

ARTICLE

Translocation breakpoint at 7q31 associated with tics: further evidence for *IMMP2L* as a candidate gene for Tourette syndrome

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Gilles de la Tourette syndrome is a complex neuropsychiatric disorder with a strong genetic basis. We identified a male patient with Tourette syndrome-like tics and an apparently balanced *de novo* translocation [46,XY,t(2;7)(p24.2;q31)]. Further analysis using array comparative genomic hybridisation (CGH) revealed a cryptic deletion at 7q31.1–7q31.2. Breakpoints disrupting this region have been reported in one isolated and one familial case of Tourette syndrome. In our case, *IMMP2L*, a gene coding for a human homologue of the yeast inner mitochondrial membrane peptidase subunit 2, was disrupted by the breakpoint on 7q31.1, with deletion of exons 1–3 of the gene. The *IMMP2L* gene has previously been proposed as a candidate gene for Tourette syndrome, and our case provides further evidence of its possible role in the pathogenesis. The deleted region (7q31.1–7q31.2) of 7.2 Mb of genomic DNA also encompasses numerous genes, including *FOXP2*, associated with verbal dyspraxia, and the *CFTR* gene.

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INTRODUCTION

Gilles de la Tourette syndrome (GTS (MIM 137580)) is a neuropsychiatric disorder manifested by multiple, involuntary motor and vocal movements (tics) that fluctuate in severity. The motor tics are usually the initial symptom of the condition, with onset occurring usually between the ages of 2 and 14 years. Echolalia, grunting and coprolalia can develop as the disease progresses. GTS was previously considered to be a rare disorder, but population-based surveys estimate the prevalence at around 1/1000 males and 1/10 000 females.¹ GTS has been reported with other behavioural disorders such as obsessive–compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD) and conduct disorder-oppositional defiant disorder.²

It is thought that GTS is inherited in an autosomal dominant manner with variable expression and reduced penetrance, as around 10% of patients have a family history of the same condition.³ Several genome-wide linkage studies have failed to identify any candidate genes, but the largest genetic linkage study conducted so far in over 2000 individuals showed strong evidence of linkage at 2p23.2, 3p, 3q, 5p, 6p and 14q.⁴ Boghosian-Sell *et al*⁵ described a family affected by Tourette syndrome segregating with a balanced chromosomal translocation [t(7;18)]. The Tourette syndrome in this family showed variable expression and reduced penetrance.⁵ No genes in the region of the breakpoint on chromosome 18 have been implicated in the aetiology of Tourette syndrome. The breakpoint on chromosome 7 was further mapped to 7q22–q31, between two genetic markers, D7S515 and D7S522. Kroisel *et al*⁶ reported on a 13-year-old boy with Tourette syndrome, minor physical anomalies and a *de novo*

partial duplication of chromosome 7q [dup(7)(q22.1–q31.1)].⁶ Molecular analysis of this case by Petek *et al*⁷ revealed that the duplication was inverted. The distal breakpoint occurred between the same two genetic markers that defined the region disrupted in the case by Boghosian-Sell *et al*,⁵ raising the possibility of a candidate gene for GTS at 7q31. Further studies identified that a novel gene, *IMMP2L* (MIM 605977), was interrupted by both the breakpoint in the duplicated fragment and the insertion site in 7q31.⁷

We describe the detailed molecular genetic analysis of an 18-year-old boy with a *de novo* translocation t(2;7)(p24.2;q31) who developed motor tics at the age of 13 years and has significant speech and language impairment. The breakpoints are further characterised and the *IMMP2L* gene is found to be disrupted and partially deleted by the translocation, along with a cryptic 7.2-Mb deletion involving a number of genes.

