SJD Formación Sant Joan de Déu

Pediatric Movement Disorders Series: KMT2B-dystonia

Course Direction
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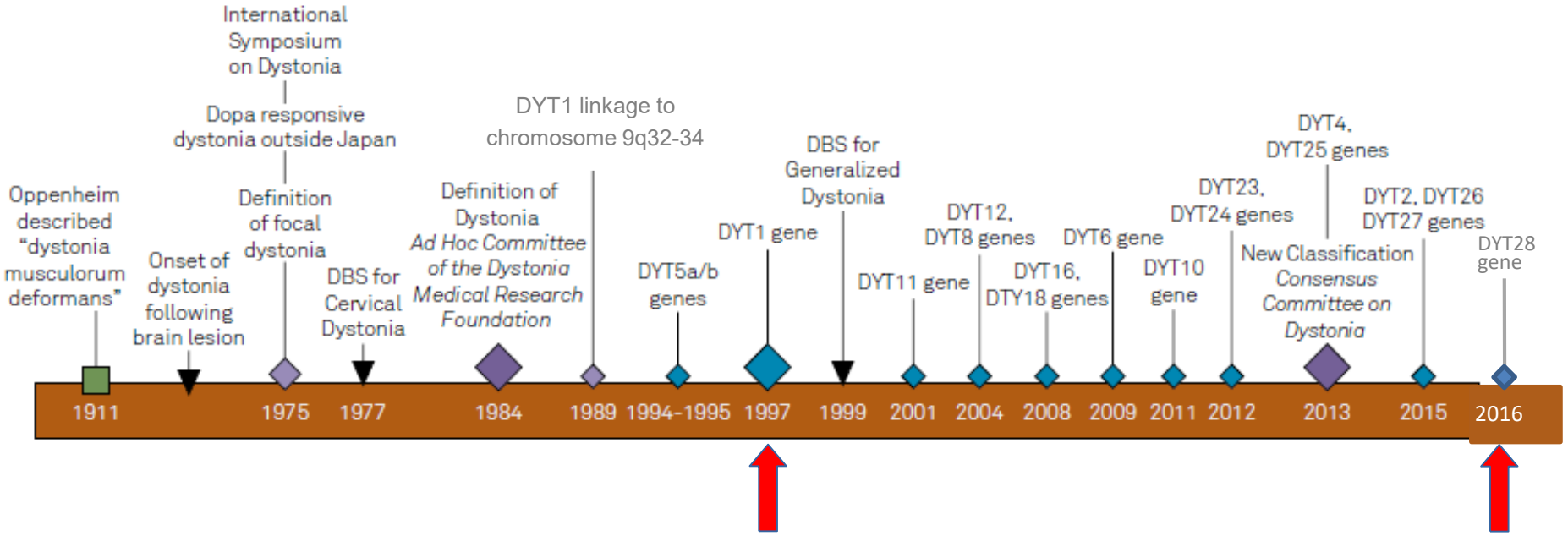
University of Padua, Italy
ERN-RND center

