \textit{FOXP2} have been strongly implicated in deficits in language development. Research over the past decade has suggested a role in the formation of underlying neural circuits required for speech. Until recently no evidence existed to suggest that the closely related \textit{FOXP1} gene played a role in neurodevelopmental processes. However, in the last few years, novel rare disruptions in \textit{FOXP1} have been reported in multiple cases of cognitive dysfunction, including intellectual disability and autism spectrum disorder, together with language impairment. As \textit{FOXP1} and \textit{FOXP2} form heterodimers for transcriptional regulation, one may assume that they co-operate in common neurodevelopmental pathways through the co-regulation of common targets. Here we compare the phenotypic consequences of \textit{FOXP1} and \textit{FOXP2} impairment, drawing on well-known studies from the past as well as recent exciting findings and consider what these tell us regarding the functions of these two genes in neural development.

Introduction

Forkhead box (FOX) proteins are an evolutionarily ancient family of transcription factors characterised by a highly conserved forkhead DNA-binding domain. Despite the similarity in the DNA-binding domain, FOX proteins have a wide range of important biological functions (Hannenhalli and Kaestner 2009). Most FOX proteins bind to their target DNA sequences as monomers, except members of the \textit{FOXP} subfamily, which includes \textit{FOXP1–4}. \textit{FOXP} proteins are somewhat atypical as they also possess a zinc finger and leucine zipper domain, both of which mediate interactions with other proteins, thus allowing FOXP proteins to form homo- and heterodimers to facilitate their binding to DNA for transcriptional regulation (Li et al. 2004). In the past, members of the \textit{FOXP} subfamily have been implicated in various human diseases (Bennett and Ochs 2001; Jin et al. 2010; Lai et al. 2001), but only \textit{FOXP1} and \textit{FOXP2} have been linked to cognitive disorders so far.

Perhaps the most prominent of the \textit{FOXP} genes is \textit{FOXP2} (OMIM 605317), whose involvement in speech and language acquisition has now been studied for more than 10 years (Fisher and Scharff 2009). \textit{FOXP2} and language development has generated extreme interest as the acquisition of spoken language is central to what makes us human. In the last 2 years, evidence has emerged that implicates \textit{FOXP1} (OMIM 605515), the closest relative of \textit{FOXP2} (64 % total protein sequence identity, 89 % in the forkhead domain), in the pathology of human cognitive disorders, which involve language impairment. \textit{FOXP1} and \textit{FOXP2} are already known to co-operate in the regulation of non-neural developmental processes (Shu et al. 2007) and it will be interesting to validate whether this co-operation extends to brain development. A comparison of the
clinical phenotypes caused by FOXP1 and FOXP2 disruption would provide important steps towards uncovering those regions of neuropathology in which these genes play a role.

**FOXP2 mutations are implicated in developmental verbal dyspraxia**

Foxp2 contributes to lung, heart and oesophagus development (Shu et al. 2001, 2007), but the most well-known role of this gene is in the development of speech and language (Fisher and Scharff 2009; Newbury and Monaco 2010). Human FOXP2 was first linked to language development in 2001, when a heterozygous missense mutation in the forkhead domain (R553H) was found to be causative for an inherited language disorder in a large 3-generation pedigree known as the KE family (Lai et al. 2001). The KE family has been extensively studied and the phenotype is now well defined, affecting expressive, receptive and written language (Table 1). A core feature of the disorder is a difficulty in the learning and production of co-ordinated sequences of orofacial movements, which impairs the production of fluent speech (Vargha-Khadem et al. 1995; Watkins et al. 2002a). Therefore the affected members have a primary diagnosis of developmental verbal dyspraxia (DVD), which is also known as childhood apraxia of speech (CAS). Studies on the KE family have also included formal evaluations of non-verbal intelligence and the average IQ of affected KE family members is lower than that of unaffected individuals (Fisher et al. 1998; Vargha-Khadem et al. 1995; Watkins et al. 2002a), raising the possibility that the missense mutation in the FOXP2 gene also impacts other cognitive functions. Nevertheless, the most prominent and consistent features of the disorder are in the domain of speech and language, with more severe and wide-ranging effects on verbal skills than on non-verbal cognition (Watkins et al. 2002a).