SUBJECTS AND METHODS

Case report

The 18-year-old male proband is the third child of healthy non-consanguineous White British parents. He was born at term with a birth weight of 2980 g (9–25th centiles). He sat unsupported at age 9 months and walked at age 17 months, later than his normal siblings. At age 3 years 6 months he had poor speech development and could utter only two-word sentences. His oromotor control was poor, resulting in constant severe dribbling. He attended a school for children with learning difficulties. At age 13 years he developed a movement disorder consisting of head and eye turning to the right, facial grimacing and puffing of his cheeks. He was partially able to control this, but it appears to be worsening with age. He was seen by a paediatric neurologist, who made a clinical diagnosis of tics rather than dystonia. He continues to have moderate

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learning difficulties and severe speech difficulties, with verbal dyspraxia, and his speech is barely comprehensible to strangers. There is no family history of mental retardation, speech delay or movement disorders.

On examination at age 18 years his weight is between the 25 and 50th centiles and height between the 50 and 75th centiles. He has no facial dysmorphism, but has an intermittent divergent squint and hypoplastic 5th toenails. Neurological findings include the tics, normal tone and power in all four limbs, but brisk deep tendon reflexes, and a broad-based unsteady gait. An electroencephalogram showed a non-specific slight increase in background activity, but no focal or generalised seizure activity. A CT scan of the brain showed an enlarged cisterna magna, but was otherwise normal.

Cytogenetic analysis

Routine cytogenetic analyses were performed on metaphase chromosomes prepared from peripheral blood leukocytes using standard methods.

Array studies

Genomic DNA was extracted from peripheral blood using the AutoPure extraction system (Qiagen, Crawley, UK) following the manufacturer's instructions. DNA concentration and purity ($A_{260-280} \sim 1.8-2.0$) were determined using a NanoDrop spectrophotometer (Labtech International, Ringmer, UK). Samples were labelled with Cy3 and Cy5 using a NimbleGen Dual Colour DNA Labelling kit (Roche NimbleGen, Madison, WI, USA) according to the manufacturer's instructions. In all, 500 ng per patient genomic DNAs were hybridised to NimbleGen 12 × 135K arrays (Roche NimbleGen) and these arrays were washed post hybridisation according to the manufacturer's instructions. Arrays were scanned using a GenePix 4000B scanner and analysed in a Nexus Copy Number v3.0 (BioDiscovery, Inc., El Segundo, CA, USA), using the Rank Segmentation algorithm at default settings. Oligonucleotide probes were mapped to NCBI36.

Fluorescent *in situ* hybridisation

DNAs for bacterial artificial chromosome (BAC) fluorescent *in situ* hybridisation (FISH) probes were obtained from Roswell Park Cancer Institute, USA, and labelled in-house with Cy3 (GE Healthcare, Chalfont St Giles, UK) using the Bioprime labelling kit (Invitrogen Ltd, Paisley, UK). Hybridisation and washing were carried out using standard protocols. Images were visualised using an Olympus BX50 microscope and captured and processed using the Isis software package (Metasystems, Altussheim, Germany).

Multiplex ligation-dependent probe amplification

Multiplex ligation-dependent probe amplification (MLPA) analysis of the *CFTR* gene was carried out using the MRC-Holland P091 kit (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's instructions and using a Tetrad PCR machine (BioRad, Hercules, CA, USA). Capillary electrophoresis was carried out on an ABI 3130 and analysed using the Soft Genetics Gene Marker v1.70 program (SoftGenetics, State College, PA, USA).

RESULTS

Identification of an apparently balanced translocation

Cytogenetic analysis identified a reciprocal translocation between the short arm of chromosome 2 at band p24.2 and the long arm of chromosome 7 at band q31 (Figure 1). This was determined to be a *de novo* finding following analysis of parental samples. The chromosome 7 breakpoint occurred in the same band as a previously described duplication that disrupted the *IMMP2L* gene, and so this gene was implicated as a candidate for a role in the pathogenesis of GTS.⁷