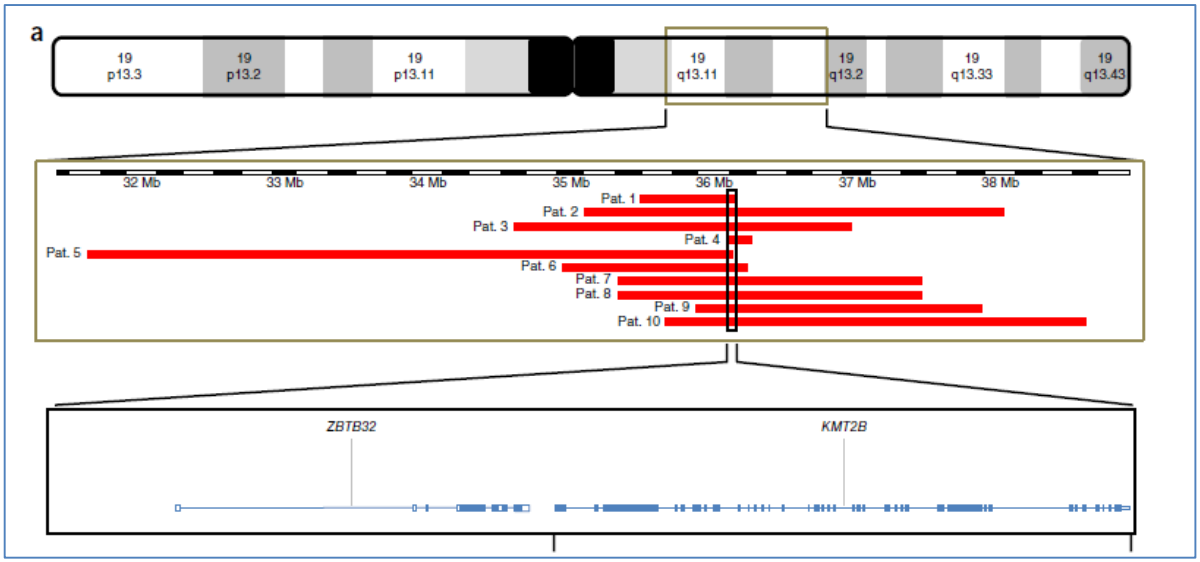
UNIVERSITÀ
DEGLI STUDI
DI PADOVA

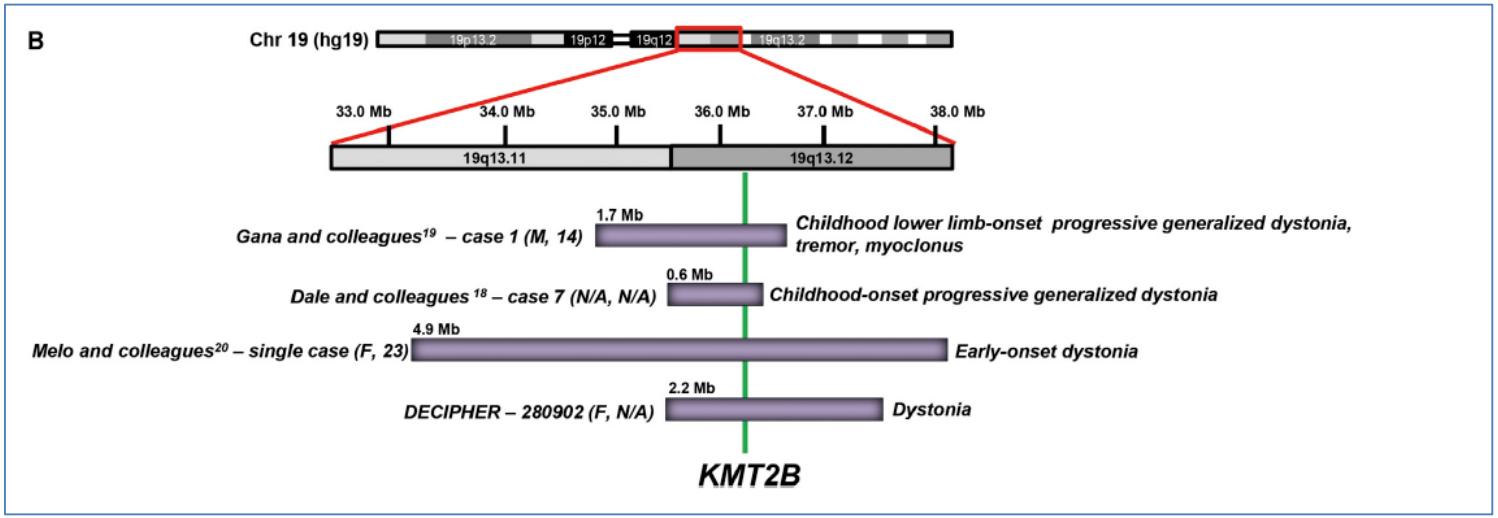
Dystonia: timeline of genetics



Adapted from: Camargos S. & Cardoso F., 2016

KMT2B gene discovery





Meyer et al., Nat Genet 2016; Zech et al., AJHG 2016

The American Journal of Human Genetics 99, 1377–1387, December 1, 2016

REPORT

Haploinsufficiency of *KMT2B*, Encoding the Lysine-Specific Histone Methyltransferase 2B, Results in Early-Onset Generalized Dystonia

6 cases

Michael Zech,[1,2] Sylvia Boesch,[3] Esther M. Maier,[4] Ingo Borggraefe,[4] Katharina Vill,[4] Franco Laccone,[5] Veronika Pilshofer,[6] Andres Ceballos-Baumann,[2,7] Bader Alhaddad,[8] Riccardo Berutti,[9] Werner Poewe,[3] Tobias B. Haack,[8,9,10] Bernhard Haslinger,[2] Tim M. Strom,[8,9] and Juliane Winkelmann[1,2,8,11,*]

Mutations in the histone methyltransferase gene *KMT2B* cause complex early-onset dystonia

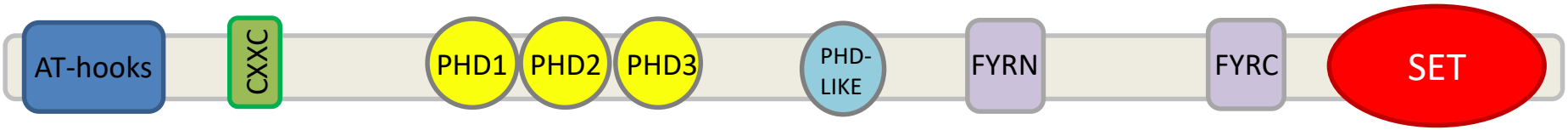
nature genetics

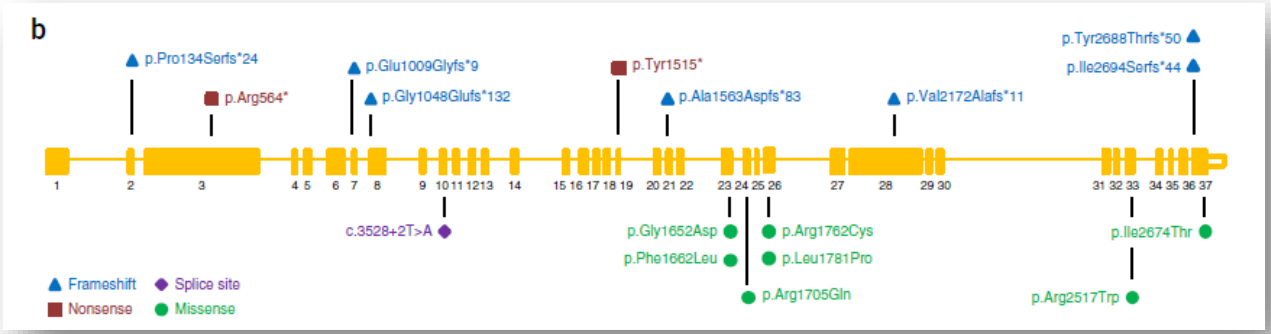
27 cases

Esther Meyer[1,48], Keren J Carss[2,3,48], Julia Rankin[4,48], John M E Nichols[5,48], Detelina Grozeva[6], Agnel P Joseph[7], Niccolo E Mencacci[8], Apostolos Papandreou[1,9], Joanne Ng[1,9], Serena Barral[1], Adeline Ngoh[1,9], Hilla Ben-Pazi[10], Michel A Willemsen[11], David Arkadir[12], Angela Barnicoat[13], Hagai Bergman[14], Sanjay Bhate[9], Amber Boys[15], Niklas Darin[16], Nicola Foulds[17], Nicholas Gutowski[18], Alison Hills[19], Henry Houlden[8], Jane A Hurst[13], Zvi Israel[20], Margaret Kaminska[21], Patricia Limousin[22], Daniel Lumsden[21], Shane McKee[23], Shibalik Misra[24,25], Shekeeb S Mohammed[24,25], Vasiliki Nakou[21], Joost Nicolai[26], Magnus Nilsson[27], Hardev Pall[28], Kathryn J Peall[29], Gregory B Peters[30], Prab Prabhakar[9], Miriam S Reuter[31], Patrick Rump[32], Reeval Segel[33], Margje Sinnema[34], Martin Smith[35], Peter Turnpenny[4], Susan M White[15,36], Dagmar Wieczorek[37,38], Sarah Wiethoff[8], Brian T Wilson[13], Gidon Winter[10], Christopher Wragg[19], Simon Pope[39], Simon J H Heales[39,40], Deborah Morrogh[41], UK10K Consortium[42], Deciphering Developmental Disorders study[42], NIHR BioResource Rare Diseases Consortium[42], Alan Pittman[8], Lucinda J Carr[9], Belen Perez-Dueñas[43,44], Jean-Pierre Lin[21], Andre Reis[31], William A Gahl[45], Camilo Toro[45], Kailash P Bhatia[22], Nicholas W Wood[8], Erik-Jan Kamsteeg[46], Wui K Chong[47], Paul Gissen[5], Maya Topf[7], Russell C Dale[24,25], Jonathan R Chubb[5], F Lucy Raymond[3,6,49] & Manju A Kurian[1,9,49]

