ARTICLE

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2p25.3 microduplications involving *MYT1L*: further phenotypic characterization through an assessment of 16 new cases and a literature review

Malek Bouassida[1✉], Matthieu Egloff[2], Jonathan Levy[3], Nicolas Chatron[4], Laura Bernardini[5], Gwenaël Le Guyader[2], Anne-Claude Tabet[3], Caroline Schluth-Bolard[4], Francesco Brancati[6,7], Maria Grazia Giuffrida[5], Rodolphe Dard[1,8], Juliette Clorennec[1,8], Juliette Coursimault[9], François Vialard[1,8✉] and Bérénice Hervé[1]

Microduplications involving the *MYT1L* gene have mostly been described in series of patients with isolated schizophrenia. However, few reports have been published, and the phenotype has still not been well characterized. We sought to further characterize the phenotypic spectrum of this condition by describing the clinical features of patients with a pure 2p25.3 microduplication that includes all or part of *MYT1L*. We assessed 16 new patients with pure 2p25.3 microduplications recruited through a French national collaboration ($n = 15$) and the DECIPHER database ($n = 1$). We also reviewed 27 patients reported in the literature. For each case, we recorded clinical data, the microduplication size, and the inheritance pattern. The clinical features were variable and included developmental and speech delays (33%), autism spectrum disorder (ASD, 23%), mild-to-moderate intellectual disability (ID, 21%), schizophrenia (23%), or behavioral disorders (16%). Eleven patients did not have an obvious neuropsychiatric disorder. The microduplications ranged from 62.4 kb to 3.8 Mb in size and led to duplication of all or part of *MYT1L*; seven of these duplications were intragenic. The inheritance pattern was available for 18 patients: the microduplication was inherited in 13 cases, and all parents but one had normal phenotype. Our comprehensive review and expansion of the phenotypic spectrum associated with 2p25.3 microduplications involving *MYT1L* should help clinicians to better assess, counsel and manage affected individuals. *MYT1L* microduplications are characterized by a spectrum of neuropsychiatric phenotypes with incomplete penetrance and variable expressivity, which are probably due to as-yet unknown genetic and nongenetic modifiers.

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INTRODUCTION

Microdeletions and single nucleotide variants (SNVs) involving the human *MYT1L* gene (coding for myelin transcription factor 1-like (MYT1L) and located on chromosome 2 at 2p25.3) have recently been linked to a syndromic presentation (OMIM#616521) consisting of developmental delay (DD), intellectual disability (ID), overweight/obesity, and several dysmorphic features [1, 2]. A better understanding of the mechanism underlying this disorder has prompted researchers to consider that *MYT1L* haploinsufficiency is responsible for the observed clinical phenotype [2–4].

MYT1L is a member of the neural-specific myelin transcription factor 1 (MYT1) family, which is characterized by the presence of two highly conserved clusters of C2HC zinc fingers [5]. In the mouse, the Myt1l transcription factor helps to determine neuronal fate by specifically repressing the expression of non-neuronal genes and negative regulators of neurogenesis (including members of the Notch signaling pathway, such as Hes1) [6, 7]. This role in promoting neuronal differentiation has been proven in vitro by showing that in combination with other transcription factors (Ascl1 and Pou3f2/Brn2), Myt1l can reprogram human and mouse fibroblasts into functional neurons, [8, 9].

Although the phenotype associated with 2p25.3 microdeletions and SNVs varies markedly from one patient to another, some clinical features have been clearly established [2]. In contrast, the published clinical data on individuals with microduplications are often limited. Partial microduplications encompassing *MYT1L* were first linked to schizophrenia [10] and have also been observed in individuals presenting neuropsychiatric diseases, such as ID and autism spectrum disorder (ASD) [4, 11–21]. A recent study therefore concluded that *MYT1L* might act as a dosage-sensitive gene involved in neurodevelopmental pathways common to both ID and schizophrenia [22].

Predicting the clinical outcomes of a 2p25.3 microduplication is very challenging - especially in a prenatal diagnostic setting. The

[1]Département de Génétique, Laboratoire de Biologie Médicale, CHI de Poissy-St Germain en Laye, F-78300 Poissy, France. [2]Service de Génétique, Centre Hospitalier Universitaire de Poitiers, F-86021 Poitiers, France. [3]Département de Génétique, Hôpital Robert Debré, APHP, F-75019 Paris, France. [4]Service de cytogénétique, Groupement Hospitalier Est, Hospices Civils de Lyon, F-69500 Bron, France. [5]Istituto CSS-Mendel, It-00198 Roma, Italy. [6]Department of Life, Health and Environmental Sciences, University of L'Aquila Piazzale Salvatore Tommasi, It-67100 Coppito - L'Aquila, Italy. [7]San Raffaele Roma, IRCCS, It-00163 Roma, Italy. [8]RHuMA Team, UMR-BREED, INRA-UVSQ-ENVA, UFR Simone Veil Santé, F-78380 Montigny-le-Bretonneux, France. [9]Department of Genetics and Reference Center for Developmental Disorders, Normandie Univ, UNIROUEN, Inserm U1245 and CHU Rouen, F-76000 Rouen, France. ✉email: malekbouassida94@hotmail.com; francois.vialard@uvsq.fr

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high observed phenotypic variability underscores the need to systematically characterize the clinical impact of these rearrangements in large numbers of carriers. To further characterize this phenotypic spectrum, we compared the 16 new patients with 27 previously reported individuals, all of whom presented 2p25.3 microduplications involving all or part of *MYT1L*.

