European Commission
Directorate-General for Health and Food Safety (DG SANTE)

ITHACA

ITHACA Board Meeting

2020 December 10 – 12

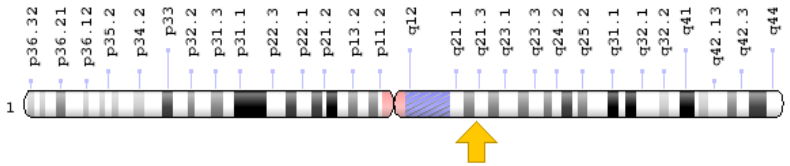
Satellite Meetings : Friday Dec. 11th

WG 7 Research

From 9 to 10:50 AM

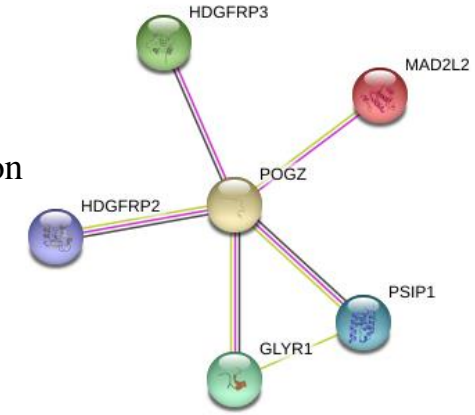
European Reference Networks

POGO TRANSPOSABLE ELEMENT WITH ZNF DOMAIN; *POGZ* (*614787)



→ heterochromatin formation and chromosomal segregation
<u>mitotic progression</u>

→ transcriptional regulator in functional <u>neuronal network</u>



616364

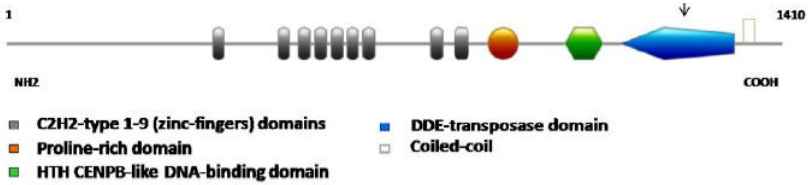
WHITE-SUTTON SYNDROME; WHSUS

Alternative titles; symbols

MENTAL RETARDATION, AUTOSOMAL DOMINANT 37; MRD37

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
1q21.3	White-Sutton syndrome	616364	AD	3	POGZ	614787



Deciphering Developmental Disorders Study.
Large-scale discovery of novel genetic causes of developmental disorders. Nature 519: 223-228, 2015.

Stessman, H. A. F., Willemsen, M. H., Fenckova, M., Penn, O., Hoischen, A., Xiong, B., Wang, T., Hoekzema, K., Vives, L., Vogel, I., Brunner, H. G., van der Burgt, I., and 39 others.
Disruption of POGZ is associated with intellectual disability and autism spectrum disorders. Am. J. Hum. Genet. 98: 541-552, 2016.

Tan, B., Zou, Y., Zhang, Y., Zhang, R., Ou, J., Shen, Y., Zhao, J., Luo, X., Guo, J., Zeng, L., Hu, Y., Zheng, Y., Pan, Q., Liang, D., Wu, L.
A novel de novo POGZ mutation in a patient with intellectual disability. J. Hum. Genet. 61: 357-359, 2016.

White, J., Beck, C. R., Harel, T., Posey, J. E., Jhangiani, S. N., Tang, S., Farwell, K. D., Powis, Z., Mendelsohn, N. J., Baker, J. A., Pollack, L., Mason, K. J., and 19 others.
POGZ truncating alleles cause syndromic intellectual disability. Genome Med. 8: 3, 2016. Note: Electronic Article.

European Reference Network
for rare or low prevalence complex diseases
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Dr Agnese Feresin
POGZ patients

IRCCS Burlo Garofolo, **Trieste**

AUSL Genetica Medica, **Reggio Emilia**
Ospedale Pediatrico Bambino Gesù, **Roma**