Received 19 April; accepted 14 November; published online 19 December 2016;

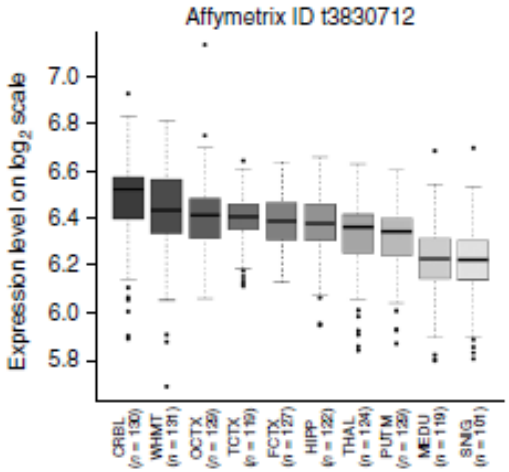
KMT2B - gene structure





- 37 exons, 20 Kb
- Inheritance: autosomal dominant
- Mutations reported: missense, nonsense, frameshift, interstitial deletions at 19q12.13, small in/del

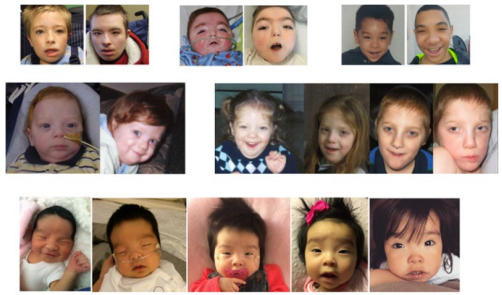
KMT2B - expression



- *KMT2B* encodes a **histone lysine methyltransferase** involved in methylation of histone H3 at lysine 4 (H3K4) → dysregulation of gene transcription
- Ubiquitously expressed in the brain (++ cerebellar cortex)
- Reduced mRNA transcript in cultured fibroblasts of patients → haploinsufficiency

Meyer et al., Nat Genet 2016; Zech et al., AJHG 2016

KMT2s-related human diseases



Rare monoallelic neurodevelopmental disorders:

- Wiedemann-Steiner syndrome (MIM 605130; *KMT2A*)
- Kleefstra syndrome type 2 (MIM 617768; *KMT2C*)
- Kabuki syndrome type 1 (MIM 147920; *KMT2D*)
- O'Donnel-Luria-Rodan syndrome (MIM 618512, *KMT2E*)

Common clinical features: global developmental delay, facial dysmorphic traits, extra-central nervous system developmental defects

De novo LOF mutations

Main clinical features: dystonia

- **Childhood-onset** dystonia (mean age at onset 5 years)
- **Lower limb onset** (21/27) → similar to DYT1
- Generalization in almost all patients (24/27), 2-11 yrs after the onset
- Prominent **laryngeal, cranial and oro-mandibular** dystonia
- Subcortical myoclonus in two cases
- Infection-induced status dystonicus in 1 patient
- Very good response to DBS
- *De novo* mutations in most cases; ~1/3 microdeletions at 19q13.12 involving *KMT2B*

