QUIZZ

ID/ASD and OVERGROWTH

ITHACA

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Overgrowth-intellectual disability (OGID)

- **Definition**: increased height and/or head circumference ≥2SD , various degrees of intellectual disability
- Heterogeneous condition
- ***NSD1*** responsible for 34%

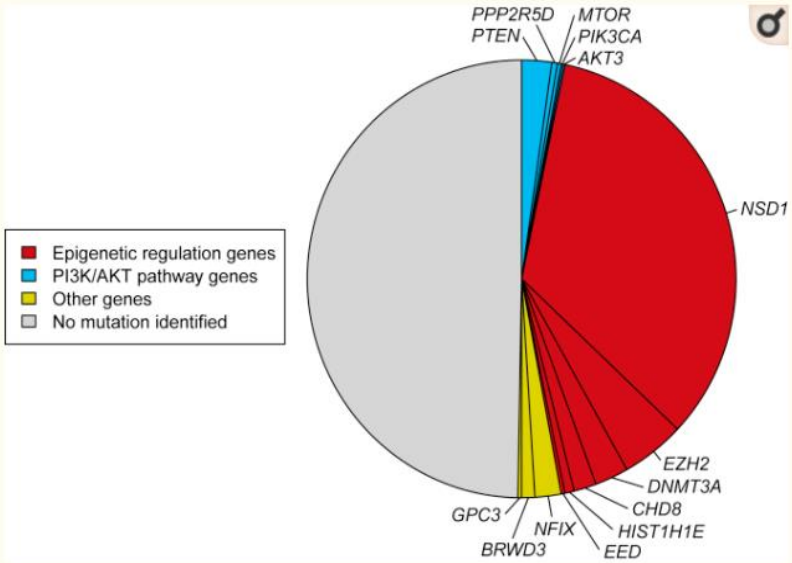

Figure 1

Causal Mutation Identified in 50% of OGID Probands

Proportion of pathogenic mutations identified in 710 individuals with OGID. Epigenetic regulation genes (red), including *NSD1* which is the predominant gene, constitute the major gene set. PI3K/AKT pathway genes (blue) also significantly contribute to OGID.

Tatton-Brown et al. *Am J Hum Genetic 2017; 100,725-736*

NSD1: Sotos syndrome
PTEN: Macrocephaly/autism syndrome
PPP2R5D: Mental retardation, aut.dom.35
MTOR: Kingsmore syndrome
PIK3CA/AKT:Megalencephaly-capillary malformation-polymicrogyria syndrome, CLOVE syndrome
EZH2:Weaver syndrome
DNMT3A:Tatton-Brown syndrome
CHD8: Susceptibility to autism, 18 (+ **CHD3, CHD4**)
HIST1H1E: Rahman syndrome
EED: Cohen-Gibson syndrome
NFIX: Malan syndrome (+ **NFIA, NFIB**)
BRWD3: Mental retardation, X-linked 93
GPC3: Simpson-Golabi-Behmel syndrome

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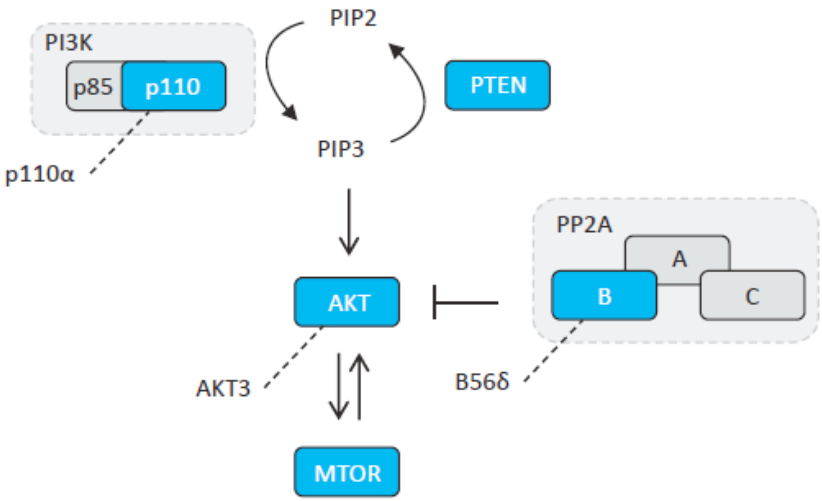
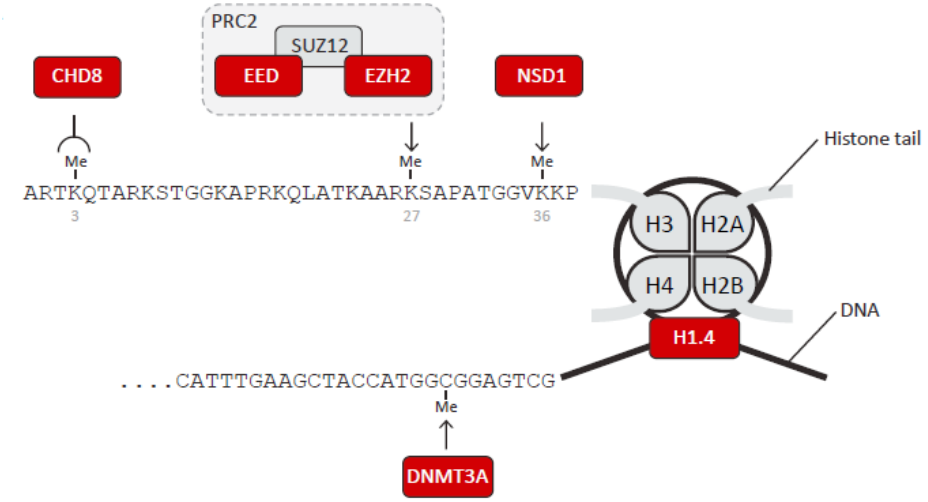
Biological Processes impacted in OGID





PI3K/AKT pathway

The PI3K/AKT pathway positively regulates growth.

- OGID mutations in *AKT3, MTOR, and PIK3CA* are **activating**
- OGID mutations in *PTEN* and *PPP2R5D* are **inactivating**

Epigenetic regulation

- *NSD1, EED, EZH2, SUZ12)* directly methylate specific histone tail lysine residues.
- *DNMT3A* is a DNA methyltransferase
- *CHD8* is a chromatin remodeling complex protein that binds methylated lysine 4 of histone H3. H1.4 (encoded by *HIST1H1E*) stabilizes chromatin structures.