Ospedale San Camillo-Forlanini, **Roma**

Ospedale Pediatrico Bambino Gesù, **Roma**

Azienda Ospedaliera San Pio, **Benevento**

IRCCS Oasi Maria SS, **Troina**

Neurodevelopmental disorder

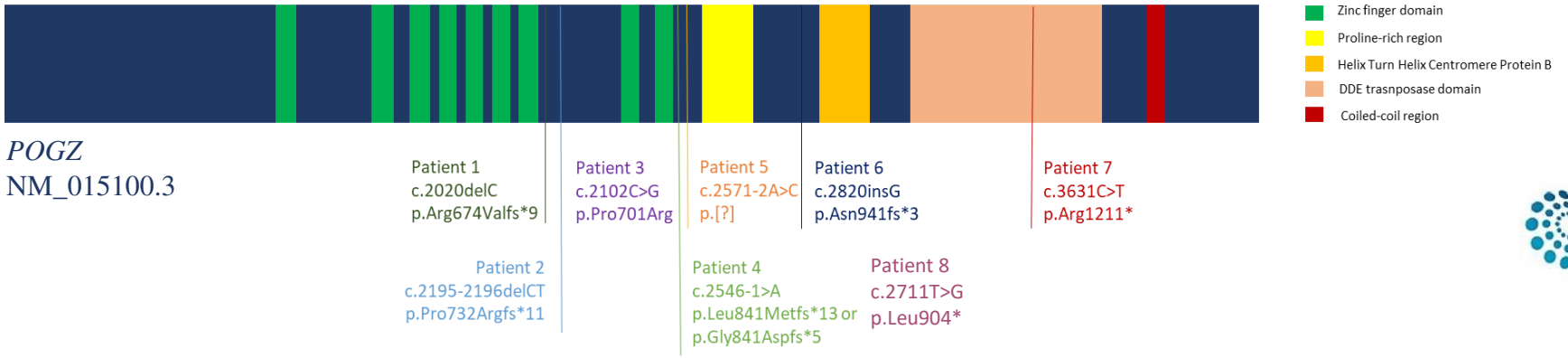
+

Neurological and other clinical manifestation

+

Facial features

- Chromosomal Microarray Analysis: **normal**
- Whole Exome Sequencing Analysis: **likely pathogenic / pathogenic *POGZ* variant**



European Reference Network
for rare or low prevalence complex diseases
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

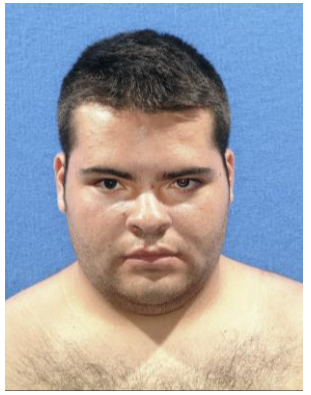
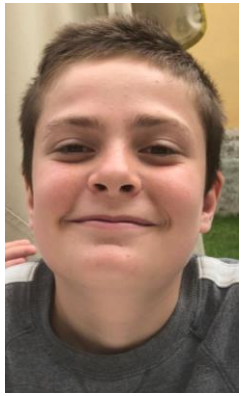
Dr Agnese Feresin
POGZ patients: clinical features