The presence of just one de novo mutation within the coding region of FOXP2 did not, by itself, provide compelling evidence that FOXP2 contributes to the pathology of DVD. To assess the contribution of heterozygous FOXP2 mutations in patient samples independent from the KE family, FOXP2 was screened in 49 unrelated children diagnosed with DVD (MacDermot et al. 2005). Three different variants altering the FOXP2 protein sequence in seven individuals were identified. The most interesting of these variants was a heterozygous nonsense mutation (not found in 252 controls) which yielded a stop codon at position 328 of the FOXP2 protein, resulting in either a truncated protein missing the functionally important forkhead, leucine zipper and zinc finger domains or a complete loss of FOXP2 due to nonsense mediated RNA decay. The child had a diagnosis of DVD and displayed articulation problems along with impaired receptive and expressive language development. The same mutation was also detected in an affected sibling as well as the mother, who was reported to have a history of speech difficulties. This finding offered further evidence that FOXP2 is of pathological importance in DVD in the absence of other cognitive disorders, which were exclusion criteria in this study.

Various large-scale 7q31 deletions that include the FOXP2 gene, ranging from 1.57 Mb to 15 Mb in size, have also been reported in patients with DVD (Feuk et al. 2006; Lennon et al. 2007; Palka et al. 2012; Rice et al. 2011; Zeesman et al. 2006; Zilina et al. 2011). DVD was reported in every case and most of the reports concluded that impaired language was due to the loss of FOXP2. However, the large size of these deletions encompassing several to many genes is a complication for understanding the links between phenotypes and FOXP2 dysfunction. Translocation breakpoints directly disrupting the FOXP2 locus in patients diagnosed with DVD provided more clear-cut support for the relevance of this gene to speech and language pathology (Table 1) (Feuk et al. 2006; Lai et al. 2000, 2001; Shriberg et al. 2006; Tomblin et al. 2009).

The reported FOXP2 variants are rare but have not been found in normal individuals from the 1,000 genome project and taken together, three translocation breakpoints disrupting FOXP2 (Feuk et al. 2006; Lai et al. 2000; Shriberg et al. 2006), one missense mutation (Lai et al. 2001) and one nonsense mutation (MacDermot et al. 2005) independently associated with a DVD phenotype provide strong genetic evidence for the role of FOXP2 in the clinical phenotype (summarised in Table 1).

**Evidence for a role of FOXP1 in neurodevelopmental disorders**

Foxp1 has been associated with a wide range of functions including development of the lung, heart, oesophagus, immune system and spinal motor neurons, as well as cancer (Banham et al. 2001; Dasen et al. 2008; Hu et al. 2006; Jepsen et al. 2008; Palmesino et al. 2010; Roussou et al. 2008; Shi et al. 2004; Shu et al. 2001, 2007; Wang et al. 2004). It has been known for some time that Foxp1 is expressed in particular neuronal subpopulations in the developing brain (Ferland et al. 2003), but its precise roles in brain development have not been defined. Given that the expression of Foxp1 and Foxp2 overlaps in certain areas of the developing brain (Ferland et al. 2003; Teramitsu et al. 2004) and that Foxp1 and Foxp2 are able to form heterodimers for transcriptional repression (Li et al. 2004), it is reasonable to hypothesize that FOXP1 could also be involved in the pathology of DVD. However, in a screen of the entire coding
Table 1  Summary of clinical phenotypes of patients reported with heterozygous intragenic mutations, deletions and disruptions of FOXP2 (in chronological order)