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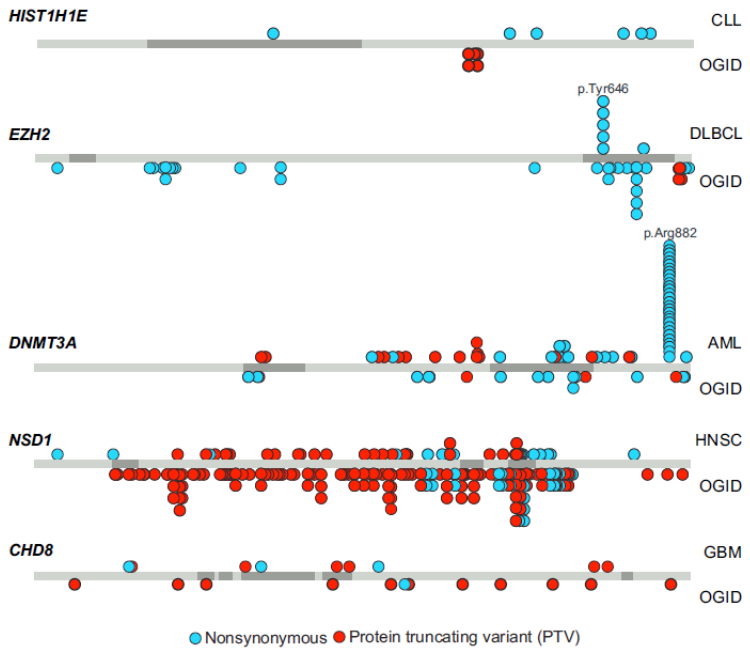
Overgrowth and increased risk of cancer

- Some genes involved in OGID are somatically mutated in various cancers (NSD1, EZH2, DNMT3A, PTEN, CHD8, HIST1H1E, MTOR, PIK3CA)
  - For the PI3K/AKT pathway genes, the mutation spectra are similar in OGID and cancer
  - For the epigenetic regulation genes, the mutation spectra in OGID and cancer have distinctive differences



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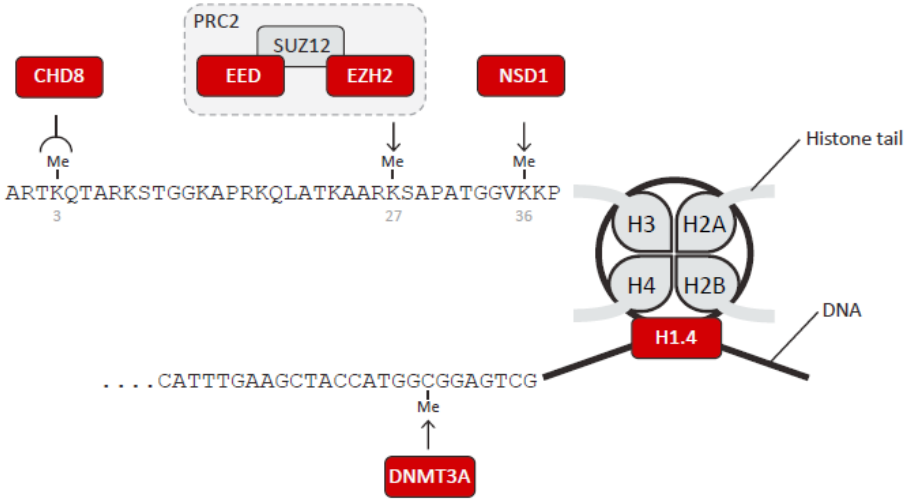

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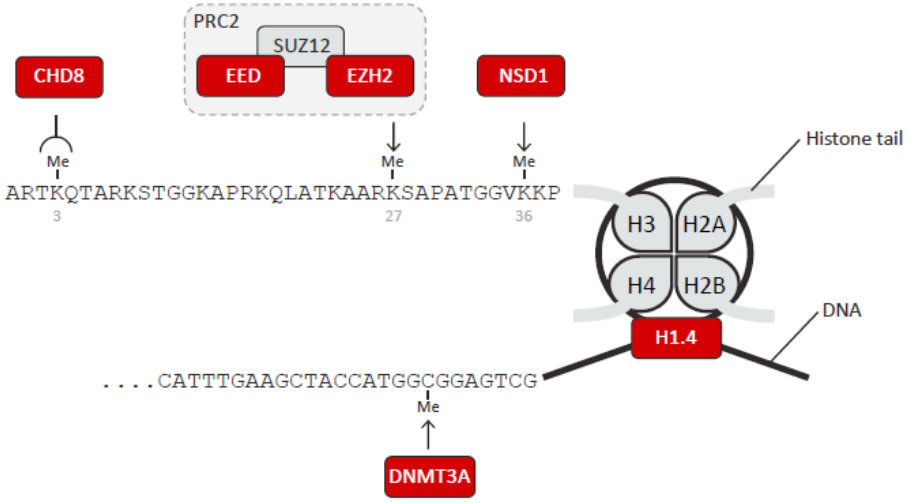
Sotos syndrome (NSD1)

- Macrosomia: H and HC >P90 (infancy / childhood), advanced bone age
- Dysmorphism: dolicocephaly, high forehead, downslanting palpebral fissures, pointed chin (more prominent with age)
- Hypotonia
- Learning difficulties: wide variability (borderline > moderate ID). Expressive speech delay. Attention deficiency.
- Malformations : heart (20%), brain (20%), kidney (15%), scoliosis (30%)
- Tumoral risk (3.5%): teratoma, neuroblastoma, leukemia

(Tatton-Brown et al, *Am J Med Genet* 2013)

Incidence:1/14000



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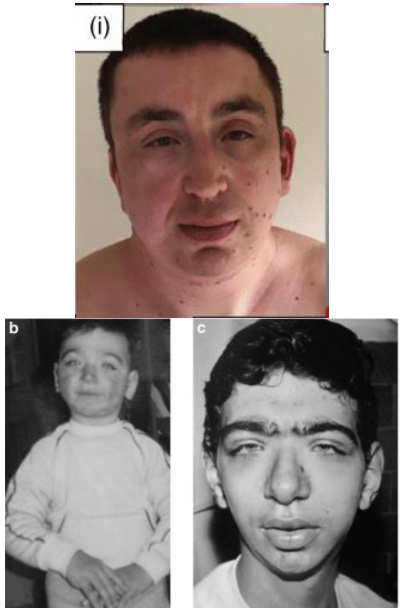
Polycomb repressive complex 2 (PCR2)

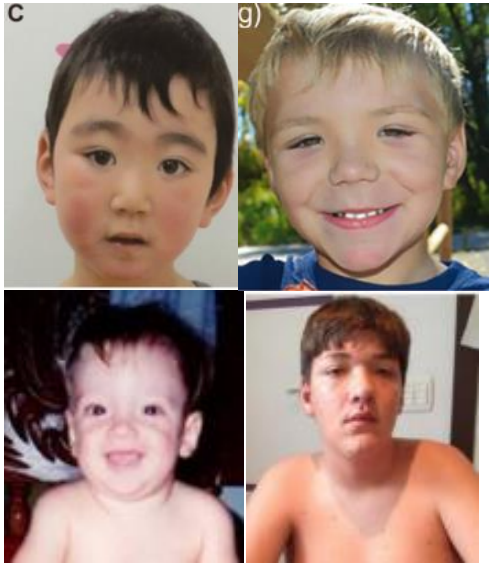
epigenetic “writer” with H3K27 methyltransferase activity

EZH2:
Weaver syndrome

EED:
Cohen-Gibson syndrome



SUZ12:
Imagawa syndrome



- De novo/autosomal dominant loss-of-function mutations
- Overgrowth, macrocephaly, advanced bone age
- Distinctive features (hypertelorism, telecanthus, large and low-set ears, micrognathia)
- Skeletal features (camptodactyly, large thumbs)
- Hypertonia
- Developmental delay, variable intellectual disability

