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2p25.3 microduplications involving MYT1L: further phenotypic characterization through an assessment of 15 new cases and a literature review

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Abstract

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 included all or part of *MYT1L*.

Through a French national collaboration and a literature review, we assessed a large cohort of patients (n = 43) with pure 2p25.3 microduplications identified by chromosomal microarray analysis. 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 (23%), mild-to-moderate intellectual disability (21%), schizophrenia (21%), 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 either duplication of all or part of *MYT1L*. There were seven cases of intragenic duplication. The inheritance pattern was available for 18 patients: the microduplication was inherited in 13 cases, and all but one of the parents had a normal phenotype.

Our comprehensive review and expansion of the phenotypic spectrum associated with 2p25.3 microduplications involving *MYT1L* (previously linked to schizophrenia) 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.

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*) (ref. 6,7). This role in promoting neuronal differentiation has been proven *in vitro* by showing 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 has been clearly established (4), it varies markedly from one patient to another. Furthermore, the published clinical data are often limited. Partial microduplications encompassing *MYT1L* have been first linked to schizophrenia (10) and also observed in individuals presenting neuropsychiatric disease 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 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 assessed clinical and genetic data on 43 patients presenting 2p25.3 microduplications that involved all or some 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 asked 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*. The microduplications were identified with microarrays that differed in their format, resolution, and manufacturer: a Human Genome CGH Microarray 60K, 150K or 180K (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. 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 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 the DECIPHER, requesting the patients' details and authorization to use this information. Only one patient, for whom a consent was obtained, could be included in the present study. To identify previously published cases, we also searched the PubMed online database (<https://pubmed.ncbi.nlm.nih.gov>) with the search terms "2p25.3 duplication" and "MYT1L duplication".

Results:

A total of 43 patients were included in the study. All harbored pure interstitial microduplications overlapping the 2p25.3 region and involving the *MYT1L* gene. The male:female ratio was 1.6 (20/12). 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 15 newly reported patients, 13 were unrelated and two (N9 and N10) were twins. Microduplication was identified during the prenatal period in two cases (N11 and N15).

CMA results

The patients' tracks are represented in Fig. 1 and 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 duplication encompassed the entire *MYT1L* gene. In 17 of the 43 cases (39%), the duplications involve only *MYT1L*, and 7 of the 17 were intragenic. In 20 of the 43 cases (46%), the microduplications involved both the *MYT1L* and *PXDN* genes. In the largest microduplications (6 out of 43, 14%), additional genes were involved: *SNTG2*, *TPO*, *RNASEH1*, *TSSC1*, *ADI1*, *COLEC11*, *RPS7*, *ALLC*, *RPS7*.

Inheritance

Data on the inheritance pattern were available for 18 of the 43 patients. The microduplication occurred *de novo* in five patients (28%). The microduplication was paternally inherited in seven cases and maternally inherited for the six remaining cases. In two 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 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 9 of the 11 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.

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 9 of the 43 cases (21%), 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 22 of *MYT1L* (chr2:1,716,437-1,815,909, hg18; 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 *MYT1L*. All the microduplications associated with both ASD and ID were intragenic. In contrast, duplications associated with ID and/or DD were randomly distributed throughout the region of interest. Overall, the minimal critical region mapped to 1.762–1.806 Mb, corresponding to exons 23–25 of *MYT1L* (Fig. 1).

Discussion:

Here, we presented clinical and molecular data on 15 new cases of individuals harboring a microduplication in the 2p25.3 region. We also reviewed the cases described in the literature and added a patient from the DECIPHER (23), from whom we obtained explicit consent for publication. Hence, we were able to describe a cohort of 43 people with a 2p25.3 microduplication involving *MYT1L* (Tables 1 and 2). These microduplications are rare, and only 27 cases had been reported previously (16). To the best of our knowledge, the present series is the largest yet reported.

The most frequently reported clinical features were psychomotor and speech delay (33%), mild-to-moderate ID (21%), ASD with or without ID (23%), schizophrenia (21%), and behavioral abnormalities (16%, including anxiety, attention-deficit/hyperactivity disorder, and aggressiveness). Our results are in line with previous observations of psychiatric and neurodevelopmental disorders as the 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 15 new cases (16). This discrepancy might be due to difference 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; $p = 0.01$) (ref. 10).

Considering the 2p25.3 microduplications including *MYT1L* were inherited from a healthy parent in nine cases, one can hypothesized 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). Haplo-insufficiency 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%) (ref. 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, defects in candidate genes that could be responsible for specific clinical findings in this syndrome were found in 26 cases only. 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.

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.

Declarations:

Data Availability Statement

The datasets generated for the study are included in the article, further inquiries can be directed to the corresponding authors.

Conflict of interest

None to declare.

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We thank the patients and their families for their cooperation.