| References                  | FOXP2 variant | IQ        | Clinical information                                                                 |
|-----------------------------|---------------|-----------|--------------------------------------------------------------------------------------|
| Vargha-Khadem et al. (1995, 1998)⁴ | R553H (KE)    | 86 affected, 104 unaffected | Impaired speech production. Grammar defects. Impaired orofacial praxis. Articulatory impairment. Abnormal activation in motor-related areas during word repetition (PET). Caudate nucleus is structurally abnormal and smaller in affected members (MRI) |
| Fisher et al. (1998)⁴       | R553H (KE)    | 63–101 affected, 82–118 unaffected | NR                                                                                  |
| Watkins et al. (2002a, b)⁴  | R553H (KE)    | 83; affected (2), 98; unaffected (3) | Expressive, receptive and written language impaired. Impaired articulation is core deficit. Affected members had reduced volume and significantly less grey matter bilaterally in the caudate nucleus (voxel-based morphometry of MRI) |
| Liegeois et al. (2003)⁴     | R553H (KE)    | NR       | Abnormal activation of Broca’s area and putamen (MRI)                                |
| MacDermot et al. (2005)⁴    | R328X         | NR       | DVD. Repetitive and expressive language scores 3 SD below mean. Problems with articulation. Affected sibling also carried variant |
|                             | Q17L          | NR       | DVD. Affected sibling did not carry variant                                           |
|                             |               | NR       | DVD. Affected sibling did not carry variant                                           |
| Lai et al. (2000)⁵          | t(5;7) (q22;q31.2) balanced translocation | NR | Language impairment. DVD. Mild delay in mental development at 3.5 years                     |
| Shriberg et al. (2006)⁵     | t(7;13) (q31.1;q13.2) balanced translocation | 95 and 87 | Both mother and daughter have spastic dysarthria and DVD. Expressive and receptive language and grammatical ability impaired |
| Tomblin et al. (2009)⁵      | t(3;7) (q23;q31.2) translocation | NR | DVD |
| Feuk et al. (2006)⁵         | Five 7q31 dels: 3 × 15 Mb, 13 Mb and 11 Mb | 3 patients below average | All five patients had DVD as well as speech delay and an articulation disorder. Two patients had general developmental delay. One patient was reported to have ASD, another to be ‘ASD-like’ |
| Zeesman et al. (2006)⁶      | Del 7q31.2–q32.2 |       | Female patient. DVD. Cognitive abilities ranged from below average to average. Did not meet criteria for autism |
| Lennon et al. (2007)⁶       | 9.1 Mb del 7q31.2–7q31.31 |       | Female patient. DVD. Moderate intellectual disability. Did not meet criteria for autism |
| Zilina et al. (2011)⁶       | ~8.3 Mb del 7q31.1–q31.31, inherited from mother | 88 | Female patient. Moderate developmental delay. Poor vocabulary. Orofacial motor defects. Some autistic features. Affected mother has speech delay and DVD |
|                             | 6.5 Mb del 7q31.1–q31.2, inherited from mother | NR | Developmental delay in all areas. Mild ataxia. Pronunciation difficulties and poor vocabulary. Affected mother has intellectual disability, DVD and mood disorder |
| Rice et al. (2011)⁶         | 1.57 Mb del (FOXP2, MDFIC, PPP1R3A), Inherited from mother | 75 patient, 89 mother | Male patient. DVD. Mother’s early verbal development similar to the patient’s |
| Palka et al. (2012)⁶        | 14.8 Mb mosaic del | 71 | Female patient. DVD. Developmental delay. Normal brain MRI. Mild psychomotor retardation. Severe language delay. Impaired receptive, expressive, comprehensive and written language |

All IQ scores are non-verbal

DVD developmental verbal dyspraxia, ASD autism spectrum disorder, NR not reported

⁴ Rows represent intragenic mutations leading to amino acid changes and insertions

⁵ Rows represent translocations

⁶ Rows represent deletions
region of \textit{FOXP1} in 49 DVD patients, (the identical cohort used in the \textit{FOXP2} screening described earlier), no potentially disease-causing variants were found (Vernes et al. 2009). Although the patient cohort was small, it suggested that, unlike \textit{FOXP2}, mutations in \textit{FOXP1} are not sufficient to cause DVD in isolation. Instead, various screening studies carried out within the last few years have revealed that \textit{FOXP1} may be of more global importance in a range of neurodevelopmental disorders, which includes but is not restricted to speech and language disorders.