Identification of deletion at chromosome 7 breakpoint using array CGH

Array analysis showed a 7.25-Mb deletion from 7q31.1 to 7q31.2 at the breakpoint of the t(2;7) translocation. The deleted region contained 338 oligonucleotide probes genomic co-ordinates 7:110 702 484–117 947 839 (Figures 2a and b). The proximal breakpoint of the

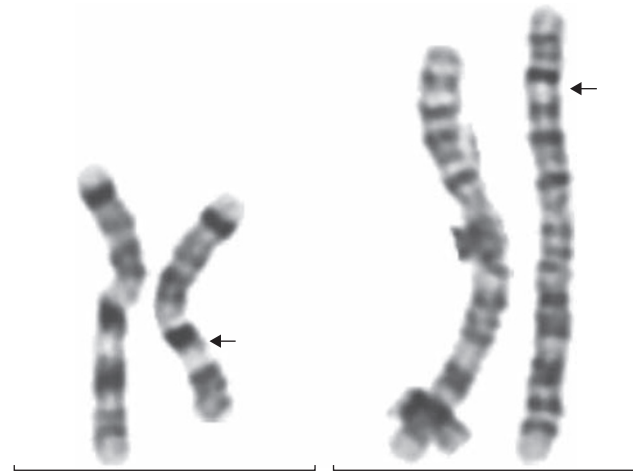


Figure 1 Partial G-banded karyogram showing t(2;7)(p24.2;q31) translocation (breakpoints arrowed).

deletion occurs within introns 2–3 of the *IMMP2L* gene, and exons 1–3 are deleted. Exons 4–6 remain intact. The deleted region also contains 21 HGNC mapped genes (Table 1), including the OMIM Morbid entries *FOXP2*, *MET* and *CFTR*. Parental samples were not analysed using array CGH as the translocation was determined to be a *de novo* finding following analysis of parental chromosomes.

FISH confirmation of partial deletion of *IMMP2L*

FISH analysis using RP11-452K21 (co-ordinates 7:110 396 144–110 575 013, overlapping the 3'-end of *IMMP2L*) showed a signal present on both the derivative and normal chromosomes 7, confirming disruption of *IMMP2L* and deletion of the 5'-end of the gene only (Figure 2c). RP11-148C1 (co-ordinates 7:110 833 766–111 014 525, overlapping the 5'-end of *IMMP2L*) showed loss of signal on the derivative chromosome 7 (no movement of the signal to the derivative chromosome 2 was observed). Clear signal for this BAC was observed on the normal chromosome 7, confirming deletion of the 5'-end of one copy of *IMMP2L* (Figure 2d). The FISH results therefore confirm the proximal breakpoint assigned by microarray analysis to lie between 110.58 and 110.83 Mb, within introns 2–3 of *IMMP2L*.

Comparison of copy number imbalance overlapping *IMMP2L* using Ensembl and DECIPHER resources

Comparison of the deleted region in this case with other copy number imbalances involving the *IMMP2L* gene was carried out using the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) (patient ID in DECIPHER: 248350). This identified nine additional cases with imbalance in this region only (DECIPHER entries 800, 801, 804, 813, 919, 1296, 1299, 1303 and 2391). Only one of these had motor and vocal tics as a clinical symptom (DECIPHER entry 919), which is the case reported by Petek *et al*⁷ of a duplication of 7q22.1–7q31.1 with the distal breakpoint between exons 3 and 4 of *IMMP2L*.⁷ Of note, there are several entries of smaller copy number variation (CNV) within the Database of Genomic Variants (DGV) within the *IMMP2L* gene (Figure 2b). Most of these encompass introns 2–3, but several of them also appear to include exons 1–3.

