International Parkinson and Movement Disorder Society European Section

5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 12

EAN/MDS-ES: Hyperkinetic movement disorders (Level 2)

What's new in paediatric movement disorders

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TC 12 - EAN/MDS-ES:
Hyperkinetic movement disorders
(Level 2)
July 1st, 2019

What's new in paediatric movement disorders?

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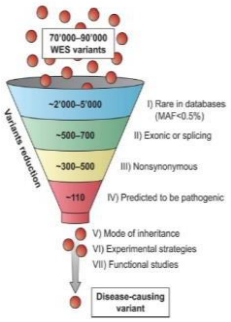
Disclosures

Nothing to disclose

Next Generation Sequencing

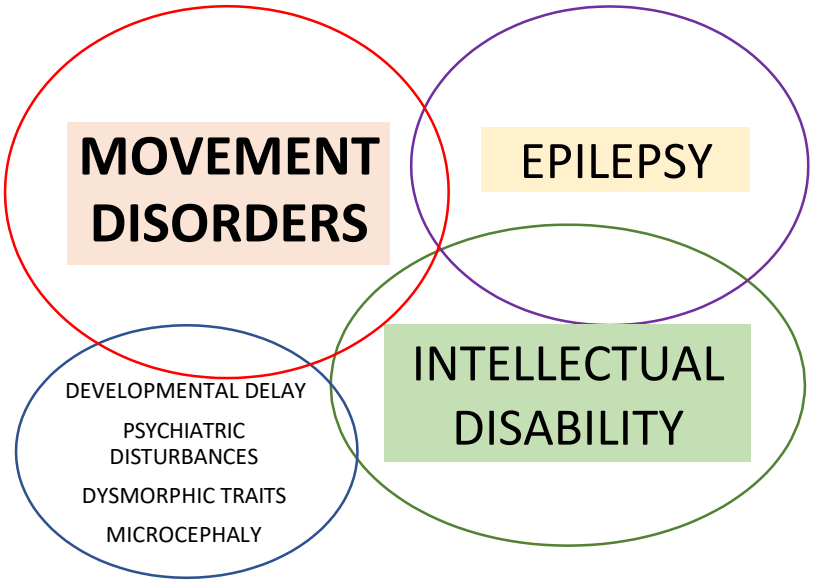
NGS refers to different sequencing technologies that allow the sequencing of a large amount of nucleic acids (DNA/RNA) sequences.

- ✓ **Whole Genome Sequencing** (WGS): sequencing of the entire human genome;
- ✓ **Whole Exome Sequencing** (WES): sequencing of the exome (~2% of the entire genome);
- ✓ **Targeted resequencing**: panels of multiple known genes linked to a specific disease/group of diseases



NGS has allowed an incredible growth in our knowledge of the genetic bases of hyperkinetic childhood-onset movement disorders

Complex hyperkinetic movement disorders



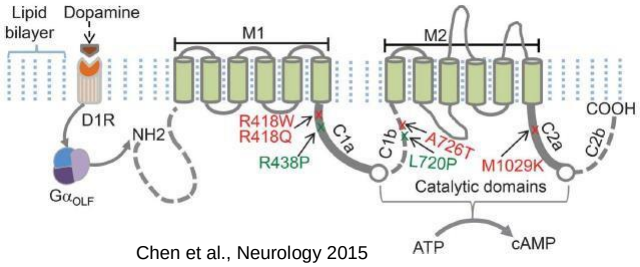
Hyperkinetic MD without epilepsy

Novel genes (2012-2019)

Gene	Gene product	Main mov. disorder
ADCY5	Adenylate cyclase 5	Chorea/dyskinesias
PDE10A	Phosphodiesterase 10A	
PDE2A (?)	Phosphodiesterase 2A	
KMT2B	Lysine-specific histone methyltransferase 2B	Dystonia
HPCA	Hippocalcin	
GNAL	Guanine nucleotide-binding protein, α_{olf} subunit	
ANO3	Anoctamin-3	
KCTD17	Potassium channel tetramerization domain-containing protein 17	Myoclonus-dystonia

What's new in pediatric chorea?