MATERIAL AND METHODS

Members of the Association des Cytogénéticiens de Langue Française (www.eaclf.org) and the AchroPuce networks (https://acpa-achropuce.com) were requested to provide all their clinical and genetic data (including age, phenotype, reason for referral, upstream and downstream breakpoints, and the inheritance pattern) on individuals with a 2p25.3 microduplication involving *MYT1L*. Through this call for collaboration, 15 new patients diagnosed between 2019 and 2022 (N1 to N15) were recruited. The microduplications were identified with microarrays that differed in their format, resolution, and manufacturer: a Human Genome CGH Microarray 60 K, 150 K, or 180 K (Agilent Technologies, Santa Clara, CA, USA) or an Illumina OmniExpress SNP microarray (Illumina Inc, San Diego, CA, USA).

Microduplications were confirmed by fluorescence in situ hybridization or qPCR. Genomic positions were relative to human genome GRCH37/hg19 Assembly. For all cases, parental blood samples were requested to determine the inheritance pattern. Parental analyses were performed using fluorescence in situ hybridization or chromosomal microarray analysis (CMA). Genetic counseling was offered to the patients and affected families. Prior to inclusion, all the patients provided their written, informed consent to participation in the study.

Additional new cases of 2p25.3 microduplications were retrieved from the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER: https://www.deciphergenomics.org/). An e-mail was sent to all the laboratories referenced in DECIPHER, requesting the patients' details and authorization to use this information. Only one patient (D1, from whom consent was obtained) could be included in the present study. We also searched the PubMed online database (https://pubmed.ncbi.nlm.nih.gov) with the search terms "2p25.3 duplication" and "*MYT1L* duplication" and identified 27 previously published cases (P1–P27).

All novel variants were submitted to public databases. The variants reported in patients N1-N5 were submitted to ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), and those reported in patients N6-N15 were submitted to DECIPHER. Statistical analyses were performed using the online tool BiostaTGV (https://biostatgv.sentiweb.fr/). Proportions were compared using the Fisher-Freeman-Halton Exact test. All tests were two-tailed, and the threshold for statistical significance was set to $p < 0.05$.

RESULTS

A total of 16 new cases were recruited into the study, and 27 cases reported in the literature were reviewed. All harbored pure interstitial microduplications overlapping the 2p25.3 region and involving the *MYT1L* gene. In the new patients (N1 to N15, and D1), the male:female ratio was 0.8 (7/9) and the age ranged from 6 months to 13 years (mean: 7 years). In the overall cohort, the male:female ratio was 1.6 (20/12) and the mean (range) age at diagnosis ($n = 28$) was 14 years (6 months to 72 years). The microduplication was diagnosed after the age of 3 years for 22 of the 28 (78%) patients. Of the 16 newly reported patients, 14 were unrelated and two (N9 and N10) were twins. The microduplication was identified during the prenatal period in two cases (N11 and N15).

CMA results

The patients' tracks are represented in Fig. 1, and the CMA results are described in Table 1. The microduplications were located within the region extending from 859,616 bp to 2,546,048 bp (hg19/GRCh37). The microduplication size ranged from 62.4 Kb to 3.8 Mb, with a mean of 330 Kb. The breakpoints involving the 2p25.3 region were highly variable. Only one large duplication encompassed the entire *MYT1L* gene and ten adjacent genes. In 17 of the 43 cases (39%), the duplications involved only *MYT1L*. Seven of these 17 were intragenic, with both of the breakpoints located within the *MYT1L* gene. The other ten microduplications overlapped partially with the 5′ or 3′ end of *MYT1L*. In 20 of the 43 cases (46%), the microduplications involved both the *MYT1L* and *PXDN* genes. In the largest microduplications (5 out 43, 12%), additional genes were involved (those coding for thyroid peroxidase (*TPO*) and syntrophin gamma 2 (*SNTG2*)).

Inheritance

Data on the inheritance pattern were available for 6 of the 16 new patients. One microduplication was de novo, four were paternally inherited, and one was maternally inherited. All parents with available clinical data ($n = 4$) were phenotypically normal. Data on the inheritance pattern were available for 12 of the 27 patients in the literature cohort. When considering the 18 patients in the overall cohort with a microduplication and inheritance data, the latter was de novo in five cases (28%), paternally inherited in seven cases, and maternally inherited for the six remaining cases. In two previously reported patients, the microduplication had been transmitted by a healthy mother via germline mosaicism. Clinical data on the parents were available for 11 of the 13 cases with inherited microduplications. In one family, P8 and P9 had inherited the microduplications from their father (P7), who presented with ID, DD, obesity, and behavioral disorders. Lastly, the microduplications were inherited from clinically healthy parents in the remaining nine cases (82%).