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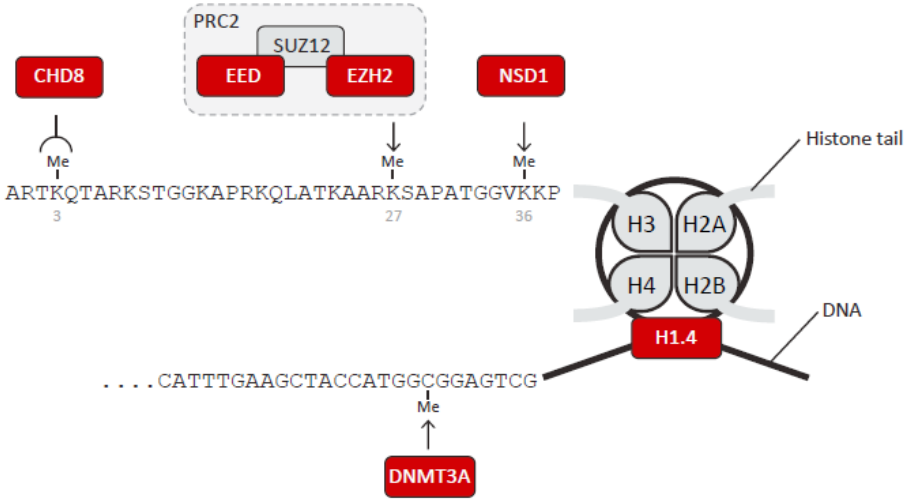

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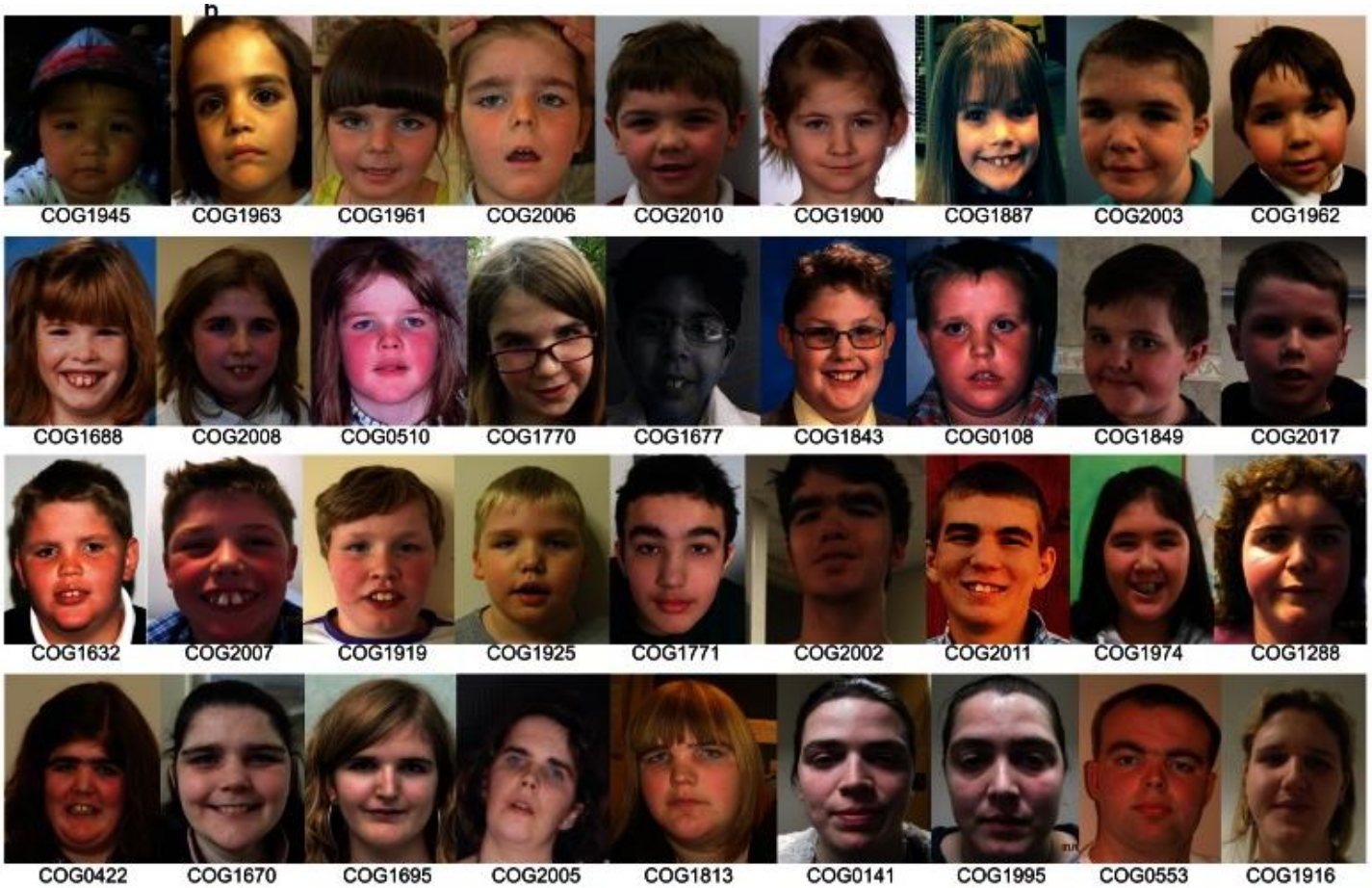
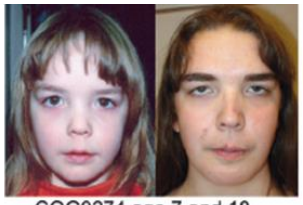
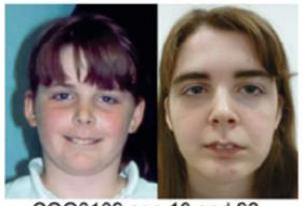
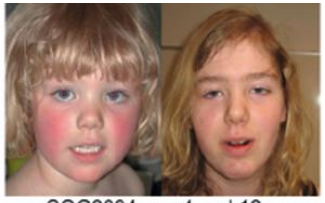
DNMT3A: Tatton-Brown syndrome

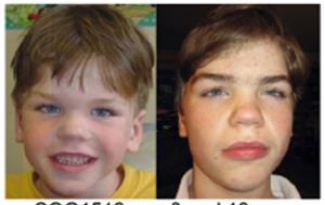
DNA methyltransferase, crucial for the establishment of new methylation marks during early embryogenesis




COG0274 age 7 and 18


COG0109 age 10 and 22


COG2004 age 4 and 12


COG1512 age 8 and 13

- Overgrowth (>80%)
- Intellectual disability (>80%): mild 18%, moderate 65%, severe 16%
- Distinctive features (low-set heavy horizontal eyebrows, prominent upper central incisors)
- Hypotonia (54%), Joint hypermoblity (74%), Obesity (67%)
- Psychiatric issues, ASD (54%)
- Kyphoscoliosis (33%)

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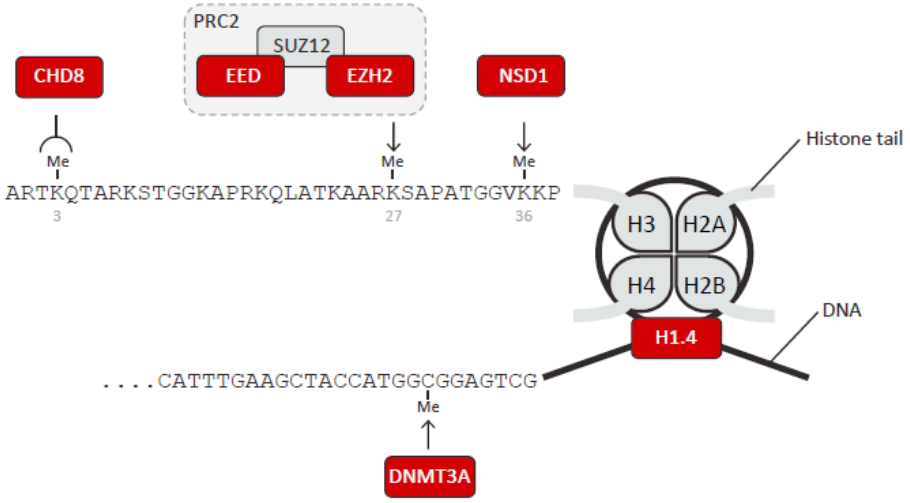