ADCY5 – Gene function



Chen et al., Neurology 2015

- ✓ ADCY5 encodes **Adenyl cyclase 5** (AC5), an enzyme converting adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP)
- ✓ AC5 activity is modulated by **dopaminergic receptors D1R** (excitatory) and **D2R** (inhibitory) via activation of the striatal stimulatory heterotrimeric G protein GαOLF
- ✓ *ADCY5* is highly expressed in **striatal Medium Spiniy Neurons** (MSNs)
- ✓ Gain of function mutations increase AC5 activity and cAMP synthesis, causing **abnormal MSNs firing**

Clinical phenotype

- ✓ AD inheritance
- ✓ **Delayed motor milestones**
- ✓ **Axial hypotonia**
- ✓ **Early-onset chorea** with perioral involvement, +/- myoclonus and dystonia
- ✓ **Episodic mov dis exacerbations**
- ✓ Dysarthric speech, myopathy-like face
- ✓ Non-progressive course
- ✓ Normal brain MRI

ADCY5 - Episodic movement disorders

- ✓ Paroxysmal dystonic/dyskinetic attacks superimposed on baseline movement disorder
- ✓ Variable duration (minutes/days) and frequency
- ✓ Triggering factors: emotions, fever, infections, sleep (either falling asleep or awakening), no triggers
- ✓ In some cases, **spontaneous improvement over disease course**
- ✓ Can be the **first disease manifestation**, preceding the onset of chronic movement disorder

Sleep-related exacerbations of movement disorders are highly suggestive of ADCY5-related dyskinesia

ADCY5: disease course

ADCY5 p.R418W

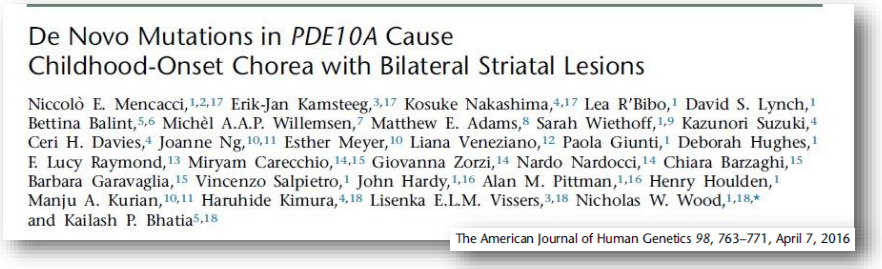
Carecchio et al., Park rel disord 2017

ADCY5: disease course

ADCY5 p.R418Q

Carecchio et al., Park rel disord 2017

PDE10A



De Novo Mutations in *PDE10A* Cause Childhood-Onset Chorea with Bilateral Striatal Lesions

Niccolò E. Mencacci,[1,2,17] Erik-Jan Kamsteeg,[3,17] Kosuke Nakashima,[4,17] Lea R'Bibo,[1] David S. Lynch,[1] Bettina Balint,[5,6] Michèl A.A.P. Willemsen,[7] Matthew E. Adams,[8] Sarah Wiethoff,[1,9] Kazunori Suzuki,[4] Ceri H. Davies,[4] Joanne Ng,[10,11] Esther Meyer,[10] Liana Veneziano,[12] Paola Giunti,[1] Deborah Hughes,[1] F. Lucy Raymond,[13] Miryam Carecchio,[14,15] Giovanna Zorzi,[14] Nardo Nardocci,[14] Chiara Barzaghi,[15] Barbara Garavaglia,[15] Vincenzo Salpietro,[1] John Hardy,[1,16] Alan M. Pittman,[1,16] Henry Houlden,[1] Manju A. Kurian,[10,11] Haruhide Kimura,[4,18] Lisenka E.L.M. Vissers,[3,18] Nicholas W. Wood,[1,18,*] and Kailash P. Bhatia[5,18]

The American Journal of Human Genetics *98*, 763–771, April 7, 2016

"…we used whole-exome sequencing to unravel the underlying genetic cause in three unrelated individuals with a very similar and unique clinical presentation of **childhood-onset chorea** and characteristic brain MRI showing symmetrical **bilateral striatal lesions**. All individuals were identified to carry **a de novo heterozygous mutation in PDE10A** (c.898T>C [p.Phe300Leu] in two individuals and c.1000T>C [p.Phe334Leu] in one individual), encoding a phosphodiesterase highly and selectively present in MSNs".