Clinical features of the patients

The clinical phenotypes are summarized in Table 2. For the two prenatally diagnosed cases, an invasive procedure was triggered by elevated levels of first trimester maternal serum markers and increased nuchal translucency. For the other (postnatally diagnosed) patients, a routine ultrasound assessment in pregnancy did not yield any specific findings, other than intra-uterine growth restriction for N14.

Six of the 16 newly reported patients (37%) were referred for DD and/or ID. Other prominent clinical findings were ASD in 4 of the 16 cases (25%), growth delay in twins (12%), and congenital malformations in two cases (12%).

When combining our cohort with previously published individuals, the three most common features observed were (i) DD in 14 of the 43 cases (33%), with a significant speech delay and language impairment, (ii) mild-to-moderate ID in 9 of the 43 cases (21%), and (iii) schizophrenia in 10 of the 43 cases (23%), which was the most common feature in patients aged 18 or over. Seven of the 43 cases (16%) were diagnosed with or exhibited features consistent with ASD (including stereotypical movements) in the absence of ID. Three of the 43 cases (7%) had a combination of ASD and ID. Behavioral disorders (including attention deficit and hyperactivity disorder, aggressivity, anxiety, and mood disorders) were reported in 7 of the 43 cases (16%). Other frequently reported features were obesity in 6 of the 43 cases (14%) and microcephaly in 4 (9%). The other features concerned one or two patients only: for details, see Table 2. A neuropsychiatric phenotype was absent in 11 patients (25%). Although most patients had some dysmorphic features (including hypertelorism, up-slanting or down-slanting palpebral fissures, strabismus, bulbous nasal tip, large mouth with downturned oral commissures, full cheeks, and abnormally hemmed ears), none appeared to be specific or distinctive.

Genotype–phenotype correlations

As reported in the literature, microduplications associated to schizophrenia covered a broad interval from intron 1 of *PXDN* through to intron 21 of *MYT1L* (chr2:1,737,430–1,836,902, hg19; Fig. 1). The same pattern was observed for microduplications associated with isolated ASD; it covered the same region (chr2:1,742,043–1,834,000, hg19) and disrupted the 3′end of