Confirmation of deletion of the *CFTR* gene by MLPA

Analysis of the *CFTR* gene using MLPA showed a heterozygous deletion of all exons of the gene at 7q31.2 confirming the array and

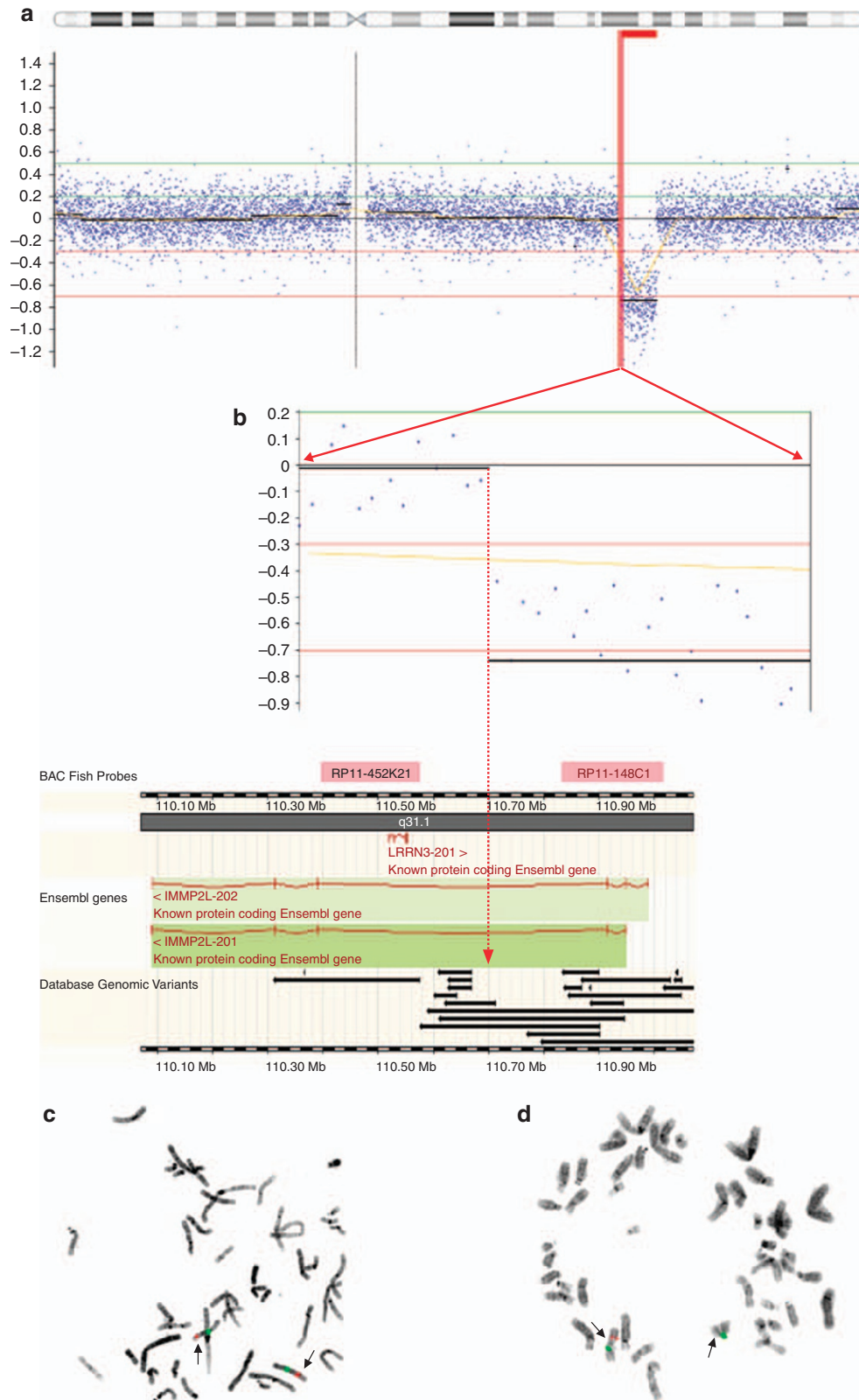


Figure 2 (a) Chromosome 7 log₂ ratio displayed in Nexus Copy Number v3.0 showing 7.2 Mb deletion (indicated with red bar). (b) Zoomed proximal 7q31.1 region showing breakpoint at 110 702 484 Mbp (red dotted line) within *IMMP2L*. Exons 1–2 and exons 1–3 are deleted from the *IMMP2L*-201 and *IMMP2L*-202 transcripts, respectively. (c) Confirmatory FISH analysis showing intact copies of RP11-452K21 (110.39–110.58 Mb). (d) Confirmatory FISH analysis showing deletion of one copy of RP11-148C1 (110.83–111.01 Mb). Red signals represent target BAC clones (locations arrowed) and green signals are control probe (CEP7, Abbott Vysis, Abbott Molecular, Maidenhead, UK).

Table 1 HGNC mapped genes in the deletion interval 110 702 484–117 947 839 (NBCI 36)

Gene	Start (Mbp)	End (Mbp)	Description and aliases
<i>IMMP2L</i>	110 090 346	110 948 739	IMP2 inner mitochondrial membrane peptidase-like (<i>Saccharomyces cerevisiae</i>). Aliases: IMP2
<i>DOCK4</i>	111 153 404	111 431 423	Dedicator of cytokinesis 4. Aliases: FLJ34238, KIAA0716
<i>IFRD1</i>	111 877 751	111 903 480	Interferon-related developmental regulator 1. Aliases: PC4, TIS7
<i>C7orf53</i>	111 908 282	111 918 171	Chromosome 7 open reading frame 53. Aliases: FLJ39575
<i>TMEM168</i>	112 193 032	112 217 714	Transmembrane protein 168. Aliases: DKFZp564C012, FLJ13576
<i>GPR85</i>	112 507 704	112 515 015	G-protein-coupled receptor 85. Aliases: SREB2
<i>PPP1R3A</i>	113 301 622	113 346 300	Protein phosphatase 1, regulatory (inhibitor) subunit 3A. Aliases