This study assessed data generated by the DECIPHER community. A full list of the centers that helped to generate the data is available from <https://deciphergenomics.org/about/stats> and by e-mail from contact@deciphergenomics.org. Funding for the DECIPHER project was provided by the Wellcome Trust. We declare that those who carried out the original analysis and collection of the data bear no responsibility for the further analysis or interpretation of the data.

Author Contribution Statement

MB, FV and BH: contributed to the study conception and design. MB: analysed 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.

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Tables:

Tables 1 and 2 are available in the Supplementary Files section.

Figures

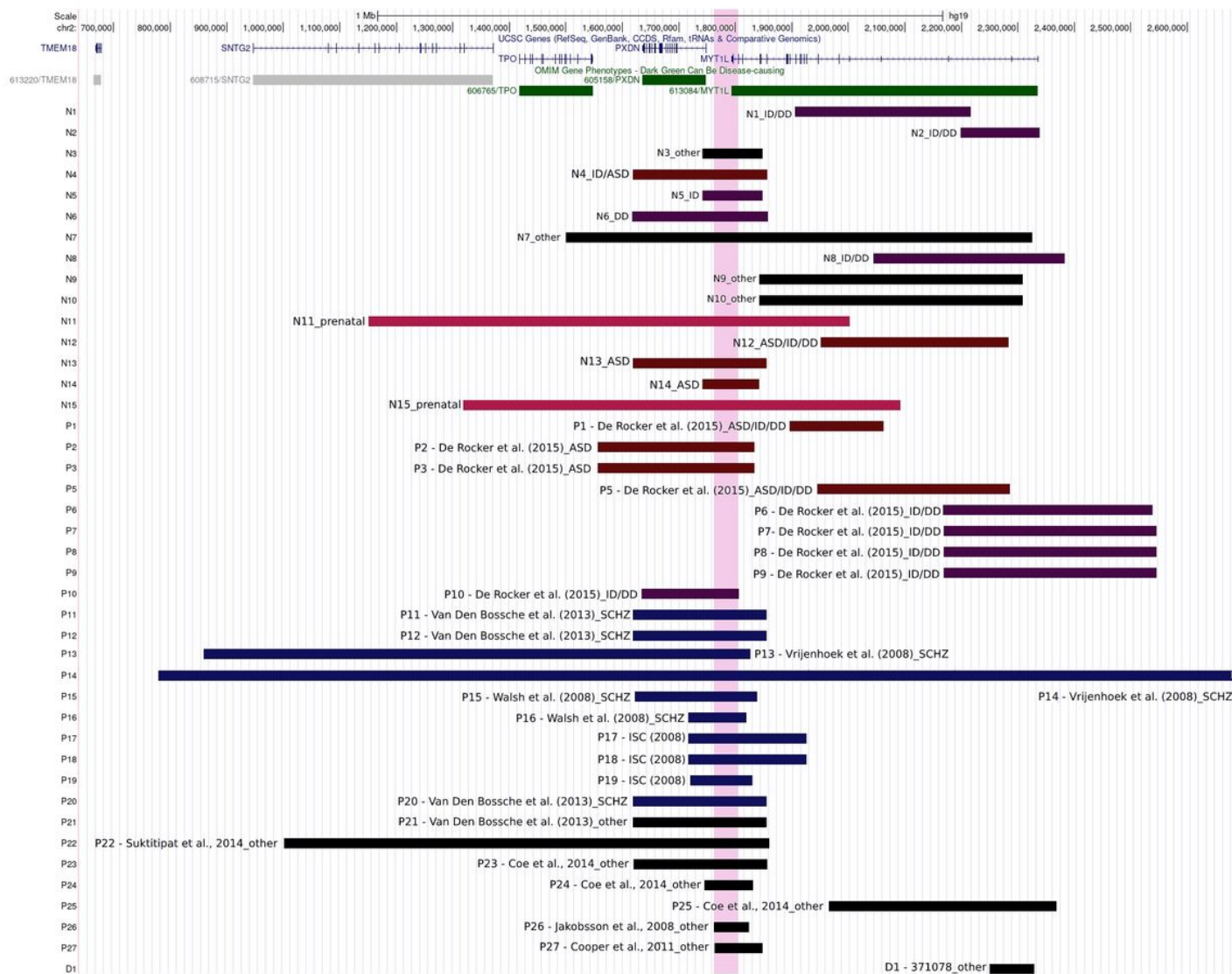


Figure 1

Mapping of the 2p25.3 duplications in the cohort, including new cases (N1-N15), patients described in the literature (P1- P27), and the case found in the DECIPHER (D1). The genes present within this region are annotated and shown at the top. The duplications are represented by horizontal bars colored according to the associated clinical phenotype (see the legend). The shortest region of duplication overlap is highlighted in pink. The figure was generated using the UCSC Genome Browser (<https://genome.ucsc.edu/>).

Supplementary Files

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- [Table2clinicalfeaturessubmitted.xlsx](#)