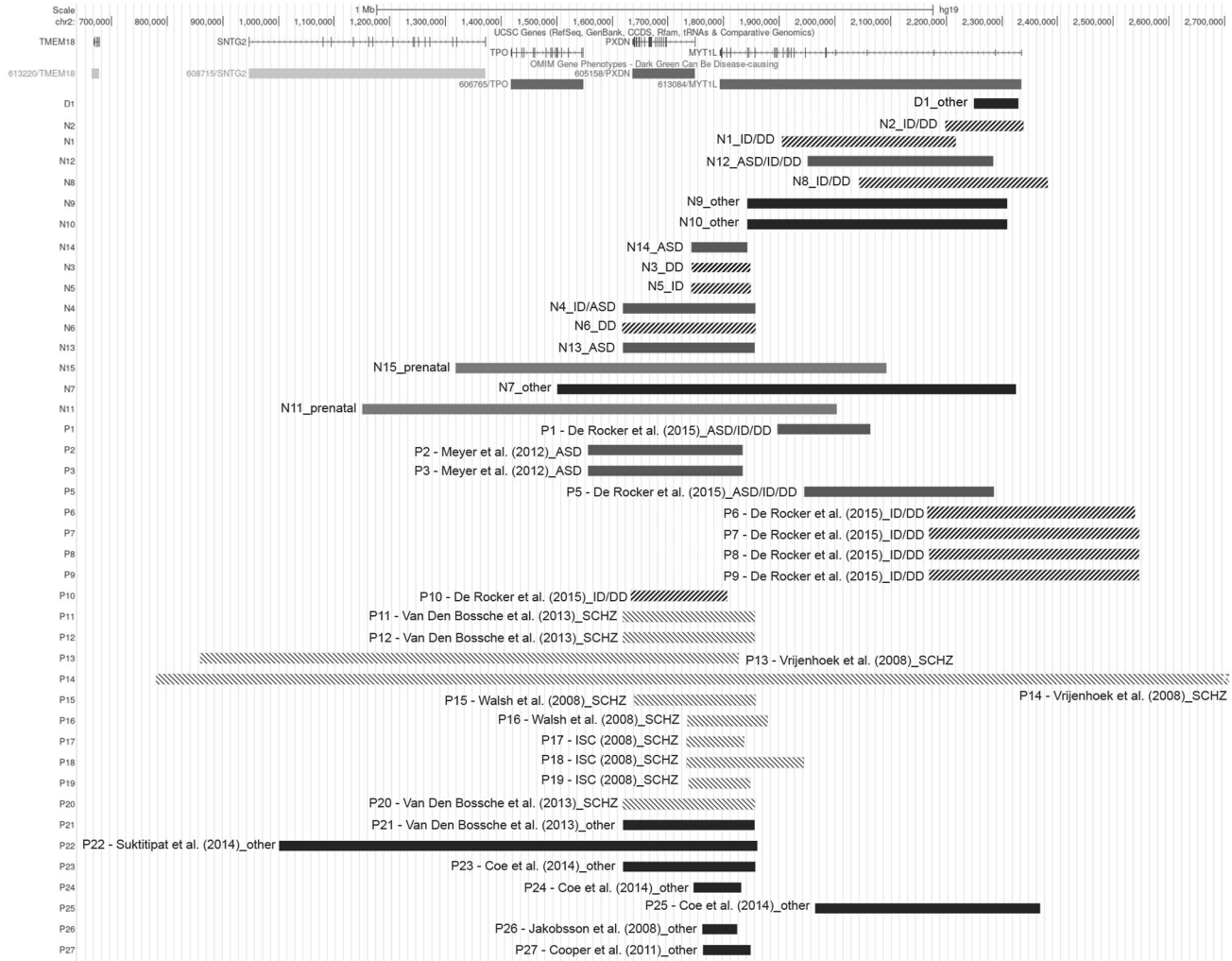

Fig. 1 Mapping of the 2p25.3 duplications in the cohort, including new cases (N1-N15), patients described in the literature (P1-P27), and the new case recruited through the DECIPHER database (D1). The genes present within this region are annotated and shown at the top. The duplications are represented by horizontal bars labeled according to the associated clinical phenotype. The figure was generated using the UCSC Genome Browser (https://genome.ucsc.edu/).

MYT1L (Fig. 1). In order to provide additional insights into genotype–phenotype correlations, we analyzed each microduplication's composition and position within *MYT1L* (Table 3). The partial duplication of P4 was not included in this comparison because we did not know which end of *MYT1L* had been affected. Although microduplications occur throughout the *MYT1L* gene, a significant correlation between the clinical phenotype and the genomic position was found (Fisher-Freeman-Halton Exact test, $p = 0.003$). In 26 of the 42 cases (62%), the microduplication was multigenic and thus extended to neighboring genes. Clustering within the 3′ end region of *MYT1L* was observed in 22 of the 42 cases (52%). In particular, schizophrenia was reported solely in patients with multigenic duplications. Whilst microduplications in probands with isolated ASD involved the *MYT1L* and *PXDN* genes, those associated with both ASD and ID tended to be intragenic. In contrast, the 11 microduplications associated with ID and/or DD were randomly distributed throughout the region of interest (chr2:1,617,873–2,546,048, hg19), although six of them (55%) involved only the 5′ end of *MYT1L*.

DISCUSSION

2p25.3 microduplications are rare, and only 27 cases had been reported previously [16]. Here, we presented clinical and molecular data on a new cohort of 16 individuals harboring a microduplication in the 2p25.3 region, including a patient from the DECIPHER database [23] whose clinical features had not previously been reported. Hence, we were able to compare the new patients' data with those previously reported in the literature (Tables 1 and 2). To the best of our knowledge, the present new series is the largest yet reported.

The 27 previously published cases were reported to have a clinical phenotype consisting of schizophrenia (37%), ID (18%) and ASD (22%), although 26% of the cases did not have a marked neuropsychiatric disorder [16]. The clinical description of our new cases further expands the phenotypic spectrum associated with 2p25.3 microduplications. The resulting data highlighted a more variable phenotypic outcome. The most frequent clinical features in the 16 newly reported patients were DD and/or ID (37%). Remarkably, developmental and language delays were more common in our new cohort (37%) than in previously reported patients (18%); this highlights the high prevalence of microduplications in the DD/ID population. Some of our clinical findings were consistent with the literature data. For instance, the frequency of ASD in our new cohort was 25%, which supports the putative association between *MYT1L* microduplications and autism. Our results are in line with previous observations in which psychiatric and neurodevelopmental disorders constituted the

Table 1. Cytogenetic findings and inheritance patterns for each case included in the study.