<i>FOXP2</i>	113 842 288	114 121 063	Forkhead box P2. Aliases: CAGH44
<i>MDFIC</i>	114 349 445	114 446 501	MyoD family inhibitor domain containing. Aliases: HIC
<i>TFEC</i>	115 362 448	115 458 103	Transcription factor EC. Aliases: TCFC, TFEC
<i>TES</i>	115 637 817	115 686 071	Testis-derived transcript (3 LIM domains). Aliases: DKFZP586B2022, TESS-2, TESTIN
<i>CAV2</i>	115 926 532	115 935 830	Caveolin 2. Aliases: CAV
<i>CAV1</i>	115 952 075	115 988 466	Caveolin 1, caveolae protein, 22 kDa. Aliases
<i>MET</i>	116 099 682	116 225 676	Met proto-oncogene (hepatocyte growth factor receptor). Aliases: HGFR, RCCP2
<i>CAPZA2</i>	116 289 799	116 346 548	Capping protein (actin filament) muscle Z-line, alpha 2. Aliases: CAPZ, CAPPA2
<i>ST7</i>	116 380 617	116 657 393	Suppression of tumorigenicity 7. Aliases: TSG7, SEN4, ETS7q, HELG, RAY1, FAM4A
<i>WNT2</i>	116 704 518	116 750 579	Wingless-type MMTV integration site family member 2. Aliases: IRP
<i>ASZ1</i>	116 790 512	116 854 779	Ankyrin repeat, SAM and basic leucine zipper domain containing 1. Aliases: Orf3, GASZ, ALP1
<i>CFTR</i>	116 907 253	117 095 955	Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)
<i>CTTNBP2</i>	117 137 944	117 300 797	Cortactin-binding protein 2. Aliases: KIAA1758, Orf4
<i>LSM8</i>	117 611 322	117 620 114	LSM8 homologue, U6 small nuclear RNA associated (<i>S. cerevisiae</i>). Aliases: YJR022W
<i>ANKRD7</i>	117 651 953	117 669 977	Ankyrin repeat domain 7. Aliases: TSA806

FISH results. The most centromeric of the probes shown to be deleted was located within the *ASZ1* gene that sits 58 kb upstream of the *CFTR* gene and the most telomeric probe deleted is located within the *CTTNBP2* gene that sits 58 kb downstream of the *CFTR* gene (data not shown).