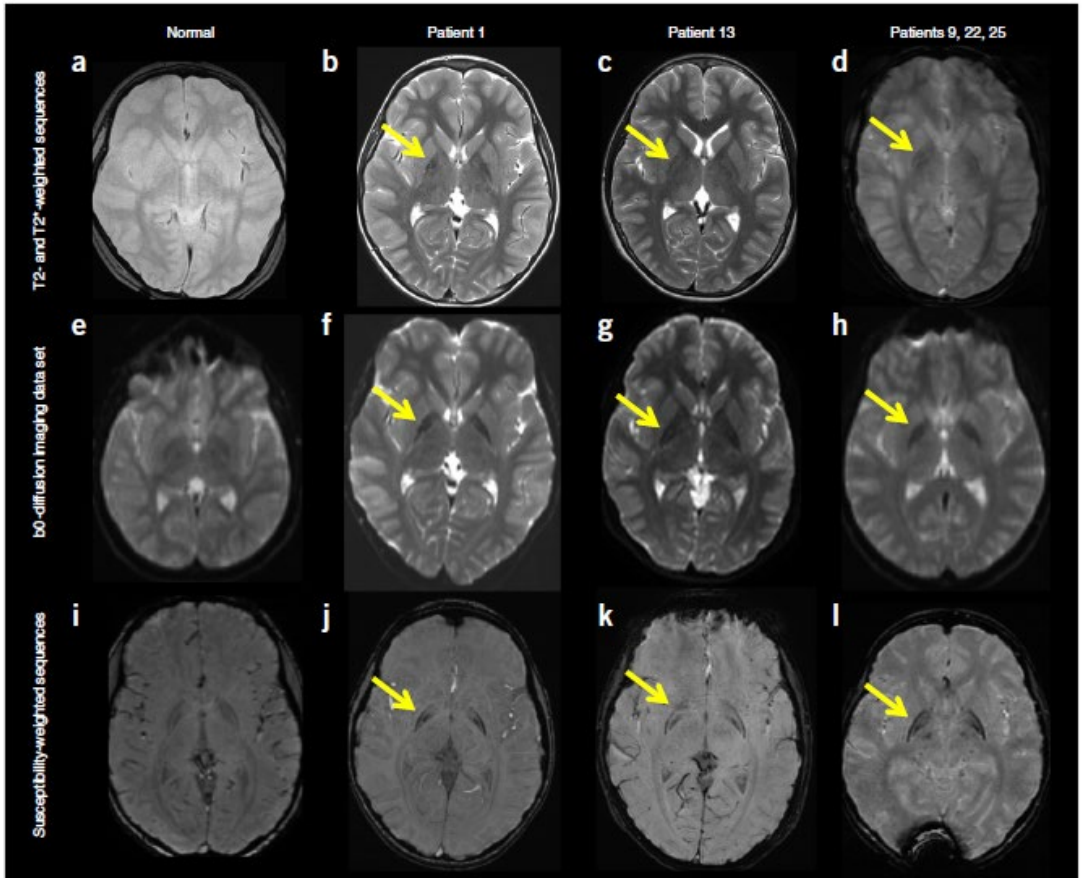
Meyer et al., 2017

Additional clinical features

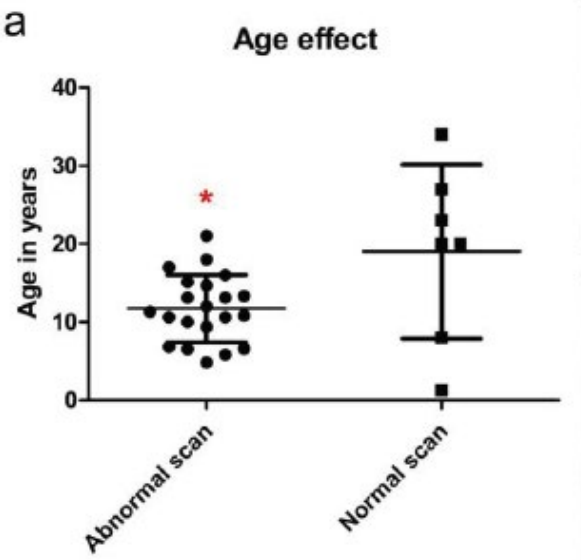
- **Microcephaly**
- **Short stature**
- **Intellectual disability**
- Psychiatric disturbances (4/27)
- Developmental delay
- Epilepsy (2/27)
- Dysmorphic features (elongated face and bulbous nasal tips)

Meyer et al., 2017; Zech et al., 2016

Radiological features



Subtle, symmetrical hypointensity of the globus pallidi (with a hypointense streak of bilateral globus pallidus externa) on MR images



Age-dependent effect?

Meyer et al., 2017

RESEARCH ARTICLE

Frequency and Phenotypic Spectrum of *KMT2B* Dystonia in Childhood: A Single-Center Cohort Study

Miryam Carecchio, MD, PhD,[1,2,3] Federica Invernizzi, MSc,[2] Paulina Gonzàlez-Latapi, MD, MSc,[4] Celeste Panteghini, MSc,[2] Giovanna Zorzi, MD,[1] Luigi Romito, MD, PhD,[5] Vincenzo Leuzzi, MD,[6] Serena Galosi, MD,[6] Chiara Reale, MSc,[2] Federica Zibordi, MD,[1] Agnel P. Joseph, PhD,[7] Maya Topf, PhD,[7] Carla Piano, MD,[8] Anna Rita Bentivoglio, MD,[8] Floriano Girotti, MD,[5] Paolo Morana, MD,[9] Benedetto Morana, MD,[9] Manju A. Kurian, MD, PhD,[10,11] Barbara Garavaglia, PhD,[2] Niccolò E. Mencacci, MD, PhD,[4] Steven J. Lubbe, PhD,[4] and Nardo Nardocci, MD[1*]

65 genetically undefined EO dystonia patients

- *No known mutations in DYT genes*
- *Onset < 18 years of age*
- *No secondary causes of dystonia*

↓

WES/customized NGS panels

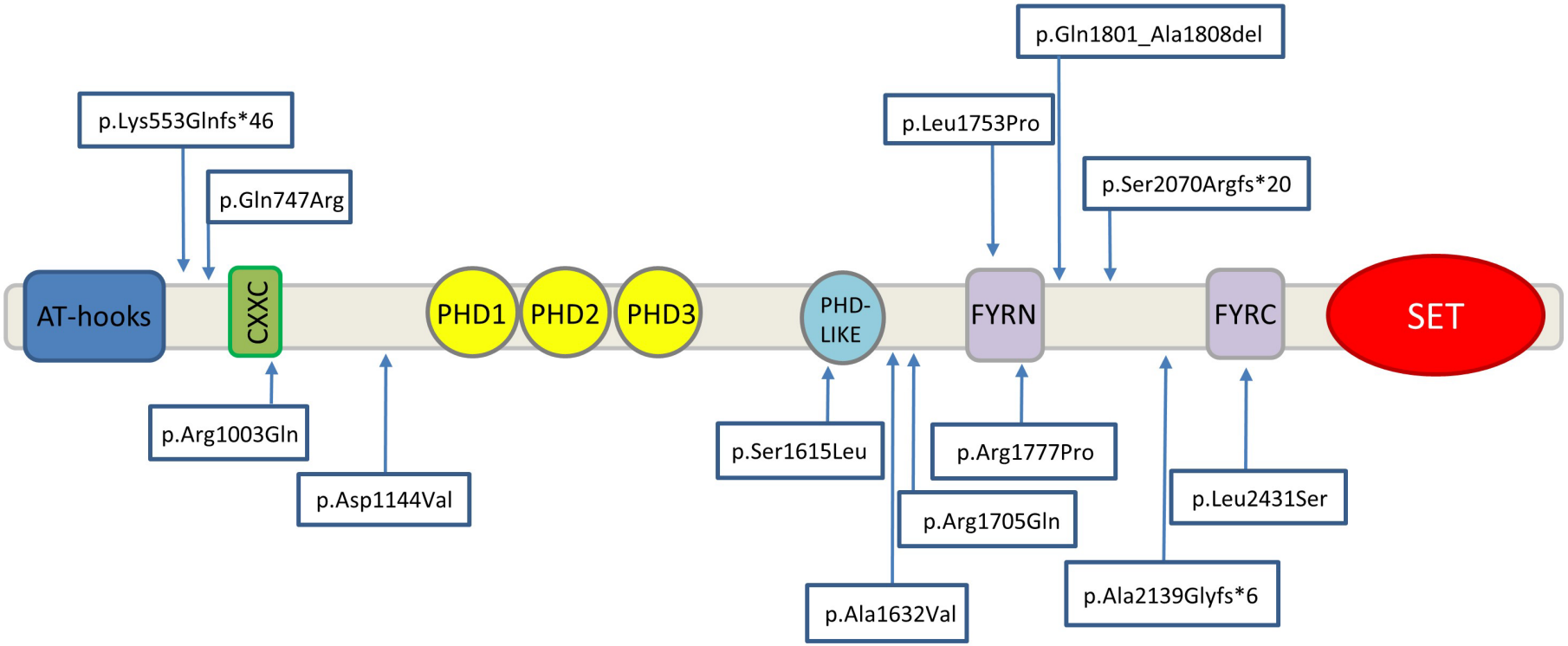
↓

14/65 KMT2B +ve (8F, 6M)

↓

21.5% mutational frequency

KMT2B mutations



Carecchio et al., MDJ 2019

No clinical differences between missense mutation carriers and frameshift mutation carriers

Clinical phenotype

- ✓ Mean age at onset: **6.2 years** (range 3-13 years)
- ✓ Mean disease duration: **21 years** (range 3-42 years)