The first hint that \textit{FOXP1} may be involved in neurodevelopmental disorders was provided by a heterozygous deletion in 3p14.1, which affected \textit{FOXP1}, \textit{EIF4E3}, \textit{PROK2} and \textit{GPR27}, in a patient with speech delay, hypertonia and additional phenotypes (for details see Table 2) (Pariani et al. 2009). The authors optimistically attributed many of the patient’s symptoms including the speech delay to the disruption of \textit{FOXP1}, but the contribution of \textit{PROK2} and \textit{GPR27} to the phenotype cannot be ruled out, especially considering that both genes were
previously implicated in developmental retardation (Petek et al. 2003). More convincing evidence was provided when a deletion exclusively affecting the FOXP1 gene was found in a male child with impaired language acquisition and motor development delay (Carr et al. 2010). Unfortunately, a confounding factor in this study was the presence of a Chiari I malformation (cerebellar tonsil abnormality) in the patient, which may have contributed to the delay in motor and speech development, therefore convincing evidence for a role of FOXP1 in cognitive disorders was still lacking. Shortly afterwards, a large-scale screen for copy number variations (CNVs) in 1,523 patients with intellectual disability, uncovered three de novo heterozygous deletions solely affecting FOXP1 (Horn et al. 2010). A large 1.3 Mb deletion affecting FOXP1 and other genes was also found in a control individual (Horn et al. 2010). The three patients had moderate intellectual disability (IQ of <50), gross motor delay and a severe speech and language defect, characterised by a delay in the onset of speech, dysgrammatism and very poor speech articulation. Two of the reported patients also had an oromotor defect, including difficulties with lip protrusion and tongue elevation, but DVD was not diagnosed. These findings provided the first compelling evidence that disruptions in the FOXP1 gene can be causative for multiple neurodevelopmental abnormalities, which include language impairment, implicating FOXP1 in more widespread cognitive processes than were previously described for FOXP2. This hypothesis gained further support from a recent independent study of 110 individuals with intellectual disability and/or autism spectrum disorder (ASD), which identified a de novo intragenic FOXP1 deletion in a patient with both intellectual disability (IQ of 58) and severe language impairment, particularly affecting expressive language (Hamdan et al. 2010). The deletion included sequences corresponding to the leucine zipper and zinc finger domains, which are important for FOXP1 dimerization and transcriptional repression. In addition to the deletion, a de novo nonsense mutation, R525X, was found in the FOXP1 forkhhead domain in another patient with non-syndromic intellectual disability (IQ of 48), severe language impairment and ASD. This study added further weight to previous findings that FOXP1 is important for language development and normal intelligence and the discovery of a FOXP1 stop mutation in a patient with ASD was exciting, as it highlighted FOXP1 for the first time as a potential ASD candidate gene.

Whole exome sequencing has the potential to identify all coding variants in an affected individual and was recently used to define rare de novo coding mutations in 20 individuals with ASD and their healthy parents, along with 20 unrelated ethnically matched controls (O’Roak et al. 2011). Among several presumably causative mutations in different genes was a single base insertion in FOXP1, introducing a frameshift and premature stop codon (A339S/+X4). This individual had severe ASD and delayed language development together with intellectual disability (IQ of 34), reminiscent of previously reported FOXP1 phenotypes (Carr et al. 2010; Hamdan et al. 2010; Horn et al. 2010). An additional inherited nonsense variant, H275R, was also detected in the CNTNAP2 gene. As CNTNAP2 has been implicated in intellectual disability (Gregor et al. 2011; Zweier et al. 2009), ASD (Alarcon et al. 2008) and in language impairment without ASD (Vernes et al. 2008; Whitehouse et al. 2012), it could also have contributed to the patient’s phenotype. As FOXP1 was found to regulate CNTNAP2 expression, the FOXP1 mutant identified in this patient could enhance any potentially damaging effects of the CNTNAP2 H275R variant, highlighting the presence of putative modifier gene effects (O’Roak et al. 2011).