DISCUSSION

Chromosome abnormalities that segregate with a disease phenotype can facilitate the identification of disease loci and genes. Patients with an abnormal clinical phenotype and an apparently balanced *de novo* chromosome rearrangement on routine karyotyping have been shown to have submicroscopic imbalances on further analysis. Using CGH arrays, De Gregori *et al*⁸ found that 40% of patients with an abnormal phenotype and an apparently balanced translocation were in fact unbalanced.⁸ The majority of patients with Tourette syndrome have a normal karyotype and, of the various chromosomal abnormalities reported in association with Tourette syndrome, only the translocation cases reported by Boghosian-Sell *et al*⁵ and Kroisel *et al*⁶ show co-segregation with features associated with Tourette syndrome.^{5,6} Together, they provided evidence that a gene located in the breakpoint region at 7q31 could be involved in the development of Tourette syndrome. Previously reported cases with 7q duplications have not shown any signs of Tourette syndrome, which again supports the notion of involvement of gene(s) at the breakpoints rather than genes within the duplicated region (with haploinsufficiency as the mechanism).

Petek *et al*⁷ identified a novel gene, *IMMP2L*, disrupted by the breakpoints in their case of an inverted duplication of 7q31, and proposed this gene to be a candidate for GTS.⁷ The *IMMP2L* (inner mitochondrial membrane peptidase-2-like) gene spans 860 kb of genomic DNA, consisting of six exons encoding a 175-amino-acid protein. The gene shows evolutionary conservation. The human protein is 41% identical to the yeast protein and 90% identical to the mouse protein. It is thought to function as a catalytic subunit of the mitochondrial inner membrane peptidase (IMP) complex. The IMP complex generates mature, active proteins in the mitochondrial

intermembrane space by proteolytically removing the mitochondrial targeting pre-sequence of nuclear-encoded proteins.⁹ Although little is known about the exact function of the protein, of note, other mitochondrial proteins (eg, COXII) have been shown to be involved in neurodegenerative and neuropsychiatric disorders.^{10–12}

Family-based association studies by Díaz-Anzaldúa *et al*¹³ in a French–Canadian GTS sample showed significant association with the region previously described by Petek *et al*⁷ in their case with the inverted duplication of 7q31. They found a significant association close to the first duplication breakpoint with markers D7S523 and D7S522 (situated 1.2 and 5 Mb distal to this breakpoint), and marker D7S1516 (situated within the *IMMP2L* gene).¹³ A further study in 2007 by Petek *et al* screening 39 unrelated patients with GTS, for mutations in *IMMP2L*, detected no coding-region variants, and so failed to provide further evidence that *IMMP2L* mutations are a common cause of GTS. However, the gene may be involved at a more subtle level or in just a small proportion of cases. They concluded that to exclude this gene from a pathogenic role in GTS, studies screening for mutations in the intronic promoter, enhancer and other regulatory elements is required.¹⁴

A number of cases of deletions and duplications overlapping the 7q31.1 region (and including *IMMP2L*) have been reported in the DECIPHER database but only one case has documented vocal and motor tics (DECIPHER entry 919) as part of the phenotype. There could be a number of explanations for this. First, some of these cases are younger than 3 years old and may be too young to have yet developed features of the condition. Both our case and that reported by Kroisel *et al*⁶ developed Tourette syndrome after age 11 years. Second, the absence of GTS could also be explained by the variable penetrance of the condition. Lastly, the cases in DECIPHER do not involve disruption of *IMMP2L*, but all involve complete deletion leading to haploinsufficiency for *IMMP2L*. Our case (with deletion of exons 1–3 out of 6) and the translocation case studied by Petek *et al*⁷ provide evidence of disruption of *IMMP2L*. A truncated gene and the inability to transcribe a full-length mRNA, along with the