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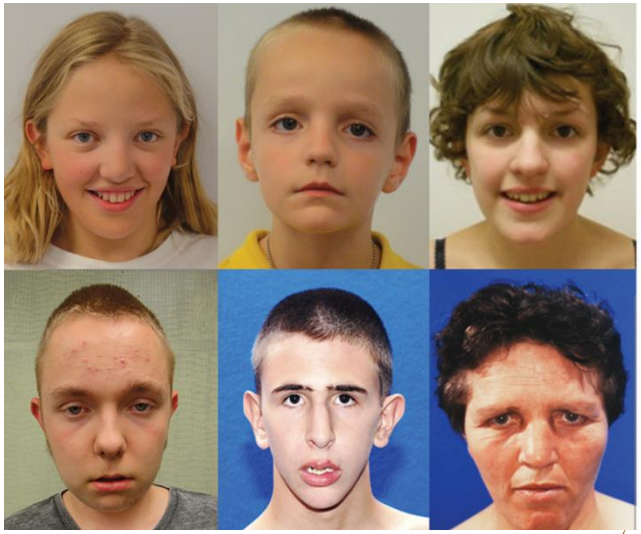
CHD8: Susceptibility to autism, 18

Chromodomain helicase DNA-binding protein 8
ATPdependent chromatin remodelling factor

Ostrowski et Al, Am J Med Genet 2019

- Loss-of-function mutations
- Mild-severe developmental delay/intellectual disability (81%)
- Overgrowth (47%), macrocephaly (63%)
- **Autism spectrum disorder (84%)**
- Sleep disorders (50%)
- Gastrointestinal troubles (40%)
- Severe speech disorder or language regression (37%)
- Epilepsy (27%)
- Hypotonia (27%)



Bernier et Al, Cell. Author manuscript; available in PMC 2015 July 17.

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Phenotypes related to « CHD » mutations

Phenotypes	CHD3 (n=37)	CHD4 (n=32)	CHD1 (n=5)	CHD8 (n=27)
Developmental delay/ Intellectual disability	100%	90%	100%	60-80%
Speech delay	100%	95%	80%	90%
Hypotonia	75%	75%	100%	27%
Macrocephaly	60%	40%	40%	80%
Autism Spectrum Disorder	30%	<1%	60%	90%
Stature	NA	Short: 50%	Short: 40%	Tall : 50%
Facial dysmorphism: Hypertelorism, periorbitar fullness, high/prominent forehead				
Other	▪ Vision problems: 30% ▪ Neonatal feeding prob.: 30% ▪ Hyperlaxity: 40% ▪ Cryptorchidism: 35%	▪ Hearing loss : 55% ▪ Heart defect: 65% ▪ Hyperlaxity: 60% ▪ Cryptorchidism: 40%	▪ Seizures: 80% ▪ Immune anomalies: 40% ▪ Translucent skin: 40%	▪ Gastro-intestinal disorders: 65% ▪ Sleep disorders: 50%
Mutations	Missense (clustering around the ATP-ase binding domain)	Missense (clustering around the ATP-ase binding domain)	Missense	Truncating (all along the protein)

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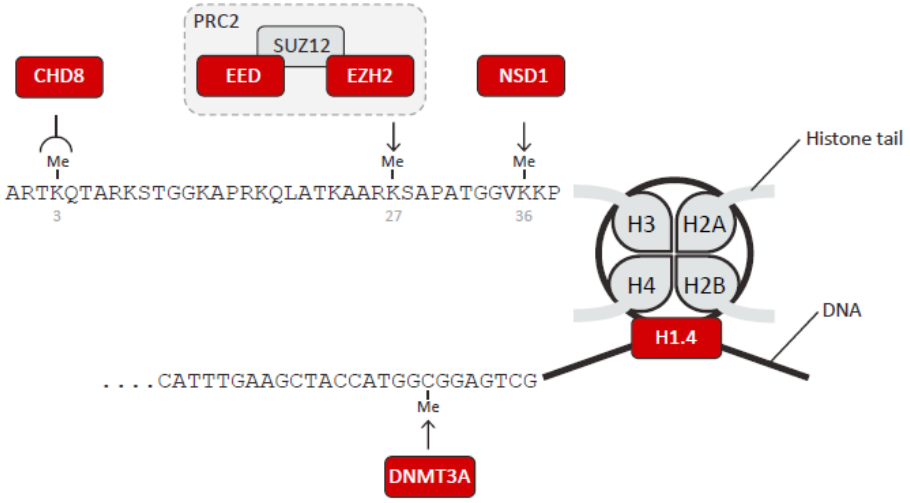

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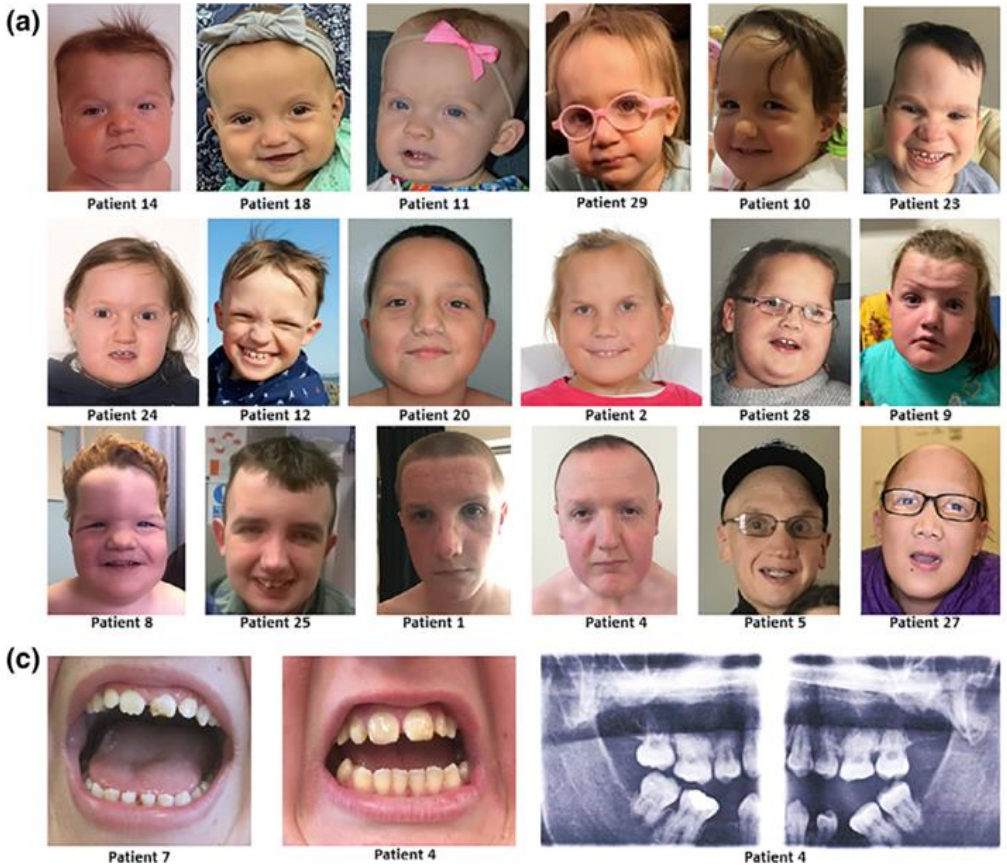
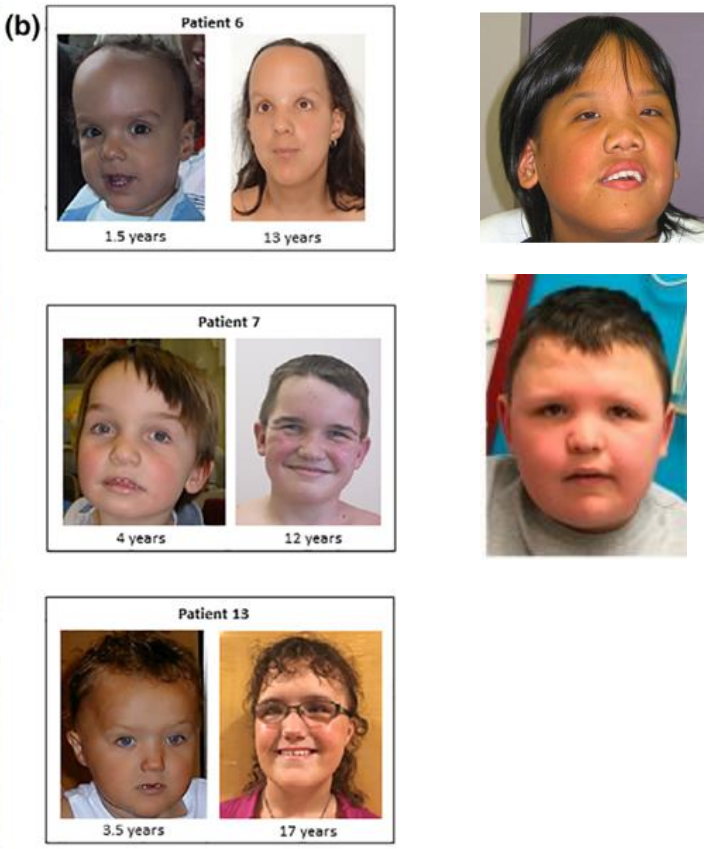
HIST1H1E: Rahman syndrome