Very recently, direct sequencing of balanced chromosomal breakpoints in 38 patients with ASD uncovered a translocation breakpoint affecting FOXP1 on chromosome 3p and ANK3 on chromosome 10q in an individual with ASD and speech delay (Talkowski et al. 2012). While ANK3 has previously been implicated in bipolar disorder and schizophrenia (Ferreira et al. 2008; Williams et al. 2011), secondary CNV analysis of FOXP1 and ANK3 in 19,566 patients with ASD revealed a significant CNV burden for FOXP1, but not ANK3 (Talkowski et al. 2012). The distinct but complementary approaches of chromosomal breakpoint sequencing followed by an extensive secondary assessment of CNV findings provided further compelling support that FOXP1 represents a gene with a widespread role in neurodevelopmental processes.

Taken together, five FOXP1 single gene deletions (Carr et al. 2010; Hamdan et al. 2010; Horn et al. 2010), two intragenic nonsense and frameshift mutations (Hamdan et al. 2010; O’Roak et al. 2011) and a chromosomal breakpoint disrupting FOXP1 supported by secondary CNV analysis (Talkowski et al. 2012) in patients with intellectual disability, ASD, language disorder and motor development delay, provide strong evidence for FOXP1 underlying various cognitive phenotypes (summarised in Table 2).

### Similarities and differences between phenotypes associated with FOXP1 and FOXP2 disruptions

#### Language disorder

In language disorders, a distinction is often made as to whether the language impairments are primarily receptive (hearing, reading and comprehending) or expressive (speaking and writing), or affect both. People with FOXP2...
mutations have both impaired expressive and receptive language (MacDermot et al. 2005; Watkins et al. 2002a), whereas expressive language appears to be more affected in patients with FOXP1 disruptions (Hamdan et al. 2010; Horn et al. 2010). A core feature of the phenotype associated with FOXP2 dysfunction is an abnormal articulation due to verbal dyspraxia, i.e. impairment in the motor programming of orofacial movements required to produce normal speech (MacDermot et al. 2005; Vargha-Khadem et al. 1995). Although articulation problems have been described in some patients with FOXP1 disruption (Horn et al. 2010), orofacial dyspraxia has not been diagnosed so far (Carr et al. 2010; Hamdan et al. 2010; Horn et al. 2010; O’Roak et al. 2011), neither have any FOXP1 variants been identified in the small DVD patient cohort (Vernes et al. 2009). As FOXP1 variants are yet to be associated solely with a language disorder without additional cognitive phenotypes, the possibility exists that the language disorder observed in patients with disruptions in FOXP1 is a consequence of more global cognitive disruption rather than a specific disruption in those neural circuits necessary for speech production. This could be elucidated by comparative brain imaging of patients with FOXP1 and FOXP2 disruptions as well as comparing behavioural, electrophysiological and morphological phenotypes of Foxp1 and Foxp2 knockout mice. Generally, a delay in language acquisition is often observed in ASD individuals along with significantly impaired comprehension, articulation and grammar, which improves with time (Boucher 2011). Similarly, language deficits are often severe in children diagnosed with intellectual disability (Kaufman et al. 2010). Thus, the impaired language observed in patients with FOXP1 disruptions could be a secondary consequence of these disorders. In summary, there is an overlap in the language phenotype of patients with disruptions in FOXP1 and FOXP2, particularly regarding expressive language impairment (Fig. 1), but how similar the mechanistic basis is remains unclear.

Autism spectrum disorder

Autism spectrum disorder is characterised by impaired social interaction and communication, language impairment and the presence of restrictive and repetitive behaviours. In most cases, ASD is inherited and the specific genetic disruptions are known in only a minority of cases (Geschwind 2011). ASD has been diagnosed in patients with various disruptions in the FOXP1 gene (Hamdan et al. 2010; O’Roak et al. 2011; Talkowski et al. 2012), implicating FOXP1 in the pathology of ASD. Chromosome 7q31 is a known autism susceptibility locus, particularly involving the language impairment of the disorder (Alarcón et al. 2002), therefore FOXP2 has been suggested as a potential ASD candidate gene. However, FOXP2 screenings in different cohorts of ASD patients have failed to identify any causative mutations (Gauthier et al. 2003; Newbury et al. 2002; Wassink et al. 2002). Yet, in a recent large-scale haplotype mapping analysis FOXP2 was identified as a novel ASD candidate gene, among 1,218 others (Casey et al. 2011). FOXP2 is also implicated in the etiological pathways of ASD through its target genes MET (Mukamel et al. 2011) and CNTNAP2 (Vernes et al. 2008), although CNTNAP2 has also been linked to language impairment where there is no diagnosis of ASD (Vernes et al. 2008). Additionally, people with isolated mutations of FOXP2 do not show any signs of ASD even though FOXP2 is involved in pathways relevant to autism. Thus, while the possibility is open that screening studies of FOXP2 in larger cohorts of ASD patients could identify causative FOXP2 variants in the future, existing evidence suggests that—in contrast to FOXP1—FOXP2 is not involved in ASD.