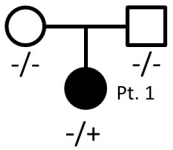
- ✓ Normal motor milestones in all cases, delayed language in 2/14

- ✓ Dystonia features: **Lower limb** onset: 78.5%
  Laryngeal dystonia: 78.5%
  Generalization: 93%
  Oromandibular dystonia: 57%
  Anarthria: 28.5%

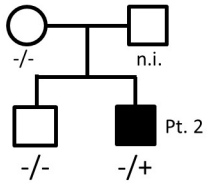
- ✓ **No brain MRI alterations** at any disease stage

- ✓ **Mild intellectual disability**: **70%**
- ✓ **Short stature** with somatic harmonic development: **64%**
- ✓ **Minor facial dysmorphisms**: 64% → bulbous nasal tips, low-set ears, thin upper lip, mild palpebral ptosis, broad nasal bridge, elongated face
- ✓ **Brisk reflexes** in the lower limbs: 43%

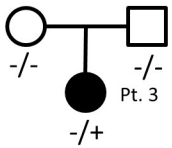
Carecchio et al., MDJ 2019



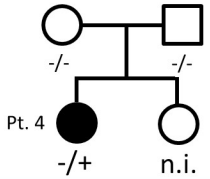
p.Ser2070Argfs*20



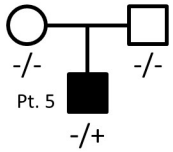
p.Lys553Glnfs*46



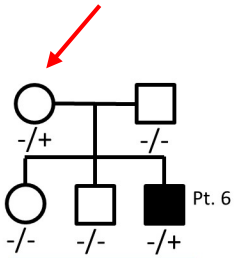
p.Ala2139Glyfs*6



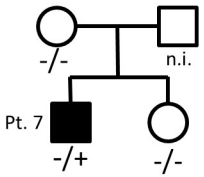
p.Gln1801_Ala1808del



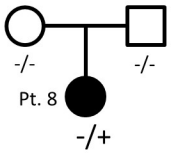
p.Arg1705Gln



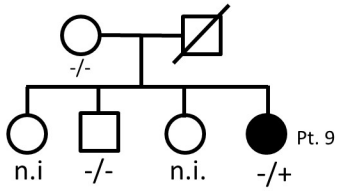
p.Gln747Arg



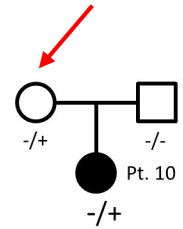
p.Arg1777Pro



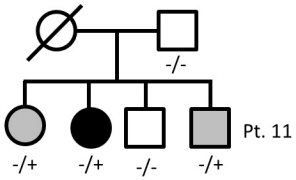
p.Leu1753Pro



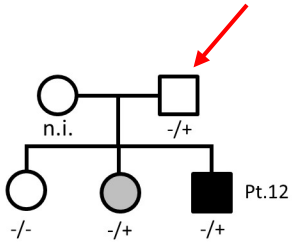
p.Ser1615Leu



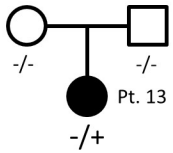
p.Asp1144Val



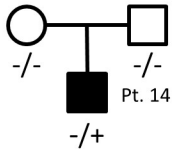
p.Leu2431Ser



p.Arg1003Gln



p.Ala1632Val



Del: chr. 19: 35,608,696-36,869,486

Incomplete pentrance

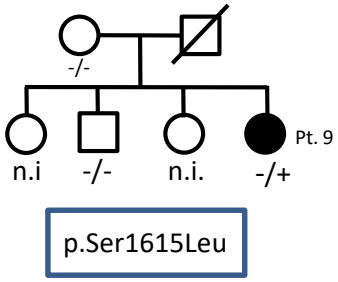
Carecchio et al., 2019

Red flags

- ✓ Generalized dystonia with anarthria
- ✓ Dysphonia
- ✓ Short stature (check parents!)
- ✓ Intellectual disability
- ✓ Microcephaly
- ✓ Brisk reflexes

Childhood-onset dystonia
+
Short stature
Mild-to-moderate ID

KMT2B: anarthria

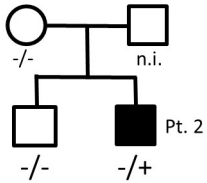


AAO: 7 years (lower limbs)
Disease duration: 37 years

KMT2B: severe axial dystonia

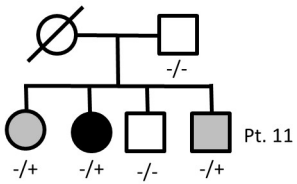
Extremely mobile dystonia with severe torsional component

KMT2B: disease history without DBS



p.Lys553Glnfs*46

AAO: 4 years (lower limbs + larynx)
Disease duration: 40 years
Anarthria and severe axial dystonia