Patients	Database ID	Genomic coordinates	Size (Kb)	Plateform	Genes	Intragenic[a]	Exons	Type of duplication[b]	Inheritance
N1	ClinVar-SCV002818537	1,905,043–2,216,475	311.43	CGH Agilent 180 K	*MYT1L*	Yes	3 to 14	Partial	Inherited (father), asymptomatic
N2	ClinVar-SCV002818538	2,198,678–2,338,333	139.65	CGH Agilent 180 K	*MYT1L*	No	1 to 2	Partial	NA
N3	ClinVar-SCV002818539	1,742,241–1,848,126	105.88	CGH Agilent 180 K	*PXDN, MYT1L*	No	20 to 25	Partial	NA
N4	ClinVar-SCV002818540	1,618,581–1,856,549	237.96	CGH Agilent 180 K	*PXDN, MYT1L*	No	19 to 25	Partial	NA
N5	ClinVar-SCV002818541	1,742,241–1,848,126	105.88	CGH Agilent 180 K	*PXDN, MYT1L*	No	20 to 25	Partial	NA
N6	DECIPHER 394720	1,617,873–1,857,227	239.35	CGH Agilent 180 K	*PXDN, MYT1L*	No	19 to 25	Partial	Inherited (father), asymptomatic
N7	DECIPHER 503996	1,500,316–2,325,614	825.29	CGH Agilent 150 K	*TPO, PXDN, MYT1L*	No	2 to 25	Partial	NA
N8	DECIPHER 384336	2,044,628–2,382,303	337.67	CGH Agilent 180 K	*MYT1L*	No	1 to 4	Partial	Inherited (mother), asymptomatic
N9	DECIPHER 504026	1,842,071–2,309,039	466.96	Agilent 60k	*MYT1L*	yes	2 to 21	Partial	NA
N10	DECIPHER 504028	1,842,071–2,309,040	466.97	Agilent 60k	*MYT1L*	yes	2 to 21	Partial	NA
N11	DECIPHER 504031	1,151,154–2,002,578	849.42	Agilent 60k	*SNTG2, TPO, PXDN, MYT1L*	No	5 to 25	Partial	NA
N12	DECIPHER 503985	1,950,858–2,284,083	333.22	Illumina OmniExpress SNP microarray (Illumina, San Diego, CA)	*MYT1L*	Yes	3 to 8	Partial	de novo
N13	DECIPHER 503986	1,619,121–1,855,717	236.59	Illumina OmniExpress SNP microarray (Illumina, San Diego, CA)	*PXDN, MYT1L*	No	19 to 25	Partial	Inherited (father), no details
N14	DECIPHER 503987	1,742,043–1,842,774	100.72	Illumina OmniExpress SNP microarray (Illumina, San Diego, CA)	*PXDN, MYT1L*	No	22 to 25	Partial	NA
N15	DECIPHER 504029	1,318,927–2,092,710	773.78	Agilent 60k	*TPO, PXDN, MYT1L*	No	4 to 25	Partial	NA
D1	DECIPHER 371078	2,250,484–2,329,086	78.60	Oligonucleotide-array analysis (180 K)	*MYT1L*	Yes	2	Partial	Inherited (father), asymptomatic
P1 - [4]	DECIPHER 252032	1,896,431–2,062,854	166.42	NA	*MYT1L*	Yes	4 to 14	Partial	de novo
P2 - [17]		1,556,000–1,834,000	281	NA	*PXDN, MYT1L*	No	22 to 25	Partial	Inherited (mother having Germline mosaicism)
P3 - [17]		1,556,000–1,834,000	281	NA	*PXDN, MYT1L*	No	22 to 25	Partial	Inherited (mother having Germline mosaicism)
P4 - [11]		NA	375.7	NA	*MYT1L*	No	NA	Partial	NA

Table 1. continued

Patients	Database ID	Genomic coordinates	Size (Kb)	Plateform	Genes	Intragenic[a]	Exons	Type of duplication[b]	Inheritance
P5 - [4]	DECIPHER 255016	1,944,993–2,285,993	341	NA	*MYT1L*	Yes	2 to 8	Partial	de novo
P6 - [4]	DECIPHER 280521	2,167,643–2,538,140	370.49	array CGH 180k, Agilent	*MYT1L*	No	1 to 3	Partial	de novo
P7 - [4]		2,169,253–2,546,048	376,79	NA	*MYT1L*	No	1 to 3	Partial	de novo
P8 - [4]		2,169,253–2,546,048	376.79	NA	*MYT1L*	No	1 to 3	Partial	Inherited (father = P7)
P9 - [4]		2,169,253–2,546,048	376.79	NA	*MYT1L*	No	1 to 3	Partial	Inherited (father = P7)
P10 - [4]	DECIPHER 314	1,633,880–1,806,213	172.33	NA	*PXDN, MYT1L*	No	23 to 25	Partial	Inherited (father), no details
P11 - [19]		1,619,121–1,855,717	236.59	HumanOmniExpress 12v1.0 BeadChip (Illumina, San Diego, CA)	*PXDN, MYT1L*	No	19 to 25	Partial	Inherited (mother), asymptomatic
P12 - [19]		1,619,121–1,855,717	236.59	HumanOmniExpress 12v1.0 BeadChip (Illumina, San Diego, CA)	*PXDN, MYT1L*	No	19 to 25	Partial	Inherited (mother), asymptomatic
P13 - [20]		859,616–1,826,716	967.1	Affymetrix's GeneChip 250 K SNP array	*SNTG2, PXDN, MYT1L, TPO*	No	22 to 25	Partial	NA
P14 - [20]		NA	3,800.00	HumanHap550v3 BeadArray (Illumina, San Diego, CA, USA)	*SNTG2, PXDN, MYT1L, TPO, RNASEH1, TSSC1, ADI1, COLEC11, RPS7, ALLC, RPS7*	No	1 to 25	Complete	NA
P15 - [21]		1,639,938–1,856,419	216.48	Affymetrix 500 K arrays and Agilent 185 K or 244 K CGH (for validation)	*PXDN, MYT1L*	No	19 to 25	Partial	NA
P16 - [21]		1,734,629–1,878,122	143.49	Affymetrix 500 K arrays and Agilent 185 K or 244 K CGH (for validation)	*PXDN, MYT1L*	No	19 to 25	Partial	NA
P17 - [14]		1,733,991–1,836,902	102.91	Affymetrix 5.0 or 6.0 arrays	*PXDN, MYT1L*	No	22 to 25	Partial	NA
P18 - [14]		1,733,991–1,943,375	209.38	Affymetrix 5.0 or 6.0 arrays	*PXDN, MYT1L*	No	10 to 25	Partial	NA
P19 - [14]		1,737,430–1,847,710	110.28	Affymetrix 5.0 or 6.0 arrays	*PXDN, MYT1L*	No	20 to 25	Partial	NA
P20 - [19]		1,619,121–1,855,717	236.59	HumanOmniExpress 12v1.0 BeadChip (Illumina, San Diego, CA)	*PXDN, MYT1L*	No	19 to 25	Partial	Inherited (mother), asymptomatic
P21 - [19]		1,619,121–1,855,718	236.59	HumanOmniExpress 12v1.0 BeadChip (Illumina, San Diego, CA)	*PXDN, MYT1L*	No	19 to 25	Partial	NA
P22 - [18]		1,001,060–1,860,529	859.47	NA	*SNTG2, PXDN, MYT1L, TPO*	No	19 to 25	Partial	NA
P23 - [12]		1,619,220–1,857,097	237.87	NA	*PXDN, MYT1L*	No	19 to 25	Partial	NA
P24 - [12]		1,745,326–1,831,562	86.23	NA	*PXDN, MYT1L*	No	22 to 25	Partial	NA
P25 - [12]		1,964,906–2,368,838	403.93	NA	*MYT1L*	No	1 to 8	Partial	NA