Encodes for Histone H1.4





Burkardt DD. et Al, Am J Med Genet 2019

- Mild to severe developmental delay/intellectual disability
- Facial gestalt (full cheeks, high hairline, telecanthus)
- Variable somatic overgrowth in infancy, advanced bone age
- Aging appearance
- Hypothyroidism
- Abnormal dentition
- Behavioral issues

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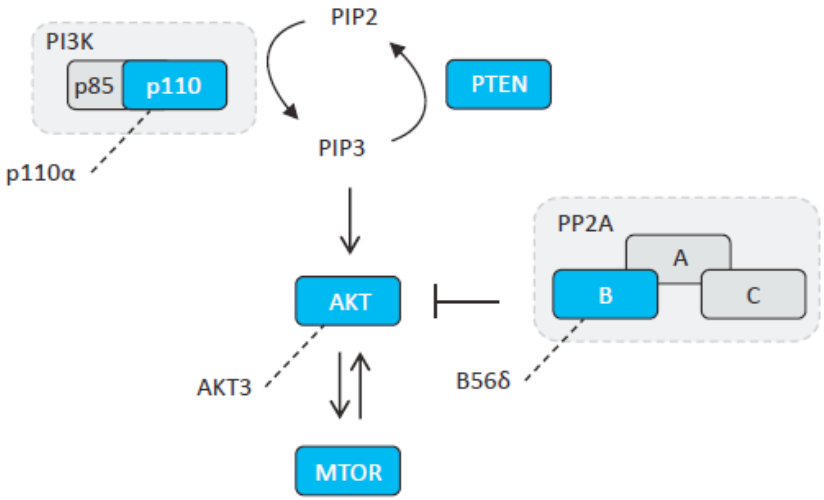


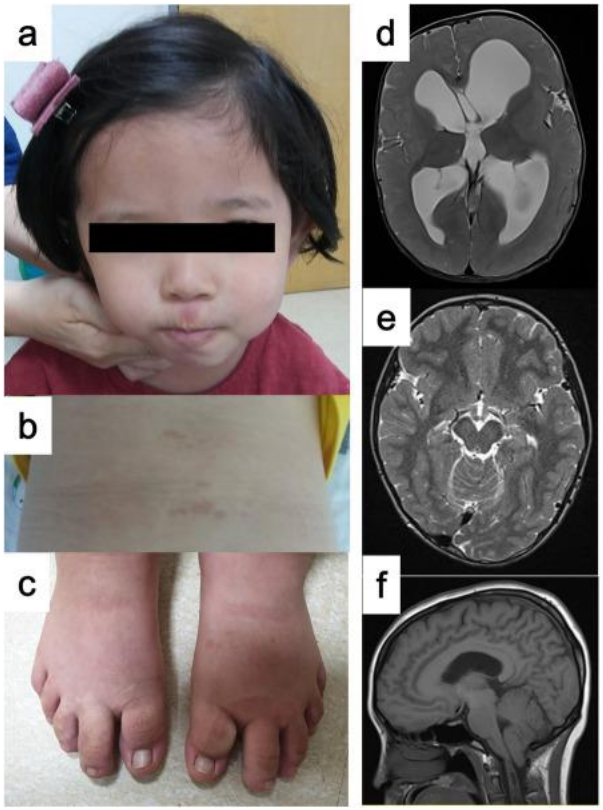
PI3K/AKT pathway

The PI3K/AKT pathway positively regulates growth.

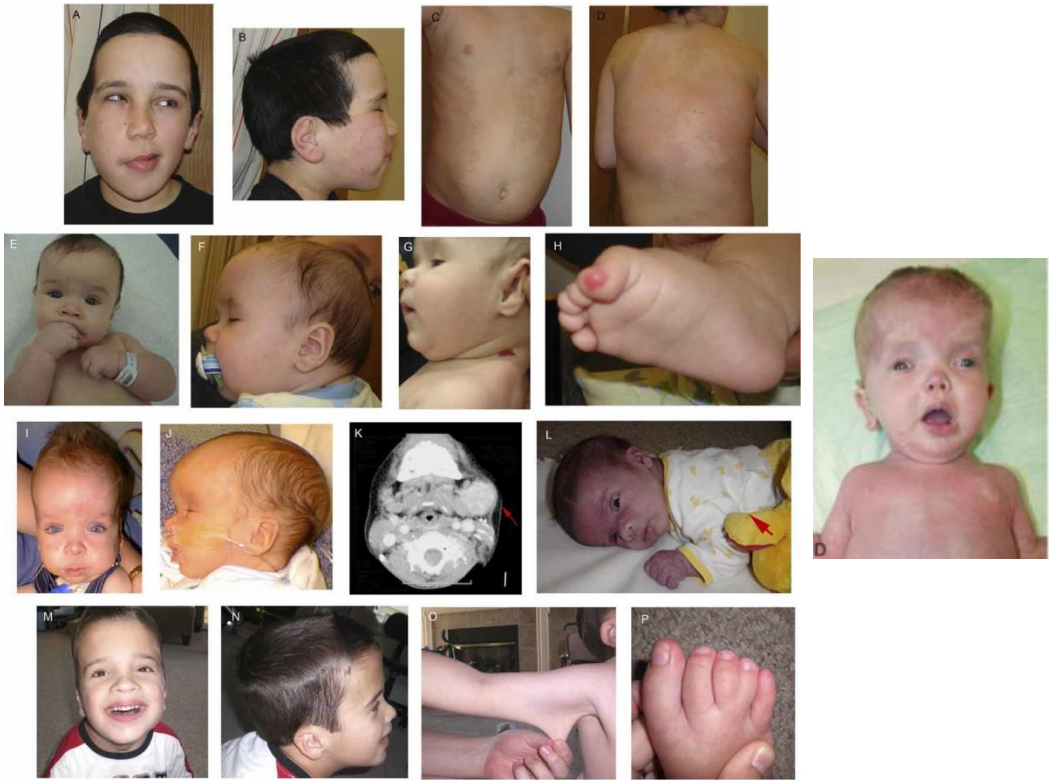
- OGID mutations in ***PIK3CA***, *AKT, MTOR* are activating
- OGID mutations in *PTEN* and *PPP2R5D* are inactivating