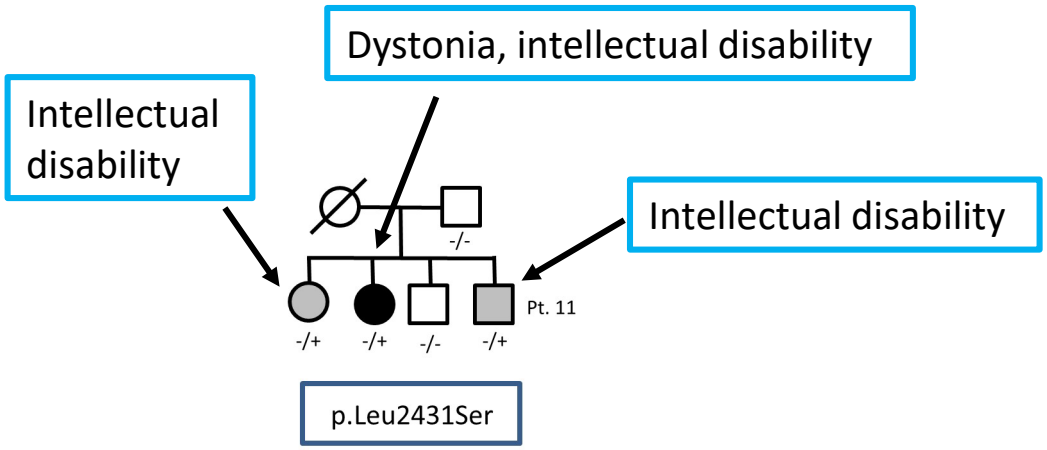
p.Leu2431Ser

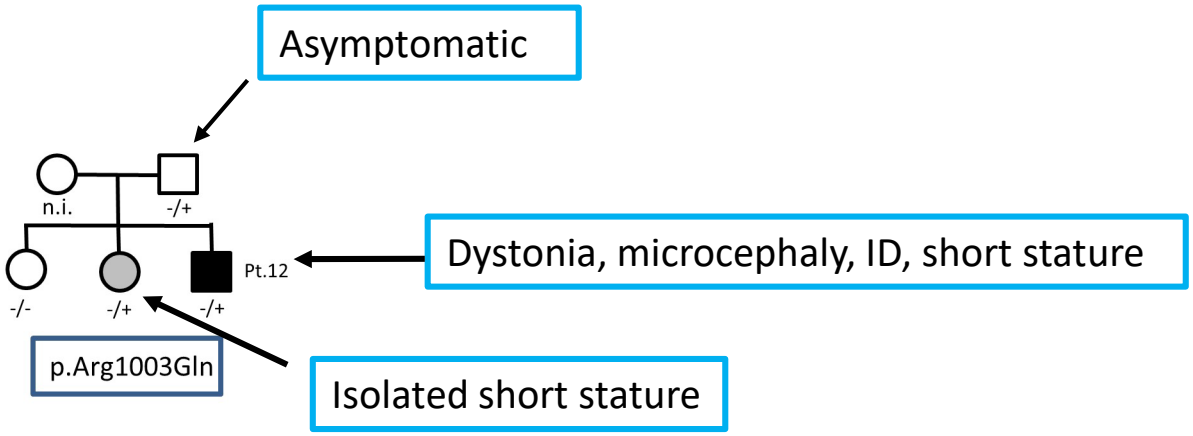
AAO: 10 years (lower limbs)
Disease duration: 42 years
Anarthria, severe generalized dystonia

Carecchio et al., 2019

KMT2B: disease history before and after DBS

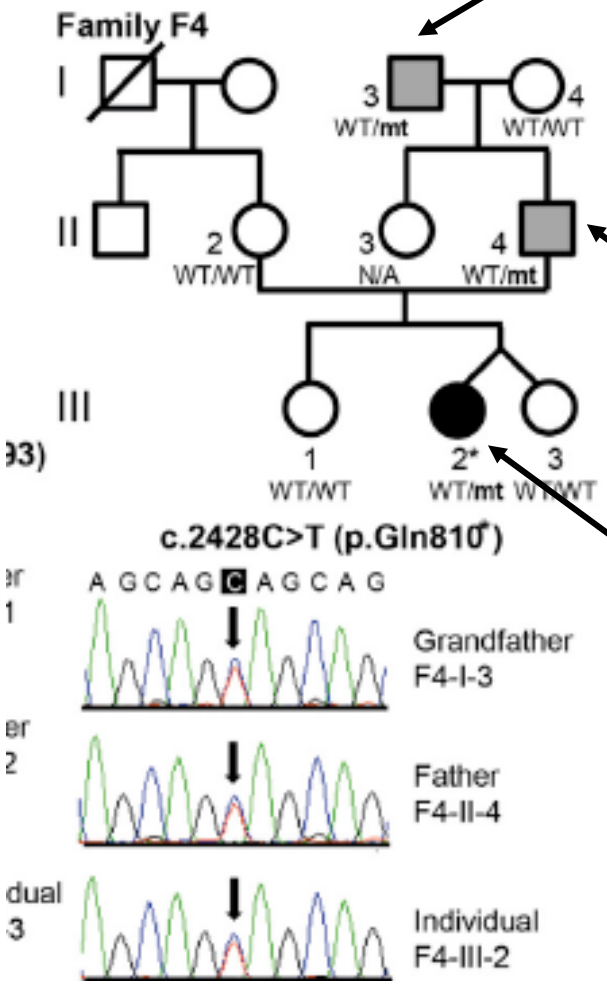
Intra-familial phenotypic variability





Carecchio et al., 2019

Phenotypic variability



- ✓ Writer's cramp + dystonic tremor
- ✓ Onset 11 years

- ✓ Writer's cramp, onset 9 years
- ✓ Microcephaly + short stature

- ✓ Generalized dystonia with lower limb onset (age 4 years)
- ✓ Microcephaly + short stature

Zech et al., 2016

Histone Lysine Methylases and Demethylases in the Landscape of Human Developmental Disorders

Víctor Faundes,[1,2] William G. Newman,[1,3] Laura Bernardini,[4] Natalie Canham,[5] Jill Clayton-Smith,[1,3] Bruno Dallapiccola,[6] Sally J. Davies,[7] Michelle K. Demos,[8] Amy Goldman,[3] Harinder Gill,[9] Rachel Horton,[10] Bronwyn Kerr,[3] Dhavendra Kumar,[7] Anna Lehman,[9] Shane McKee,[11] Jenny Morton,[12] Michael J. Parker,[13] Julia Rankin,[14] Lisa Robertson,[15] I. Karen Temple,[10] Clinical Assessment of the Utility of Sequencing and Evaluation as a Service (CAUSES) Study,[9] The Deciphering Developmental Disorders (DDD) Study,[16] and Siddharth Banka[1,3,*]

The American Journal of Human Genetics *102*, 1–13, January 4, 2018

Asymptomatic carriers> Isolated ID/short stature > dystonia±additional features

JAMA Psychiatry | Original Investigation

Diagnostic Yield and Novel Candidate Genes by Exome Sequencing in 152 Consanguineous Families With Neurodevelopmental Disorders

Miriam S. Reuter, MD; Hasan Tawamie, MA; Rebecca Buchert, MA; Ola Hosny Gebril, MD; Tawfiq Froukh, PhD; Christian Thiel, MD; Steffen Uebe, PhD; Arif B. Ekici, PhD; Mandy Krumbiegel, PhD; Christiane Zweier, MD; Juliane Hoyer, MD; Karolin Eberlein, MD; Judith Bauer, MD; Ute Scheller, MD; Tim M. Strom, MD; Sabine Hoffjan, MD; Ehab R. Abdelraouf, MD; Nagwa A. Meguid, MD, PhD; Ahmad Abboud, MD; Mohammed Ayman Al Khateeb, MD; Mahmoud Fakher, MD; Saber Hamdan, MD; Amina Ismael, MD; Safia Muhammad, MD; Ebtessam Abdallah, MD, PhD; Heinrich Sticht, PhD; Dagmar Wieczorek, MD; André Reis, MD; Rami Abou Jamra, MD

JAMA Psychiatry. 2017;74(3):293-299. doi:10.1001/jamapsychiatry.2016.3798
Published online January 11, 2017.