Table 1. continued

Patients	Database ID	Genomic coordinates	Size (Kb)	Plateform	Genes	Intragenic[a]	Exons	Type of duplication[b]	Inheritance
P26 - [15]		1,761,661–1,824,122	62.46	NA	*MYT1L*	No	22 to 25	Partial	NA
P27 - [13]		1,762,828–1,848,310	85.48	NA	*MYT1L*	No	20 to 25	Partial	NA

[a]Both of the duplication's breakpoints lie within the *MYT1L* gene.
[b]Duplication of all or part of the *MYT1L* gene sequence.

main phenotype [4, 10, 16, 21, 24]; however, the clinical feature most frequently reported in the literature (schizophrenia) was not observed in any of the 16 new cases [16]. This discrepancy might be due to differences in the various studies' inclusion criteria. Most of the previous studies focusing on schizophrenia [10, 14, 19–21], which explains why an association between microduplications involving *MYT1L* and schizophrenia (odds ratio: 15.7; $p = 0.001$) was identified in large case-control studies of patients of all ages. This association is reportedly stronger for childhood-onset schizophrenia than for adult-onset schizophrenia (odds ratio: 16.6; $p = 0.01$) [10].

When considering the nine *MYT1L*-including 2p25.3 microduplications that were inherited from a healthy parent, one can hypothesize that the penetrance is variable. Furthermore, the highly heterogeneous phenotype is suggestive of variable expressivity. This might be due to differences in the breakpoints and duplication sizes, although these genetic features did not appear to be correlated with the clinical severity. For example, patients P17 and P14 (harboring duplications of 110 kb and 3.8 Mb, respectively) had much the same phenotype.

The microduplication size ranged from 62.4 kb to 3.8 Mb, and involved all or part of the critical *MYT1L* gene [4, 22]. Haploinsufficiency of *MYT1L* is not tolerated in humans [25], and the probability of loss of function intolerance score is 1. To date, disease-causing variants in *MYT1L* have been reported in 62 patients; the phenotype is more homogeneous but the clinical presentations resemble those seen in cases of microduplication syndrome [1]. The most frequent clinical features are behavioral disorders (seen in 98% of cases), DD with language delay (95%), ID (70%), overweight or obesity (58%), and epilepsy (23%) [1]. Furthermore, gene expression profiling of a *MYT1L* knockout cell line has shown that *MYT1L* haploinsufficiency can disrupt the expression of critical genes during brain development – suggesting that *MYT1L* regulates a network of genes involved in the etiology of neurodevelopmental disorders [25]. Chen *et al*. (2021) generated a *Myt1l* haploinsufficiency mouse model that mimicked common clinical phenotypes associated with loss-of-function mutations in human *MYT1L* or 2p25.3 deletions, including obesity, white-matter thinning, microcephaly, hyperactivity, muscle weakness, and social alterations [3].

The phenotypic variability might be explained by a "two-hit" model. The second hit might be another copy number variation, a single-base-pair mutation disrupting a functionally related gene, or even an environmental factor that affects the phenotype. This second hit might be responsible for the development of more severe neurological phenotypes, such as ID/DD, ASD, and schizophrenia [26, 27].