Intellectual disability

Intellectual disability is a cognitive disorder characterised by an IQ of <70 (Kaufman et al. 2010). All non-verbal IQs reported in patients with FOXP1 variants are below this threshold (Table 2) indicating that intellectual disability is a consistent feature of the phenotype associated with FOXP1 disruption. Most but not all affected KE family members with FOXP2 missense mutations have a lower IQ than unaffected members (Fisher et al. 1998, 2003; Vargha-Khadem et al. 1995; Watkins et al. 2002a) but normal IQs have been reported in other patients with perturbations in the FOXP2 gene (MacDermot et al. 2005; Tomblin et al. 2009). Intellectual disability therefore cannot be considered a reliable characteristic of the phenotype associated with FOXP2 disruption at this time. The reported IQs of patients

![Fig. 1 Summary of similarities and differences between FOXP1 and FOXP2 neuronal phenotypes](image-url)
with FOXP1 disruptions are much lower than those reported for people with FOXP2 variants (Tables 1, 2); therefore intelligence appears to be influenced more strongly by FOXP1 than FOXP2 dysfunction.

Motor development delay

Although difficulties with fine motor movement and coordination are sometimes present in DVD patients with FOXP2 mutations, gross motor and developmental delay appear to be more predominant in patients with FOXP1 disruption (Tables 1, 2). The delayed motor development described in most human patients with disruptions in the FOXP1 gene (Carr et al. 2010; Hamdan et al. 2010; Horn et al. 2010; Pariani et al. 2009) is interesting, as Foxp1 defines the identity of motor neurons in the mouse spinal cord and influences motor neuron migration, axon projection and axonal branching at muscle targets (Dasen et al. 2008; Palmesino et al. 2010; Rousso et al. 2008). Therefore the delayed motor development in individuals with FOXP1 disruptions may be influenced by pathologies in both the central and peripheral nervous system.

Steps towards elucidating neurodevelopmental pathways influenced by FOXP1 and FOXP2

Disruptions of FOXP1 and FOXP2 cause distinct phenotypes with some overlapping features (Fig. 1), pointing to both shared and distinct neurodevelopmental roles for these two genes. Below we discuss potential approaches to elucidate the molecular pathways and circuits involved.

Defining the neural phenotype of patients

The neural basis of behavioural abnormalities can be identified by structural and functional brain imaging of patients. MRI analyses of some FOXP1 patients have been performed but have revealed no obvious structural brain abnormalities (Carr et al. 2010; Horn et al. 2010). Conventional neuroradiological assessment of MRI scans performed on affected members of the KE family also revealed no obvious abnormalities at first (Vargha-Khadem et al. 2005), but application of voxel-based morphometry, which can detect more subtle differences in grey and white matter and additional volumetric analysis revealed significant differences in specific brain regions of affected KE members (Watkins et al. 2002b). The neuroanatomical effects of the KE mutation have been extensively reviewed elsewhere (Vargha-Khadem et al. 2005), but in brief involve abnormalities in the cortex, cerebellum and basal ganglia, particularly the striatum (Liegeois et al. 2003; Vargha-Khadem et al. 1998; Watkins et al. 2002b). These findings from brain imaging implicate FOXP2 in the development of cortico-striatal circuits, which are involved in sensorimotor integration required for vocal motor learning. This would suggest that the phenotype observed in the KE family stems from disruption in the underlying neural circuits of language development, an idea that has received support from animal studies (see below).