DBS in KMT2B dystonia

- 18 patients with DBS
- Median age at DBS: 11.5 years (4.5-37)
- Post-surgical follow-up from 0.25 to 22 years
- Significant improvement (BFMDRS-M and BFMDRS-D) evident at 6 months, 1 year and last follow-up
- **At 1 year FU >50% of subjects showed BFMDRS-M and BFMDRS-D improvements of >30%**
- Beyond 5 years, improvement of >30% was maintained in 5/8 and 3/8 subjects for the BFMDRS-M and BFMDRS-D, respectively
- **The greatest BFMDRS-M improvements were observed for trunk (53.2%) and cervical**
- **(50.5%) dystonia, with less clinical impact on laryngeal dystonia**

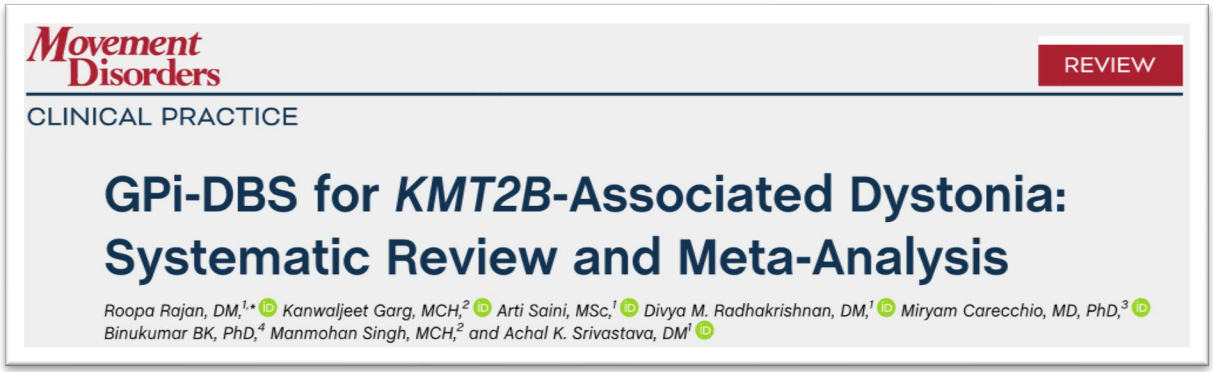
RESEARCH ARTICLE

Frequency and Phenotypic Spectrum of *KMT2B* Dystonia in Childhood: A Single-Center Cohort Study

Miryam Carecchio, MD, PhD,[1,2,3] Federica Invernizzi, MSc,[2] Paulina Gonzàlez-Latapi, MD, MSc,[4] Celeste Panteghini, MSc,[2] Giovanna Zorzi, MD,[1] Luigi Romito, MD, PhD,[5] Vincenzo Leuzzi, MD,[6] Serena Galosi, MD,[6] Chiara Reale, MSc,[2] Federica Zibordi, MD,[1] Agnel P. Joseph, PhD,[7] Maya Topf, PhD,[7] Carla Piano, MD,[8] Anna Rita Bentivoglio, MD,[8] Floriano Girotti, MD,[5] Paolo Morana, MD,[9] Benedetto Morana, MD,[9] Manju A. Kurian, MD, PhD,[10,11] Barbara Garavaglia, PhD,[2] Niccolò E. Mencacci, MD, PhD,[4] Steven J. Lubbe, PhD,[4] and Nardo Nardocci, MD[1*]

- 8 patients with DBS
- Median disease duration 8.5 years
- Median patients' age at surgery 10 years
- Median post-surgery FU: 12 years (range 8-17 yrs)
- Mean long term improvement on BFMDRS-M: 38.5%
- **No improvement of laryngeal dystonia**

Carecchio et al., MDJ 2019



- 42 individual patients
- mean age at onset 6.4 +/- 5.7 years, 60% F, 40% M
- Median follow-up 12 months (range: 1–264 months)
- Median BFMDRS-M improvement **42.7%**
- Pooled proportion of patients experiencing >50% clinical improvement **41%**
- **Male gender** (P = 0.004), and **higher pre-operative BFMDRS-M score** (P < 0.001) were independently associated with better outcome

Variable	Coefficient (univariate)	Coefficient (multivariate)
Male gender	11.50 (−4.50 to 27.50) $P = 0.154$	22.60 (7.95 to 37.26) $P = 0.004$
Age at onset	−0.12 (−1.49 to 1.26) $P = 0.863$	−1.05 (−20.03 to 17.93) $P = 0.911$)
Age at DBS	−0.08 (−0.86 to 0.71) $P = 0.843$	1.65 (−17.25 to 20.55) $P = 0.860$
Duration at DBS	−0.06 (−1.00 to 0.87) $P = 0.891$	−1.83 (−20.73 to 17.08) $P = 0.845$
Follow up duration	0.01 (−0.09 to 0.12) $P = 0.794$	0.00 (−0.09 to 0.10) $P = 0.931$
Pre-operative BFMDRS-M score	0.46 (0.22 to 0.71) $P < 0.001$	0.62 (0.36 to 0.87) $P < 0.001$

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Childhood-onset dystonia-causing *KMT2B* variants result in a distinctive genomic hypermethylation profile

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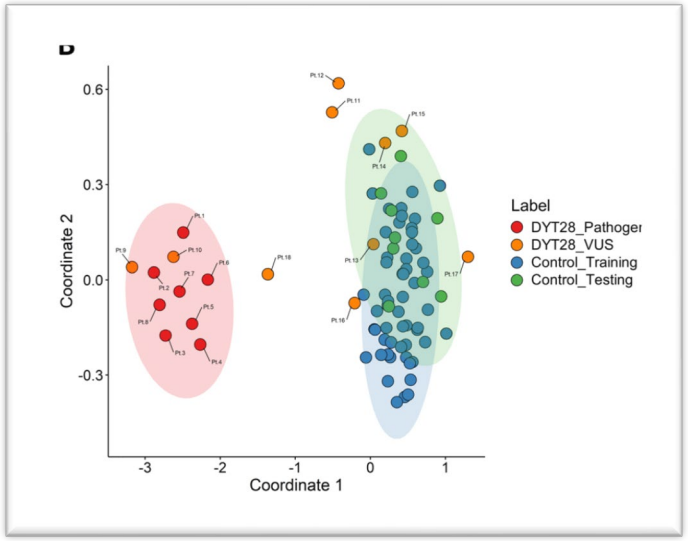