PDE10A

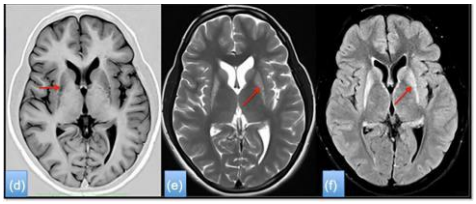
Dominant *de novo* mutations
(Mencacci *et al.*, AJHG 2016)

- ✓ Early onset (5-10 yrs) generalized chorea
- ✓ Non-progressive course
- ✓ Normally achieved motor milestones and intelligence
- ✓ T2 striatal hyperintensity
- ✓ 2 missense mutations in 3 unrelated subjects

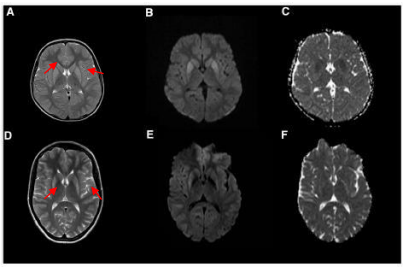
Biallelic mutations
(Diggle et al., 2016; Knopp et al., 2019)

- ✓ Generalized chorea presenting in the first months, with axial hypotonia
- ✓ Delayed motor and language milestones
- ✓ Normal brain MRI
- ✓ 10 subjects from 3 consanguineous families
- ✓ Response to Levodopa in 3 cases

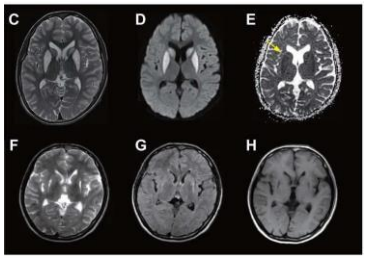
PDE10A



Narayanan et al., AJHG 2017



Mencacci et al., AJHG 2016



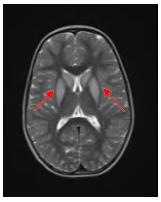
Miyatake et al., MDJ 2018

Age 15

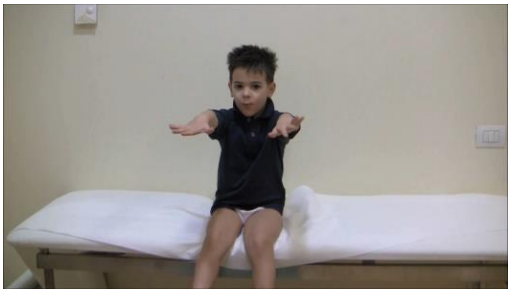
Age 43

- ✓ Bilateral striatal lesions
- ✓ «Swallen» putamen in early stages
- ✓ Atrophic putamen in adulthood

Early-onset non progressive chorea + bilateral striatal lesions



Patient's brain MRI



PDE10A c.1000T>C (p.Phe334Leu), *de novo*

LETTERS: NEW OBSERVATIONS

A *PDE10A* De Novo Mutation Causes Childhood-Onset Chorea With Diurnal Fluctuations

Silvia Esposito, MD, PhD,[1] Miryam Carecchio, MD,[1,2,3] Davide Tonduti, MD, PhD,[1] Veronica Saletti, MD,[1] Celeste Panteghini, MSc,[2] Luisa Chiapparini, MD,[4] Giovanna Zorzi, MD,[1] Chiara Pantaleoni, MD,[1] Barbara Garavaglia, PhD,[2] Dimitri Krainc, MD, PhD,[5] Steven J. Lubbe, PhD,[5] Nardo Nardocci, MD,[1]* Niccolò E. Mencacci, MD, PhD[5]