Animal studies

Studies using animal models have taken us a long way towards elucidating the role of Foxp2 in brain development. Several Foxp2 knockout and mutant mouse models have been generated and the different phenotypes have already been extensively reviewed (Fisher and Scharff 2009). In brief, these phenotypes include developmental delay, motor impairment, cerebellar abnormalities and disrupted synaptic plasticity in the striatum. Recently, it was further demonstrated that motor skill learning is significantly impaired in mice carrying the equivalent mutation to that found in affected KE family members, which was explained by aberrant striatal activity during motor skill learning (French et al. 2011).

Two amino acid substitutions in the human FOXP2 protein have emerged during human evolution, possibly linked to the development of speech and language (Enard et al. 2002) and a partially humanised form of the FOXP2 gene has been shown to increase synaptic plasticity in the striatum of mice (Enard et al. 2009). This phenotype is additional missense variant in the CNTNAP2 gene was also present in this individual.

![Fig. 2 Summary of different FOXP1 (below) and FOXP2 (above) mutations described. See Tables 1 and 2 for reference details. Variant S339AfsX4 was identified by whole exome sequencing and an](image-url)
opposite to what has been described in mice with Foxp2
dysfunction (French et al. 2011; Groszer et al. 2008)
suggesting that the emergence of human FOXP2 may have
enhanced cortico-striatal circuits or circuit properties
during the evolution of spoken language. Taken together, these
animal studies have revealed that Foxp2 is involved in the
development of neural plasticity in circuits contributing to
language and a possibly wider cognitive function, which is
in agreement with the findings from neuroimaging of KE
family members (see above) (Fig. 2).

Foxp1 knockout mouse models have been used to
investigate the importance of Foxp1 in a range of non-
nervous developmental processes (Feng et al. 2010; Hu et al.
2006; Shu et al. 2007; Wang et al. 2004; Wu et al. 2006)
and in the development of motor neurons in the spinal cord
(Dasen et al. 2008), but have not been used to define the
role of Foxp1 in brain development. Homozygous loss of
Foxp1 causes embryonic death at E14.5 due to heart failure
(Wang et al. 2004). Conditional removal of Foxp1 in the
brain will therefore be the key to elucidating the import-
ce of Foxp1 during later stages of brain development. It
will be interesting to see whether brain-related aspects of
the Foxp1 knockout phenotype are distinct from the Foxp2
knockout phenotype, as is the case in the human situation.

Foxp1 and Foxp2 expression overlaps in the striatum,
thalamus, superior colliculus and inferior olive in the
mature mouse brain, but their expression differs in other
regions including the cortex, hippocampus and inferior
colliculus (Ferland et al. 2003). It is interesting that hist-
ological analyses of brains from Foxp2 knockout mice
only revealed gross morphological abnormalities in the
cerebellum, where Foxp1 is not co-expressed (French et al.
2007), suggesting that Foxp1 may compensate for the loss
of Foxp2 and that a level of redundancy exists between
these two genes. It will be interesting to see whether layers
3, 4 and 5 of the cortex or the hippocampus which express
Foxp1 only are exclusively abnormal in the Foxp1
knockout mouse.