PIK3CA-related overgrowth spectrum (PROS):

megalencephaly-capillary malformation-polymicrogyria syndrome (+Syndrome CLOVES, Syndrome Cowden,…)



Park. et al, Orphanet J Rare Dis 2020



Mirzaa. et al, Am J Med Genet 2012

- Somatic gain-of-function mutations in PIK3CA
- Macrocephaly (92%), Megalencephaly or hemimegalencephaly (92%), Arnold Chiari (90%)
- Somatic overgrowth, facial and limb asymmetry, syndactyly or polydactyly
- Cutaneous vascular malformation (83%) : capillary malformations of the nose, philtrum, and/or upper lip
- Developmental delay
- Joint laxity or soft skin.

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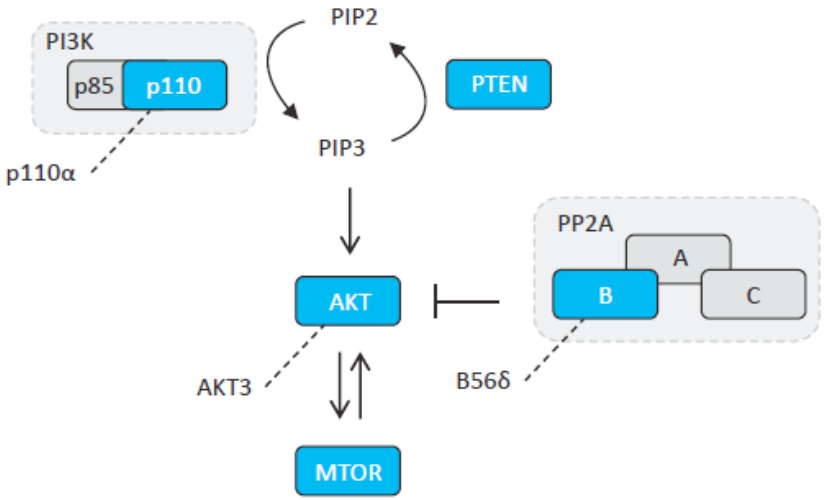

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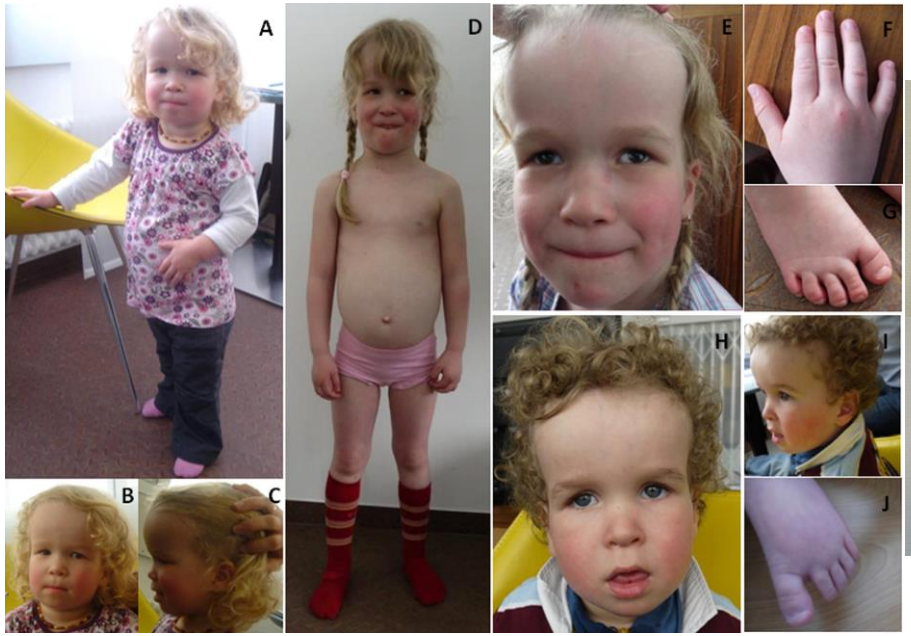
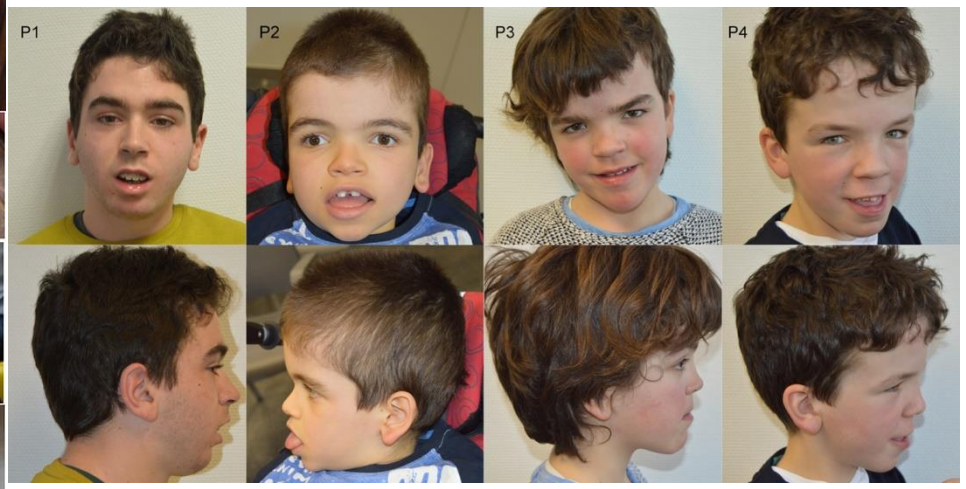
MTOR: Kingsmore syndrome

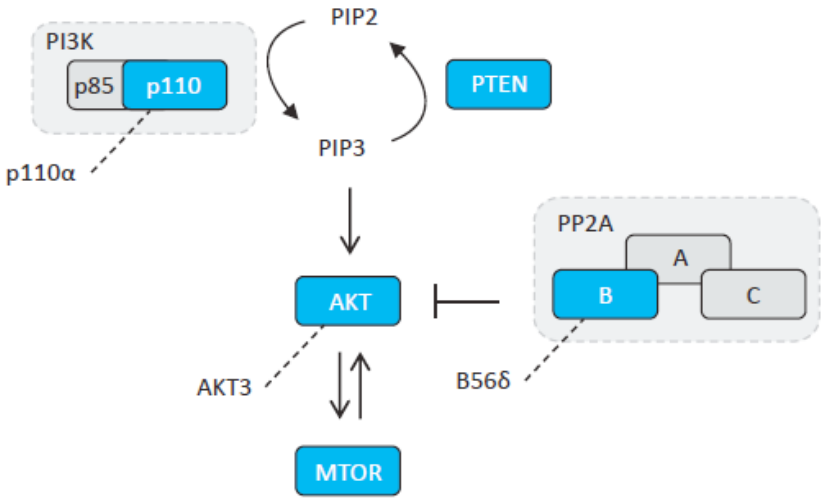


Moosa S. et al, AmJMedGenet Part A, 2017; 173(1), 264–267



Gordo S. et al, Clin Genet, 2018; 93(4), 762-775.