Lastly, one can hypothesize that the phenotype is due to duplication of another gene. However, when considering the 43 patients described in our study and in the literature, duplications in candidate genes that could be responsible for specific clinical findings in this syndrome were found in only 26 cases. Interestingly, 20 of the 43 duplications (particularly those associated with schizophrenia) affected *MYT1L* and *PXDN*. This prompts us to wonder whether *PXDN* is involved in schizophrenia susceptibility. *PXDN* encodes an extracellular, matrix-associated peroxidase thought to participate in peroxide-driven oxidations, phagocytosis, and immune defense. Many studies have shown that oxidative stress is part of the disease mechanism of schizophrenia [28]. However, there are no literature data on the potential involvement of *PXDN* in schizophrenia or other neuropsychological features. Some microduplications ($n = 6$) included additional proximal genes (*TPO* and *SNTG2*). Thyroid peroxidase is a key enzyme in thyroid hormone biosynthesis and was reportedly associated with ASD in a study of the contribution of immune-related genes to the pathogenesis of this disease [29]. Syntrophin gamma 2 is a scaffolding protein that interacts with the neuroligins. It has been suggested that *SNTG2* is involved in neurodevelopmental disorders,

Table 2. Summary of the clinical features of cases described in the present work.

Clinical feature	Patient N1	Patient N2	Patient N3	Patient N4	Patient N5	Patient N6	Patient N7	Patient N8	Patient N9	Patient N10	Patient N11	Patient N12	Patient N13	Patient N14	Patient N15	Patient D1-DECIPHER 371078	Number of patients ($n = 16$)
Gender (M/F)	F	F	F	M	M	M	M	F	F	F	F	M	F	M	F	M	
Age at diagnosis	7 years	3 years	6 months	5 years	6 years	7 years	13 years	5 years	13	13	fœtus	2 years	7 years	3 years	fœtus	1 years	
ID	Yes	Yes		Yes	Yes	-	-	Yes	-	-		-	-	-			5/16
DD	Yes	Yes	Yes	NA	NA	Speech delay	-	Sitting up at 10 months, walking at 19 months/ language delay	-	-		Sitting up at 10 months, Gait at 16 months/ language delay	Speech delay	-			7/16
ASD	-	-		Yes	-	-	-	-	-	-		Yes	Yes	Yes			4/16
Schizophrenia							-		-	-							0/16
Behavior	NA	NA		NA	NA	Anxiety disorder	-	Attention deficit	-	-							2/16
Cerebral defects		Agenesis of the corpus callosum	Microcephaly, cerebral lesion caused by fetal viral infection		Macrocephaly, SPC			Macrocephaly				-	Cystic dilatation of the Virchow-Robin spaces	T2/FLAIR subcortical WMH		Agenesis of the corpus callosum	7/16
Prenatal											Yes				Yes		2/16
Growth delay									Yes	Yes							2/16
Dysmorphic features	-	-	-	-	Yes	Yes : Long face, relatively short forehead, arched eyebrows, synophrys, epicanthus, DPF, anteverted nostrils, long philtrum, thick lips, ogival palate, bifid uvula, long fingers, low posterior hairline	-	Yes : Long face, high frontal hairline, telecanthus, broad base and flattened tip of the nose, anteverted nostrils, short philtrum, thick upper lips, dysplastic ears, DPF, small square hands, marked fetal pads	-	-		-	-	-		Yes : turricephaly	4/16
Other clinical features		Hypotonia, CHD, asplenia				Obesity	Congenital malformations of the feet and hands	Obesity			1st trimester MSM	Sensory Processing Disorder		Intra-uterine growth delay, fetal alcohol exposure	Increased NT (3.5 mm)	Bilateral 2–3 toe syndactyly	

Clinical feature	P1 - [4]	P2 - [17]	P3 - [17]	P4 - [11]	P5 - [4]	P6 - [4]	P7 - [4]	P8 - [4]	P9 - [4]	P10 - [4]	P11 - [19]	P12 - [19]	P13 - [20]
Gender (M/F)	M	M	M	M	F	M	M	M	F	M	M	F	M
Age at diagnosis	7 years	NA	NA	5 years	26 years	3 years	Adult	10 years	6 years	6 years	44 years	46 years	18 years
ID	Yes				Yes	Yes	Yes	Yes	Yes	Yes			
DD	Yes				Yes	Yes	Yes	Yes	Yes	Yes			
ASD	Yes	Yes	Yes	Yes	Yes	-	-	-	-	-	-	-	
Schizophrenia		-	-		-		-	-			Yes	Yes	Yes
Behavior					Aggressiveness	ADHD, aggressiveness	hyperactive, mood disorder, aggressiveness	hyperactive, mood disorder, aggressiveness	hyperactive, mood disorder, aggressiveness				
Cerebral defects	Microcephaly				Tonic-clonic seizures. On MRI: glioma, a low-grade astrocytoma	Microcephaly			Microcephaly				

Table 2. continued

Clinical feature	P1 - [4]		P2 - [17]	P3 - [17]	P4 - [11]	P5 - [4]	P6 - [4]	P7 - [4]	P8 - [4]	P9 - [4]	P10 - [4]	P11 - [19]	P12 - [19]	P13 - [20]
Prenatal														
Growth delay														
Dysmorphic features	-		-	-	-	Yes : thick lips, everted lower lip, high-arched palate, small hands	Yes : epicanthus, thick and everted lower lip, full cheeks, Sparse lateral eyebrows, micrognathia, clinodactyly	Yes : coarse facial features	Yes : bulbous nasal tip, wide mouth, overfolded helix	Yes : bulbous nasal tip, wide mouth, overfolded helix	Yes : brachycephaly	-	-	-
Other clinical features	Mild strabismus				Obesity	Obesity, sleep problems, genu valgum, strabismus	Sleep disorders	Obesity	Obesity, pectus excavatum, macroglossia, strabismus	Inguinal hernia, hyperlaxity, strabismus				