Identification of target genes

Common FOXP1 and FOXP2 neurodevelopmental path-
ways seem likely, considering their potential to form het-
erodimers and their co-expression in certain brain tissues.
On the other hand, the distinct phenotypes seen in patients
with FOXP1 and FOXP2 disruption would suggest they
participate at least to some degree, in independent path-
ways. The identification and classification of target genes
hold the key to determining which pathways and networks
involve FOXP1 and FOXP2 during brain development. For
FOXP2, genome wide in vivo ChIP-chip screens coupled
to expression profiling have already been used to define
transcriptional targets in the developing brain; many of
these targets were found to be involved in pathways reg-
ulating neurite outgrowth, axon guidance and synaptic
plasticity (Konopka et al. 2009; Spiteri et al. 2007; Vernes
et al. 2007, 2011). Elsewhere, it has been shown that
FOXP2 directly regulates CNTNAP2, mutations in which,
like FOXP2, were found to be linked to language impair-
ment (Vernes et al. 2008), the autism candidate gene MET,
involved in neuronal differentiation (Mukamel et al. 2011)
as well as the schizophrenia susceptibility gene Disrupted
in schizophrenia 1 (DISC1) in HEK293 cells (76). Whether
the identification of DISC1 as a FOXP2 target places
FOX2 in schizophrenia-related pathways remains unclear.
There is conflicting evidence for a role of FOXP2 in
schizophrenia; significant associations have been reported
between certain FOXP2 SNPs and schizophrenia (Sanjuan
et al. 2006; Tolosa et al. 2010), but the FOXP2 missense
and nonsense mutations associated with DVD (Table 1)
were not found in patients with schizophrenia (Sanjuan
et al. 2005). In conclusion, the published targets of FOXP2
implicate this transcription factor in pathways regulating
neurite outgrowth, axon guidance and synaptic plasticity,
which is in agreement with a role of Foxp2 in the
development of neural circuits for language development.

The genes regulated by FOXP1 in developing brain
tissue have not yet been identified by genome-wide ChiP
screens. Overexpression of Foxp1 in a murine striatal cell
line has recently revealed a repression of immune-related
genes (Tang et al. 2012), which is in agreement with pre-
vious studies demonstrating a role of Foxp1 in immune
development. Given the level of cognitive disruption caused
by FOXP1 variants, it is reasonable to assume that FOXP1
targets will be uncovered in many neurodevelopmental
pathways and not limited to immune function. There is
evidence that CNTNAP2 expression is regulated by FOXP1
(O’Roak et al. 2011), which has also been shown for
FOX2 (Vernes et al. 2008), providing the first evidence
for a common FOXP1–FOX2 pathway involving CNT-
NAP2 in neurodevelopmental processes. On the other
hand, the fact that CNTNAP2 is implicated in both ASD
(Alarcon et al. 2008) and in language impairment without
ASD (Vernes et al. 2008) suggests distinct CNTNAP2
pathways exist. Elsewhere, Foxp1 has also been shown to
regulate Pitx3 transcription during the differentiation of ES
cells into midbrain dopaminergic neurons (Konstantoulaus
et al. 2010).

Typically, transcription factors do not act alone but
rather in complexes together with other transcription fac-
tors, chromatin remodelers and cofactor proteins to bind to
promoter sequences and regulate target gene expression.
FOXP1 and FOXP2 interact with various proteins to reg-
ulate gene expression in different tissues (supplementary
Table 1) (Chokas et al. 2010; Datta et al. 2008; Jepsen
et al. 2008; Li et al. 2004; Otaegi et al. 2011; Ravasi et al.
2010; Takayama et al. 2008; Wu et al. 2006; Zhou et al. 2008) but identification of the combinatorial interactions of FOXP1 and FOXP2 with other proteins specifically in the brain will be needed to understand the roles they play in brain development. The interactions of FOXP1 and FOXP2 with different proteins represent another dimension to the regulation of their target genes.

Concluding remarks

Disease-causing variants in both FOXP1 and FOXP2 are relatively rare, but play a significant role in the pathology of cognitive diseases. While the importance of FOXP2 in the pathology of cognitive diseases is a popular topic of investigation for more than 10 years, it remains to be seen whether perturbations in FOXP2 are confined to language impairment or whether there is also some risk for other diagnostic entities. Genetic evidence emerging in the last 2 years provides compelling evidence that FOXP1 variants are responsible for a more global cognitive phenotype, encompassing language impairment, intellectual disability, ASD and motor development delay. The phenotypic spectra of FOXP1 and FOXP2 disruptions suggest that these two closely related transcription factors are involved in both shared and distinct neurodevelopmental pathways underlying cognitive diseases through the regulation of common and exclusive targets. The findings discussed in this review show that FOXP1 and FOXP2 may provide crucial insight into the molecular pathways involved in human cognitive diseases.

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Conflict of interest

The authors declare that they have no conflict of interest.

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