Movement Disorders, Vol. 32, No. 11, 2017

PDE2A

A Homozygous *Loss-of-Function* Mutation in *PDE2A* Associated to Early-Onset Hereditary Chorea

Salpietro et al., MDJ 2018

- **Generalized dystonic/choreic attacks** at age 2 years (up to 100/day; few seconds)
- Triggers: emotions, sudden or purposeful movements
- No loss of consciousness, no EEG correlates
- At age 9 **chronic slowly-progressive generalized chorea** + dystonia
- **Intellectual disability**
- Language delay
- **Normal brain MRI**
- Improvement with pallidal DBS

What's new in childhood-onset dystonia?

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;

Main clinical features: dystonia

- **Childhod-onset** (mean AAO: 6 years)
- Dystonia features: **Lower limb** onset: 78.5%
  Laryngeal dystonia: 78.5%
  Generalization: 93%
  Oromandibular dystonia: 57%
  Anarthria: 28.5%
  Severe axial dystonia
  Extreme «torsional» dystonic pattern
- Very good response to DBS in the long term
- *De novo* mutations in most cases; incomplete penetrance in some adults

Carecchio *et al*., MDJ 2019, *in press*

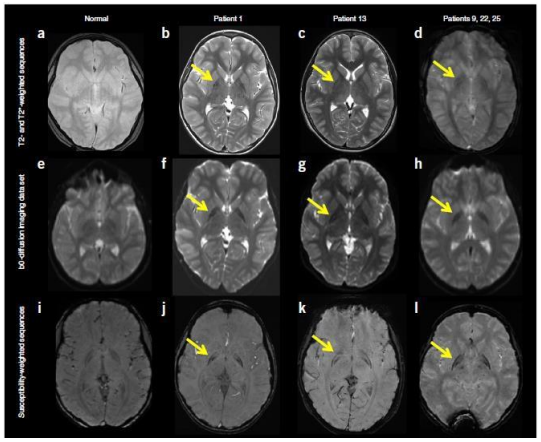
Additional clinical features

- **Microcephaly**
- **Short stature** with somatic harmonic development: **64%**
- **Mild intellectual disability** - low range of intelligence: **70%**
- **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%

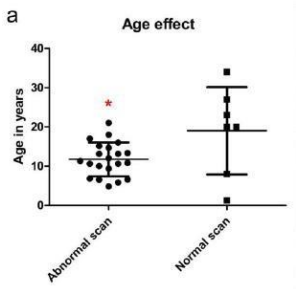
- Psychiatric disturbances
- Developmental delay
- Cutis aplasia
- Epilepsy