Clinical feature	P14 - [20]	P15 - [21]	P16 - [21]	P17 - [14]	P18 - [14]	P19 - [14]	P20 - [19]	P21 - [19]	P22 - [18]	P23 - [12]	P24 - [12]	P25 - [12]	P26 - [15]	P27 - [13]	Total patients ($n = 43$)
Gender (M/F)	M	NA	NA	NA	NA	NA	M	M	NA	NA	NA	NA	NA	NA	
Age at diagnosis	20 years	NA	NA	NA	NA	NA	41 years	72 years	NA	NA	NA	NA	NA	NA	
ID								-	-	-	-	-	-	-	12/43
DD								-	-	-	-	-	-	-	14/43
ASD							Yes	-	-	-	-	-	-	-	10/43
Schizophrenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	-	-	-	-	-	-	10/43
Behavior															7/43
Cerebral defects															11/43
Prenatal															2/43
Growth delay															2/43
Dysmorphic features	-	-	-	-	-	-	-	NA	NA	NA	NA	NA	NA	NA	10/43
Other clinical features							Asperger syndrome	No neuro-psychiatric phenotype	No neuro-psychiatric phenotype	No neuro-psychiatric phenotype	No neuro-psychiatric phenotype	No neuro-psychiatric phenotype	No neuro-psychiatric phenotype	No neuro-psychiatric phenotype	

ADHD attention deficit hyperactivity disorder, *ASD* autism spectrum disorder, *CHD* congenital heart defect, DD developmental delay, *DPF* downslanting palpebral fissures, *ID* intellectual disability, *MSM* maternal serum markers, *MRI* magnetic resonance imaging, *NA* not available, *NT* nuchal translucency, *SPC* septum pellucidum cyst, *WMH* white matter hyperintensity.

Table 3. Summary of the genotype–phenotype correlations in patients with a *MYT1L* microduplication.

Clinical phenotype	Genomic composition of the microduplication and position within *MYT1L*				
	Intragenic*	5′ end multiexon[a]	3′ end multiexon[a]	multigenic[b] microduplication	Fisher-Freeman-Halton Exact test (*p* value)
Schizophrenia	0% (0/10)	0% (0/10)	0% (0/10)	100% (10/10)	0.003[c]
ID/DD	9% (1/11)	55% (6/11)	0% (0/11)	36% (4/11)	
ASD	37% (3/8)	0% (0/8)	0% (0/8)	63% (5/8)	
No neuropsychiatric phenotype	27% (3/11)	9% (1/11)	18% (2/11)	46% (5/11)	
Prenatal cases	0% (0/2)	0% (0/2)	0% (0/2)	100% (2/2)	
All	17% (7/42)	17% (7/42)	4% (2/42)	62% (26/42)	

[a]Microduplications involving only *MYT1L* gene.
[b]*MYT1L* microduplications extending to neighboring genes.
[c]Significative *p* value.

as a partial *SNTG2* deletion was identified in a patient with autistic features [30]. However, there were no data on the neuropsychiatric phenotype or the exact age at diagnosis for one of the four patients with microduplications including *SNTG2* (P22).

Regarding the mechanism underlying the duplication and given the absence of recurrent breakpoints or flanking segmental duplications, non-allelic homologous recombination can be ruled out [10]. Hence, the involvement of other underlying mechanisms (such as non-homologous end joining, fork stalling and template switching, and microhomology-mediated break-induced replication) could be postulated.

Lastly, our findings reveal that *MYT1L* duplications are associated with variable, unpredictable phenotypic outcomes. Microduplications are often inherited from a phenotypically normal parent, making it difficult to establish a direct pathogenic effect. In this context, genetic counseling and a clinical prognosis are major challenges for clinicians. The enrichment of this microduplication in patients with neurodevelopmental disabilities and the more frequent occurrence of a second copy number variation in affected carriers suggest that 2p25.3 microduplications involving *MYT1L* can act as a susceptibility/risk locus for neurodevelopmental impairments.

DATA AVAILABILITY

The datasets generated for the current study are included in this article, further inquiries can be directed to the corresponding authors. The variants reported in patients N1–N5 and described in this study have been submitted to the ClinVar repository (SUB12521627, accession numbers SCV002818537-SCV002818541). All the other newly reported variants have been submitted to the DECIPHER database.

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AUTHOR CONTRIBUTIONS

MB, FV and BH: contributed to the study conception and design. MB: analyzed the data and wrote the manuscript. JL, GL, FB, MGG, RD: performed the clinical evaluation of the patients. ME, NC, LB, ACT, CSB, JCo: performed the genetic investigations. JCl: participated in the collection of clinical data. FV, BH: did the supervision, review and editing of the manuscript. All authors contributed to data acquisition.

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ETHICAL APPROVAL

In compliance with the Declaration of Helsinki, informed written consent for genetic study was obtained for participated individuals.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Malek Bouassida or François Vialard.