production of a defective protein, may be responsible for the appearance of features of GTS, and our case provides further evidence for this. This may be an important pathogenetic mechanism rather than deletion or duplication of the entire gene. Reported cases of CNV within *IMMP2L* also exist in the DGV, although, given the variable penetrance associated with GTS and the lack of phenotypic data available for 'healthy control cohorts' generally assessed for studies of 'normal' variation recorded in the DGV, it is not possible to exclude the involvement of *IMMP2L* in GTS on the basis of these cases. These points also highlight the importance of follow-up of all cases with overlapping deletions and duplications encompassing *IMMP2L* gene, to allow not only early detection and management of features of GTS, but also further understanding of the genetic mechanisms by which the *IMMP2L* gene is implicated in the pathogenesis of GTS.

Our case has significant verbal dyspraxia and speech difficulties. He sometimes omits the end sound in words and has difficulty in producing the sound of some consonants. He has problems in producing words with three or more syllables, especially when used in sentences and conversation. Array CGH analysis in our case identified the *FOXP2* gene (MIM 605317) to be completely deleted. The *FOXP2* gene encodes a transcription factor thought to regulate gene expression in defined areas of the developing neural, lung, cardiovascular and intestinal tissue, and was the first gene to be implicated in a developmental communication disorder. Abnormalities of *FOXP2* are associated with difficulties in the learning and production of sequences of oral movement, which impair speech, known as developmental verbal dyspraxia. Affected individuals have variable levels of impairment in expressive and receptive language, sometimes extending to problems with production and comprehension of grammar. Hurst *et al*¹⁵ described a large multigenerational family with a severe speech and language disorder inherited in an autosomal dominant manner.¹⁵ A similar speech and language disorder was presented by Lai *et al*¹⁶ in a patient with a *de novo* balanced reciprocal translocation t(5;7)(q22;q31.2).¹⁶ They mapped the 7q31.2 breakpoint to a single clone, containing several exons of the *FOXP2* gene, showing disruption of this gene in their case. They also identified a point mutation in the *FOXP2* gene in the family reported by Hurst *et al*,¹⁵ which co-segregated perfectly with the speech and language disorder in this family.¹⁷ Case reports of deletions within the 7q31 region including *FOXP2*,¹⁸ and studies showing mutations within *FOXP2* in isolated cases of verbal dyspraxia,¹⁹ have further supported the evidence of this gene being important for normal speech and language development. It is very likely that the speech impairment, verbal dyspraxia, and possibly oropharyngeal dyspraxia and dribbling seen in our case are due to haploinsufficiency of this gene.

The *IMMP2L* gene (along with numerous other neurodevelopmental genes) has also recently been implicated in structural variation studies carried out on cohorts of patients with autistic spectrum disorder,²⁰ and ADHD.²¹ Our case does not display any of the classical features of autism, except speech impairment (which is likely to be accounted for by deletion of the *FOXP2* gene) or ADHD. Autism or autistic spectrum disorder (ASD (MIM 209850)) is a severe neurodevelopmental disorder that presents at an early age and persists throughout life. Individuals display impairments in social interaction and communication coupled with repetitive and/or obsessive-compulsive behaviours. Data from family and twin studies suggest a strong genetic component, with the likelihood of numerous genes contributing to the pathogenesis in an additive manner. Genetic and cytogenetic studies have provided evidence to suggest one or more autism susceptibility genes within the 7q22–q31 region.²² Hutcheson *et al*²³ further defined this region to be a 3-cM region on 7q31–q33

between markers D7S496 and D7S523, containing several interesting functional candidate genes, including some neuronally expressed genes: *NRCAM* (MIM 601581) and *LRRN3*.²³ Neither of these genes is within our deleted region, but *LRRN3* is located centromeric to the proximal deletion breakpoint and very near the last few exons of the *IMMP2L* gene.