Meyer et al., 2017; Zech et al., 2016; Carecchio et al., 2019

Radiological features



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

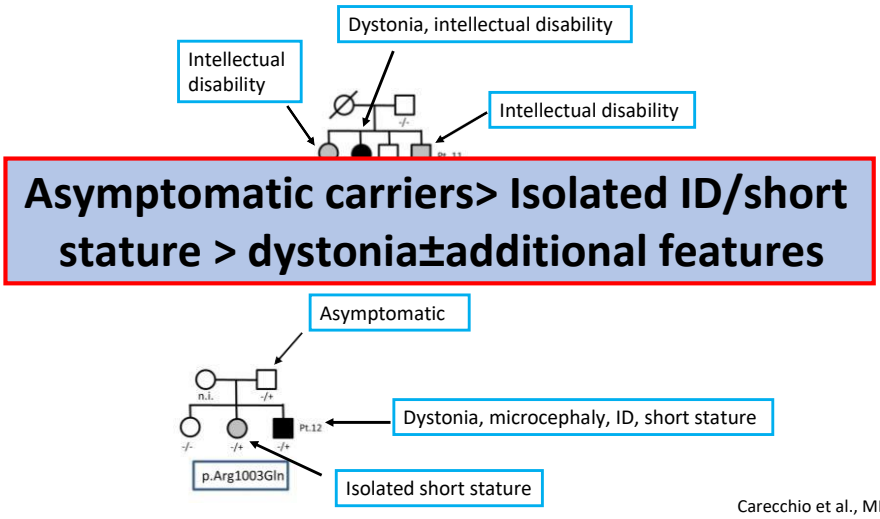


Mean age at MRI 11.7 yrs 19 yrs

Age-dependent effect?

Meyer et al., 2017

Intra-familial phenotypic variability



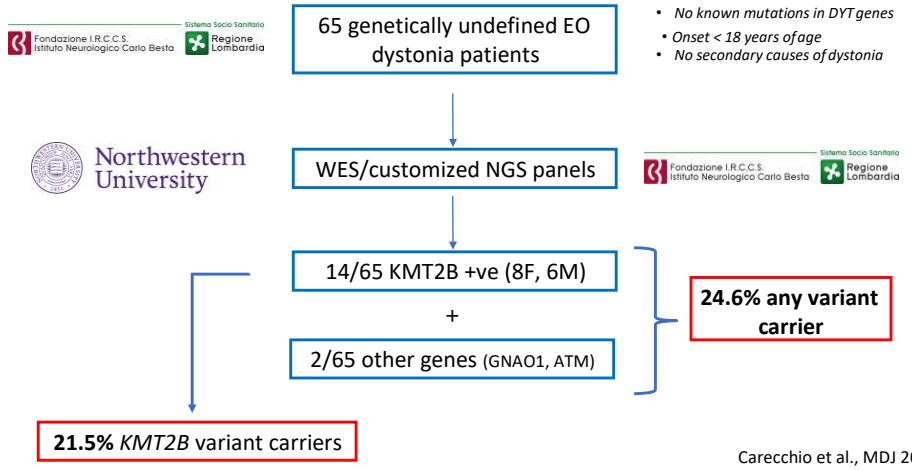
Carecchio et al., MDJ 2019

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*]

What is the frequency of *KMT2B* mutations in childhood-onset dystonia?



Carecchio et al., MDJ 2019

Red flags

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

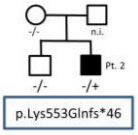
Childhood-onset dystonia
+
Short stature
Mild-to-moderate ID

KMT2B: severe axial dystonia

Extremely mobile dystonia with severe torsional component

Carecchio et al., under review

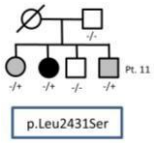
KMT2B: disease history without DBS



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

Carecchio et al., MDJ 2019

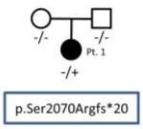
KMT2B: disease history without DBS

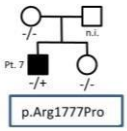


AAO: 10 years (lower limbs)
Disease duration: 42 years
Anarthria, severe generalized dystonia

Carecchio et al., MDJ 2019

DBS outcome





What's new in pediatric movement disorders and epilepsy?

Hyperkinetic MD with epilepsy/ID

(«Epileptic-dyskinetic encephalopathies»)

Gene	Gene product	Movement disorder
FOXG1	Forkhead Box G1	
GNAO1	Gαo subunit of GPCR	
GRIN1	GluN1 subunit of NMDAR	Chorea/ Dyskinesias/ Dystonia/ Status dystonicus
FRRS1L	Ferric Chelate Reductase 1-like	
GPR88	G protein-coupled receptor 88	
ARX	Aristaless-related homeobox protein	
STXBP1	Syntaxin-binding protein 1	
UNC13A	Unc-13 homolog A	
CACNA1E	α_1 subunit of $Ca_v2.3$ channel	
ATP6V1A	A subunit of v-ATPase	
PCHD12	Protocadherin-12	
….		
ATP1A3	Na+/K+ ATPase, α3 subunit	Dystonia/parkinsonism/ataxia