- Brain anomalies : Delayed myelination and white matter abnormalities, Hydrocephaly, Ventriculomegaly,…
- Global developmental delay, Intellectual disability (may be severe, moderate or mild)
- Macrocephaly / megalencephaly
- Delayed or absent speech
- Seizures (including nocturnal focal epilepsy)
- Behavior disorder
- Dysmorphic features (high forehead, short nose)
- Pigmentary abnormalities



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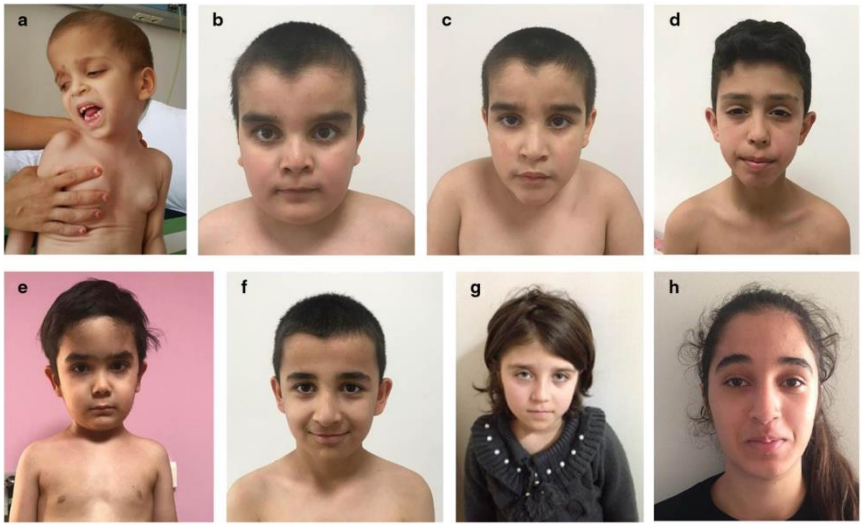
PTEN: Macrocephaly/autism syndrome

(+ Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome)

Kato et al, Brain & Development 2018



Isik. et al, Annals of Human Genetics 2020

- Macrocephaly
- Frontal bossing, dolichocephaly, horizontal eyebrows, depressed nasal bridge
- Skin lesions, hamartomas
- Psychomotor delay
- Autism spectrum disorder

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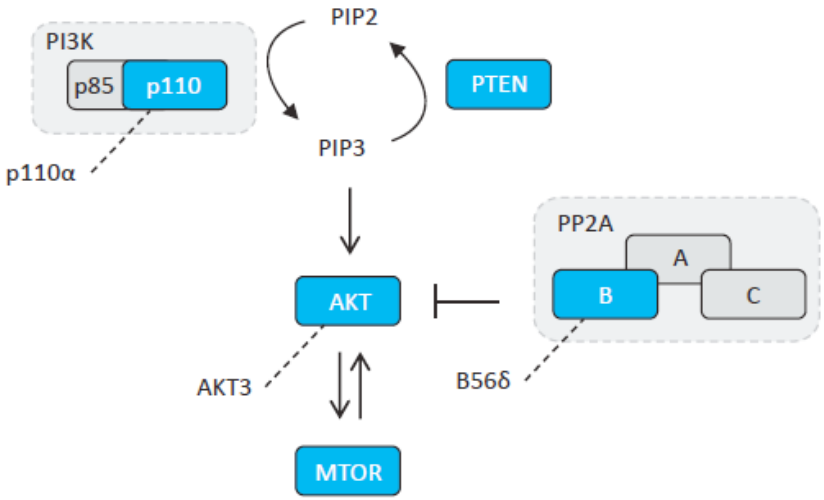

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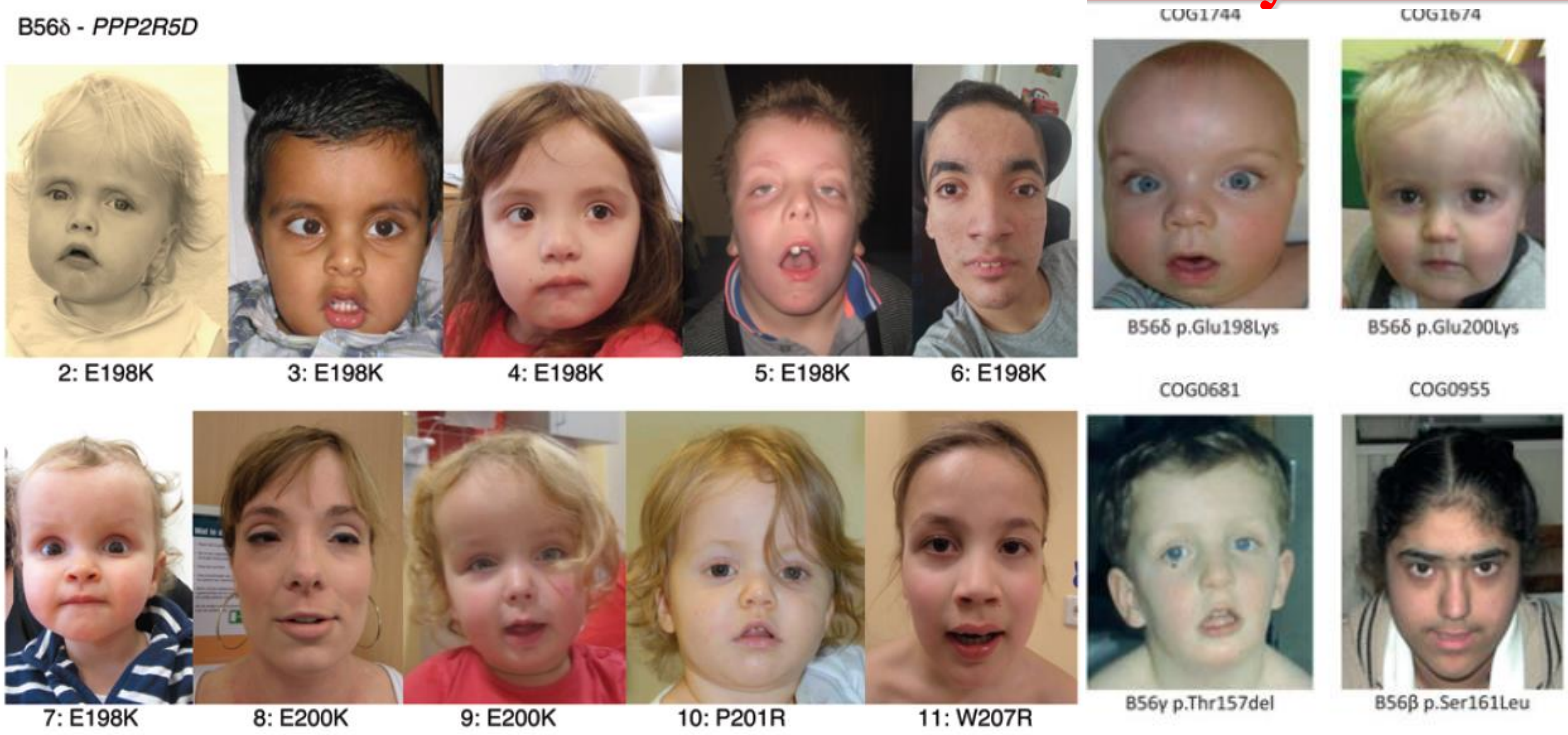
PPP2R5D: Macrocephaly/ID syndrome