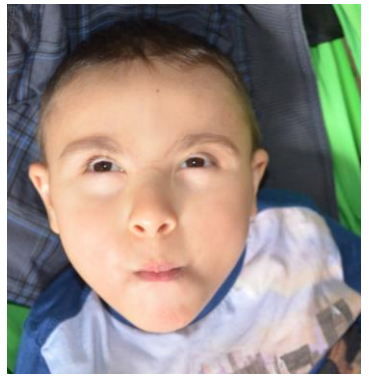
	Patient 1 c.2020delC p.Arg674Valfs*9	*Patient 2* c.2195-2196delCT p.Pro732Argfs*11	*Patient 3* c.2102C>G p.Pro701Arg	*Patient 4* c.2546-1>A p.Leu841Metfs*13 or p.Gly841Aspfs*5	*Patient 5* c.2571-2A>C p.[?]	*Patient 6* c.2820insG p.Asn941fs*	*Patient 7* c.3631C>T p.Arg1211*	*Patient 8* c.3631C>T p.Arg1211*	**Total**
Intellectual disability	Mild	Mild	Mild	Mild	Severe	Severe	Mild	Severe	**8/8**
Global developmental delay	+	+	+	+	+	+	+	+	**8/8**
Autism spectrum disorder	-	-	-	-	+	+	+	+	**4/8**
Other behavioural concern	Obsessive-compulsive disorder	-	Unspecified emotional disorder, anxiety, ADHD, hyperphagia	-	Stereotypies, hyperactivity, no ocular contact	Poor eye contact, stereotypic movement	Unspecified, various neurobehavioral anomalies	Absence of speech, autistic features	**6/8**
Seizures	-	-	-	-	-	+	-	+	**2/8**
Neurologic finding	-	-	High pain threshold, Sleep disorder	Hypotonia, synchronous movements, dystonia	Hypertonia, Clumsiness	Waddling gait with externally rotated feet	Hypotonia, motor coordination problems, High pain tolerance Severe sleep disorder	Hypotonia, Seizures, Clumsiness	**6/8**
Eye abnormality	Variable exophoria extropia	Right hyperopia and amblyopia	-	-	Strabismus, myopia	-	Astigmatism	-	**4/8**
Hearing loss	-	-	-	Bilateral, sensorineural, mild	-	Unilateral, profound	Absent cocleo-stapedial reflexes	Sensorineural, bilateral	**4/8**
Gastrointestinal involvement	-	-	Cyclic vomit	-	Swallowing, constipation, feeding difficulties	Constipation, gastroesophageal reflux	Dysphagia, feeding difficulties, hepatomegaly	Feeding difficulties	**5/8**
Genitourinary involvement	-	-	-	-	Undescended testes	Olygoamenorrhea	-	-	**2/8**
Cardiac involvement	-	-	-	Patent foramen ovale and ductus arteriosus	Atrial septal defect, aortic coarctation, ventricular septal defect	Atrial septal defect closed spontaneously	Aortic bicuspid valve with mild ascending aorta dilatation	Patent foramen ovale	**5/8**
Brain imaging (MRI)	-	Above and subtentorial gliotic foci	-	Blake's pouch cyst, reduction of supratentorial white matter, square ventricles and hippocampal malrotation	Dilated lateral ventricles, cerebellar vermis hypoplasia	Cerebellar atrophy, thin corpus callosum, abnormally simplified gyral pattern, mild brainstem hypoplasia	Partial hypoplasia of cerebellar vermis, wide communication between the IV ventricle and pericerebellar fluid spaces	Cerebral atrophy and slightly thinned aspect of the anterior part of the corpus callosum.	**6/8**
Other	-	Post-natal obesity	-	Bilateral adducted thumb	-	Vitiligo	Diastasis recti, drooling	-	

European Reference Network
for rare or low prevalence complex diseases
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Dr Agnese Feresin
POGZ patients: phenotypic features

Facial features		Body features	
Midface		Head	
Midface hypoplasia	2/8	High, broad forehead	5/8
Prognathisms	3/8	Brachicephaly	2/8
Eyes		Hands	
Sparse eyebrows	3/8	Brachydactyly	1/8
Hypertelorism	2/8	Clinodactyly	1/8
Upslanting palpebral fissures	1/8		
Nose		Skeleton	
Broad nasal root	6/8	Large toes	4/8
Flat nasal bridge	4/8	Pes planus	3/8
Anteverted nares	1/8		
Ears		Growth	
Small ears	2/8	Overweight	3/8
Thick elices	2/8	Height (10-90°centile)	3/8
Mouth		Other	
Tented	3/8	Clubfoot	1/8
Smooth philtrum	3/8	Kiphosis	1/8
Thick upper lip	3/8	Congenital thumb adduction	1/8

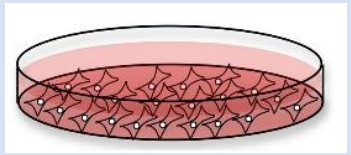






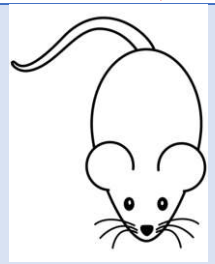
European Reference Network
for rare or low prevalence complex diseases
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Dr Agnese Feresin
Perspectives for POGZ related conditions

Pathogenetic variant of *POGZ* is responsible on neurodevelopmental disorder, physical features and clinical manifestations



Definition of **pathogenic mechanisms of damaging variants in POGZ**: alteration of chromatin remodeling, neuronal proliferation and synaptic function



Knock-in mice show abnormally **elevated activation of excitatory neurons** resulting in impaired neuronal development, social deficit and altered behavioral performances

Elucidation of the improving role of **inhibition of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated synaptic transmission** in POGZ-dysregulated neural activity

Administration of an orally active, selective, non-competitive AMPA receptor agonist, to candidate POGZ patients to evaluate the **neurophysiologic response.**


nature COMMUNICATIONS

ARTICLE

OPEN

Pathogenic POGZ mutation causes impaired cortical development and reversible autism-like phenotypes

Kensuke Matsumura et al.

...Let's join!

European Reference Network
for rare or low prevalence complex diseases

Network Intellectual Disability and Congenital Malformations (ERN ITHACA)