FOXG1

FOXG1 Is Responsible for the Congenital Variant of Rett Syndrome

Francesca Ariani,[1] Giuseppe Hayek,[2] Dalila Rondinella,[1] Rosangela Artuso,[1] Maria Antonietta Mencarelli,[1] Ariele Spanhol-Rosseto,[1] Marzia Pollazzon,[1] Sabrina Buoni,[2] Ottavia Spiga,[3] Sara Ricciardi,[4] Ilaria Meloni,[1] Ilaria Longo,[1] Francesca Mari,[1] Vania Broccoli,[4] Michele Zappella,[2] and Alessandra Renieri[1,*]

- ✓ Primary (congenital) or secondary (postnatal) microcephaly
- ✓ Severe intellectual disability with absent speech
- ✓ Epilepsy
- ✓ Brain MRI: hypogenesis of corpus callosum, simplified gyral pattern, reduced white matter volume in the frontal lobes, frontal pachygyria

FOXG1-associated movement disorders

- ☑ **Cardinal feature of FOXG1-syndrome**
- ☐ Onset in the first year of life
- ☐ Complex hyperkinetic MD: **chorea** (88%), **oro-facial dyskinesia** (80%), **dystonia** (76%), myoclonus, hand stereotypies
- ☐ **Progressive course**
- ☐ Marked disability
- ☐ Levodopa, tetrabenazine and pimozide partially beneficial in single cases

- ✓ Trunkating mutations in the N-terminal → severe phenotype
- ✓ Missense mutations in the conserved site 1 → milder phenotypes, independent ambulation, spoken language, normal head growth, and ability to use hands

Papandreou et al., 2016; Mitter et al., 2017

[redacted]

[redacted]

Cellini et al., 2015

GNAO1

ARTICLE

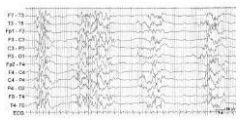
De Novo Mutations in *GNAO1*, Encoding a $G\alpha_o$ Subunit of Heterotrimeric G Proteins, Cause Epileptic Encephalopathy **2013**

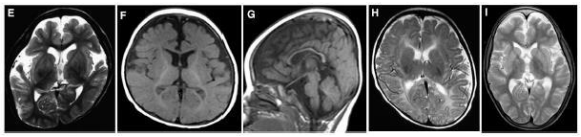
Kazuyuki Nakamura,[1,2,9] Hirofumi Kodera,[1,9] Tenpei Akita,[3,9] Masaaki Shiina,[4] Mitsuhiro Kato,[2]

4 *de novo* mutations in 4 unrelated subjects with **Ohtahara Syndrome**

- ✓ Early onset drug-resistent (first months) tonic seizures
- ✓ Severe motor delay and ID
- ✓ Burst-suppression pattern on EEG
- ✓ Brain MRI: cerebral atrophy, thin corpus callosum, delayed myelination

2 patients → hyperkinetic movement disorders (dystonia/chorea)





GNAO1

Phenotypic spectrum of *GNAO1* variants: epileptic encephalopathy to involuntary movements with severe developmental delay 2016

Hirotomo Saitsu[*,1], Ryoko Fukai[1,2], Bruria Ben-Zeev[3,4], Yasunari Sakai[5], Masakazu Mimaki[6], Nobuhiko Okamoto[7], Yasuhiro Suzuki[8], Yukifumi Monden[9], Hiroshi Saito[9], Barak Tziperman[3], Michiko Torio[5], Satoshi Akamine[5], [10], Yoshinori Tsurusaki[1], Naomichi Matsumoto[*,1]

Recurrent *GNAO1* Mutations Associated With Developmental Delay and a Movement Disorder 2016

Leonie A. Menke, MD, PhD[1], Marc Engelen, MD, PhD[2],

Expanding Phenotype of De Novo Mutations in *GNAO1*: Four New Cases and Review of Literature 2017