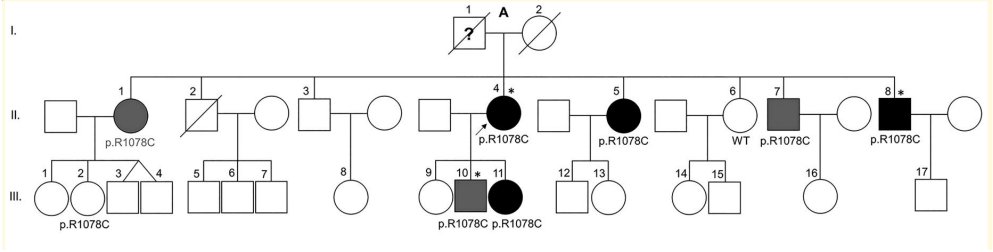
KMT2B mutations → DNA hypermethylation of promoters and other regulatory regions positively controlling gene expression → **repression of transcriptional activity**

https://doi.org/10.1093/braincomms/fcac276 BRAIN COMMUNICATIONS 2022: Page 1 of 8 | 1

BRAIN COMMUNICATIONS

Adult-onset KMT2B-related dystonia

Edoardo Monfrini,[1,2] Andrea Ciolfi,[3] Francesco Cavallieri,[4,5] Marco Ferilli,[3] Paola Soliveri,[6,7] Lucia Pedace,[8] Roberto Erro,[9] Francesca Del Sorbo,[6,7] Franco Valzania,[4] Valentina Fioravanti,[4] Giovanni Cossu,[10] Maria Pellegrini,[11] Leonardo Salviati,[12] Federica Invernizzi,[13] Valentina Oppo,[10] Daniela Murgia,[10] Bruno Giometto,[11] Marina Picillo,[9] Barbara Garavaglia,[13] Francesca Morgante,[14,15] Marco Tartaglia,[3] Miryam Carecchio[16,17,*] and Alessio Di Fonzo[2,*]



- Adult-onset focal/segmental dystonia
- Dystonic tremor
- Normal development
- Rare additional features
- Intermediate epigenetic signature (methylation profile)

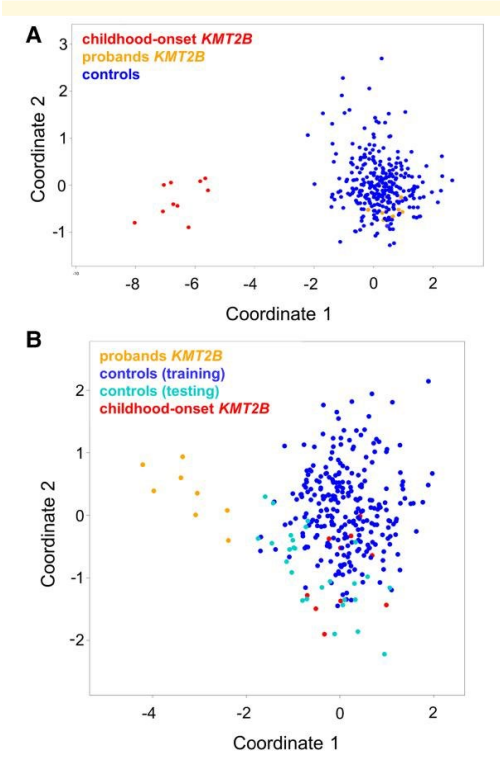
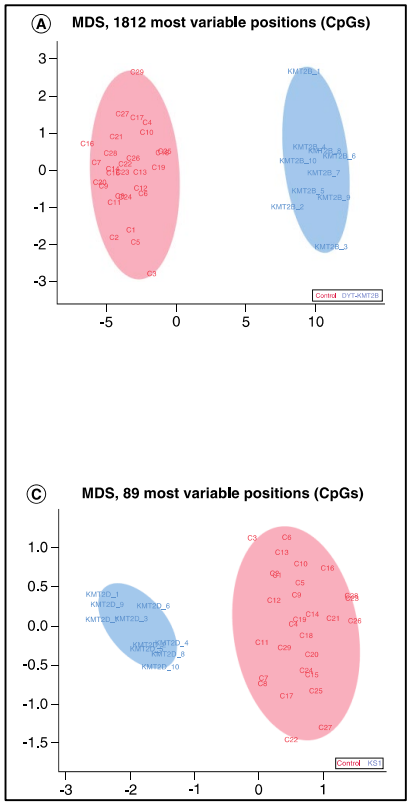


Table 1 Clinical and genetic features of KMT2B variants carriers

Family	Subject	Dystonia	Age at onset (dystonia)	Dystonia onset localization	Other localizations	Dystonic tremor	Short stature	Hearing loss	Intellectual disability	*KMT2B* variant
A	II.1	–	NA	NA	NA	–	–	+	–	c.3232C > T (p.R1078C)
A	II.4	+	69	Blepharospasm	–	–	–	–	–	c.3232C > T (p.R1078C)
A	II.5	+	62	Head	Both arms	+	–	–	–	c.3232C > T (p.R1078C)
A	II.7	–	NA	NA	NA	–	–	+	–	c.3232C > T (p.R1078C)
A	II.8	+	56	Blepharospasm	Neck	–	–	–	–	c.3232C > T (p.R1078C)
A	III.10	–	NA	NA	NA	–	–	+	–	c.3232C > T (p.R1078C)
A	III.11	+	6	Hand	–	–	–	–	–	c.3232C > T (p.R1078C)
B	I.2	–	NA	NA	NA	–	+	–	+	c.7016G > A (p.R2339Q)
B	II.3	+	19	Left arm	Larynx, left lower limb	–	–	–	–	c.7016G > A (p.R2339Q)
C	II.1	+	34	Both arms	–	+	–	–	–	c.7016G > A (p.R2339Q)
D	II.2	+	23	Larynx	Face, both arms	+	–	–	–	c.2909G > A (p.R970Q)
E	II.2	+	43	Right arm	–	–	–	–	–	c.1918T > A (p.S640T)

Comparison of methylation episignatures in *KMT2B*- and *KMT2D*-related human disorders

Sunwoo Lee[1], Eguzkine Ochoa[1], Katy Barwick[2], Laura Cif[3], Fay Rodger[1,4], France Docquier[1,4], Belén Pérez-Dueñas[2], Graeme Clark[1,4], Ezequiel Martin[1,4], Siddharth Banka[5], Manju A Kurian[2] & Eamonn R Maher*,[1]



Different methylation pattern between KMT2B dystonia and Kabuki syndrome (KMT2D)

Potential diagnostic relevance in clinical practice!

THANKS FOR YOUR ATTENTION