Our case does have moderate mental retardation and this could be accounted for by haploinsufficiency of an as yet unknown mental retardation gene within the deleted region. Some of the genes within the deleted region may be good candidate genes for a role in the pathogenesis of mental retardation (eg, *DOCK4*, *GPR85*, *MET*, *WNT2* and *CTTNBP2*). The *DOCK4* gene (MIM 607679) has been shown to regulate dendritic growth in neuronal cell lines in rats.²⁴ A recent case-control study in families linked to the autism susceptibility locus 1 (*AUTS1*) detected single-nucleotide polymorphisms (SNPs) and CNV within *DOCK4* and *IMMP2L*, implicating them in autism susceptibility.²⁰ A *DOCK4* deletion segregating in a family with dyslexia, and undetectable in > 2500 controls, suggested that *DOCK4* may have a role in the aetiology of dyslexia.²⁵ The *GPR85* gene (MIM 605188) is predominantly expressed in the central nervous system, especially in structures exhibiting high levels of plasticity (eg, hippocampal dentate gyrus); it has high evolutionary conservation across three mammalian species,²⁶ and has been implicated as a potential risk factor for psychiatric disorders.²⁷ The *MET* gene (MIM 164860) encodes for a receptor tyrosine kinase and participates in neocortical and cerebellar growth and maturation, as well as immune and gastrointestinal functions. In 204 families with autism, Campbell *et al*²⁸ found a significant association between autism and a G–C transversion in the promoter of the *MET* gene. Functional assays showed that the C allele resulted in a two-fold decrease in *MET* promoter activity and altered binding of specific transcription factor complexes.²⁸ The WNT family of genes influences the development of the central nervous system, and a mouse knockout of the *DVLI* gene (a member of a gene family essential for the function of the WNT pathway) exhibited a behavioural phenotype characterised by diminished social interaction. Wassink *et al*²⁹ screened the *WNT2* gene (MIM 147870) in a large number of autistic probands and found two families containing a non-conservative coding sequence variant that segregated with autism in those families.²⁹ Cheung *et al*³⁰ showed high levels of expression of *CTTNBP2* (MIM 609772) in the brain and screened it for mutations in 90 unrelated individuals with autism, and identified two variants.³⁰ It is possible though that speech and language impairment and autistic traits may be influenced by a single gene or multiple interacting genes within this region.

The *CFTR* gene (MIM 602421) is also located within the deleted region in our patient, therefore making him a carrier of cystic fibrosis (CF) (MIM 219700). This will have implications for future offspring and the necessity to offer carrier testing to any future partners. This case, in addition to providing supportive evidence for disruption of *IMMP2L* gene function causing GTS, has highlighted some very important genetic counselling issues for the patient: (1) standard 'balanced' translocation (and the risk of larger chromosomal imbalance in any offspring), (2) offspring risk for GTS, (3) offspring risk for mental retardation, (4) offspring risk for verbal dyspraxia and (5) implications of being a CF carrier.

CONCLUSION

Our case adds to evidence from previous reports of the importance of genes within the 7q31 region, particularly the association of *IMMP2L* with GTS, and *FOXP2* with verbal dyspraxia. There is evidence for considerable genetic heterogeneity in GTS, and the number of cases

attributable to abnormalities of *IMMP2L* is yet to be determined. Further studies are required to determine the role of *IMMP2L* in the aetiology of GTS. We also highlight the value of array CGH in obtaining a cytogenetic diagnosis in an apparently balanced translocation with an abnormal phenotype, and the identification of new candidate genes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

WEB RESOURCES

Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER), <http://decipher.sanger.ac.uk>
Database of Genomic Variants (DGV), <http://projects.tcag.ca/variation/>
Ensemble, <http://www.ensembl.org/index.html>
Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/OMIM/>.

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