David C. Schorling[1] Tobias Dietel[2] Christina Evers[3] Katrin Hinderhofer[3] Rudolf Korinthenberg[1] Daniel Ezzo[4] Carsten G. Bönnemann[4] Janbernd Kirschner[1]

Movement disorder in *GNAO1* encephalopathy associated with gain-of-function mutations 2017

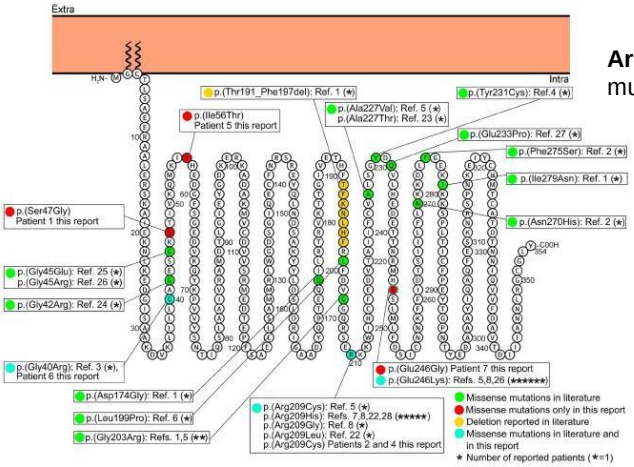
Huijie Feng, BS*
Benita Sjögren, PhD*
Behirda Karaj, MS
Vincent Shaw, BS
Aysegul Gezer, BS
Richard R. Neubig, MD, PhD

GNAO1-associated movement disorders

- **Generalized chorea/dyskinesia + dystonia**
- Facial and **oro-lingual dyskinesia** and complex stereotypies
- **Onset:** first months or years of life, median age **2 years**
- **Chronic course**

- **Episodic MD exacerbations/recurrent status dystonicus**
  - Triggers: fever, infections, emotions, purposeful movements
  - Duration: minutes to days-months
  - Marked **dysautonomic manifestations** (flushing, sweating, tachycardia, hypertermia, diaphoresis)
  - Pallidal DBS interrupts status dystonicus, modest benefit on chronic MD

Danti et al., 2017



Arg209 and **Glu246**: mutational hot spots

Danti et al., 2017

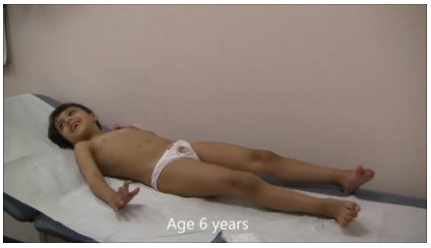
GENOTYPE-PHENOTYPE CORRELATION

- LOF GNAO1 mutations → epileptic encephalopathy (Ohtahara syndrome)
- GOF or normally-functioning alleles → hyperkinetic movement disorder without epilepsy

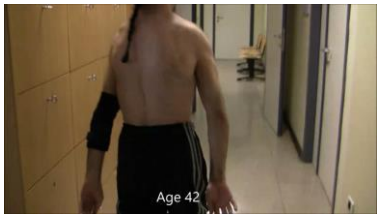
Feng et al., 2017

GNAO1: the complexity of phenomenology

GNAO1 p.Glu246Lys (*De novo*)



GNAO1 p.Arg209Cys (*De novo*)



GNAO1 p.Cys215Tyr (*De novo*)

GNAO1 p.Glu246Lys (*De novo*)

Emerging molecular pathways in complex hyperkinetic MD

Disruption of G-Protein-cAMP pathway → ADCY5, PDE10A, PDE2A, GNAL, GPR88, GNAO1

Altered/increased glutamatergic transmission → FRRS1L, GRIN1

Altered gene transcription in early developmental stages → KMT2B, FOXG1, ARX

Altered neurotransmitter release at synapses → SYT1, UNCH13

Altered Ca++ signalling/currents → HPCA, ANO-3, GNAO1, CACNA1E