Houge G. et al. *J Clin Invest*. 2015;125(8):3051–3062

Loveday et al. *Hum Mol Genet* 2015

- Macrocephaly: 85%
- ID (mild to severe): 100%, Severe speech delay: 100% (non verbal in 30%)
- Severe hypotonia: 100%
- Facial dysmorphism: abnormal palpebral fissures, high forehead, hypertelorism
- Epilepsy: 25%
- ASD: 35%
- Brain MRI anomalies: 40% (ventricular dilatation, thin corpus callosum)
- Ataxia: 20%
- Ophthalmologic abnormalities: 80% (strabismus, astigmatism, esotropia, ptosis, and myopia)

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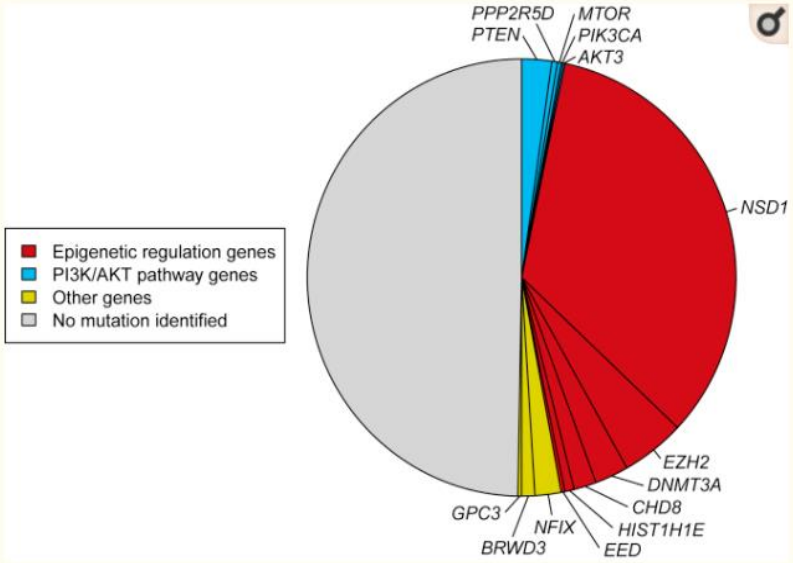

Figure 1

Causal Mutation Identified in 50% of OGID Probands

Proportion of pathogenic mutations identified in 710 individuals with OGID. Epigenetic regulation genes (red), including *NSD1* which is the predominant gene, constitute the major gene set. PI3K/AKT pathway genes (blue) also significantly contribute to OGID.

Tatton-Brown et al. *Am J Hum Genetic 2017; 100,725-736*

Other genes

- **NFIX**: Malan syndrome (+ **NFIA, NFIB**)
- **BRWD3**: Mental retardation, X-linked 93
- **GPC3**: Simpson-Golabi-Behmel syndrome

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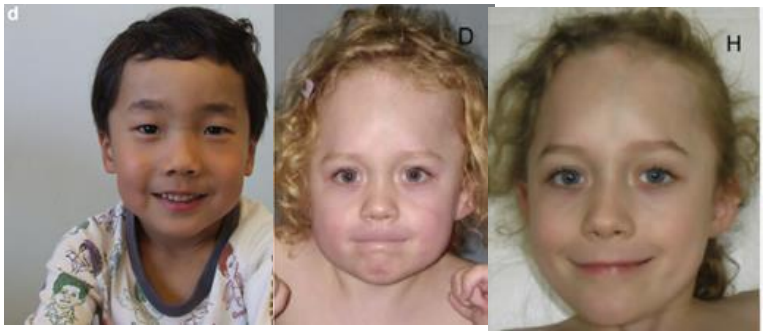
NFIX: Malan Syndrome

NFI: Nuclear Factor one family of transcription factors

Mutation nonsense NFIB
(Schanze et al, Am J Hum Genet 2018)

Mutation nonsense NFIX
Malan syndrome (Sotos type 2)
(with Nonsense-mediated mRNA Decay)
(Malan et al, Am J Hum Genet 2010)



Mutation nonsense NFIA
(Negishi et al, Hum Genome Var 2015)
(Rao et al, Eur j Med genet 2014)

- Macrosomia, macrocephaly
- Sotos-like dysmorphism
- Hypotonia
- Brain anomalies (Corpus callosum hypoplasia, ventricular dilatation)
- Developmental delay
- Variable intellectual disability
- Autistic features, behavioral anomalies

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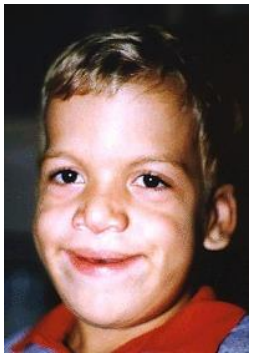
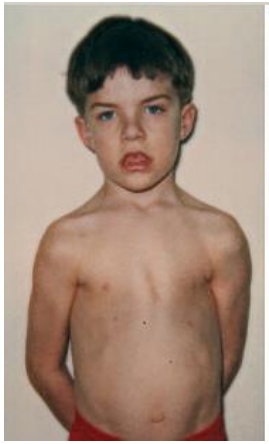
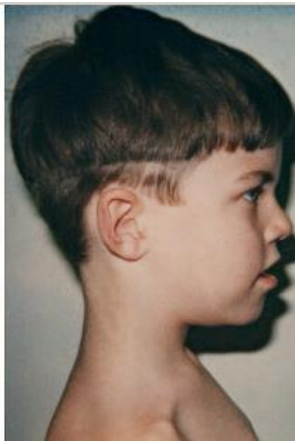
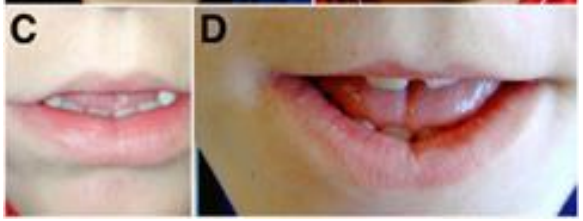
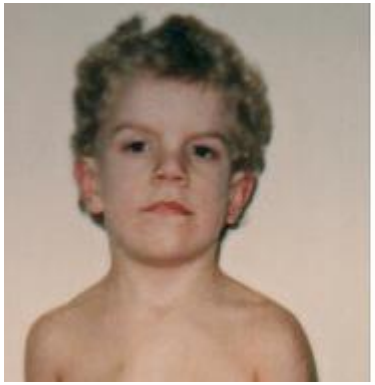
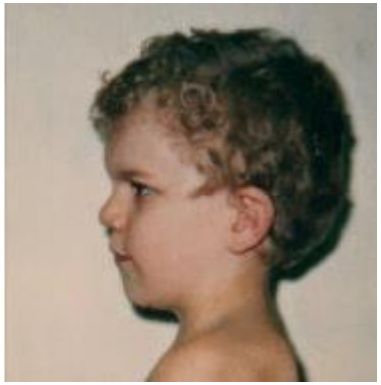
GPC3: Simpson-Golabi-Behmel Syndrome

- Pre/post-natal overgrowth
- Macrocephaly
- Coarse facies, broad nasal bridge, anteversed nares, thin upper lip, dental anomalies
- Postaxial polydactyly
- Increased risk (10%) for embryonic neoplasm (Wilms tumour, neuroblastoma and hepatoblastoma)

IPG

Don’t forget to send back the evaluation form to

isabelle.maystadt@ipg.be

Thanks!!!