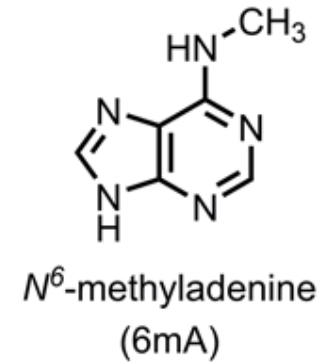
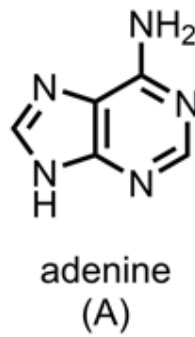
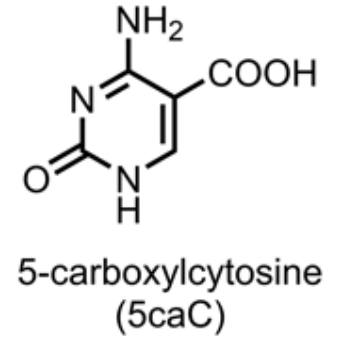
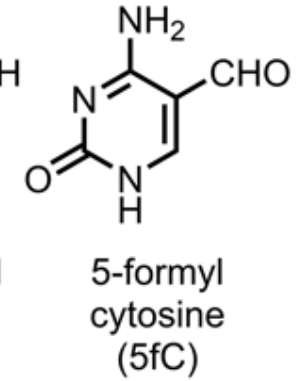
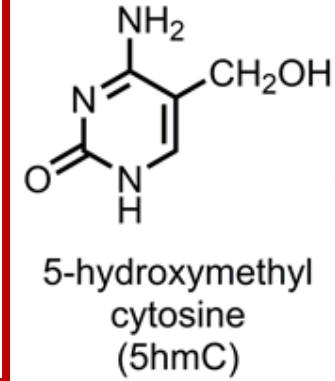
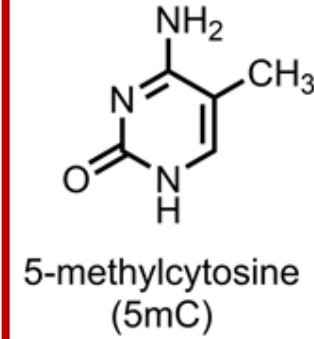
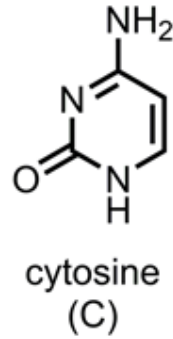
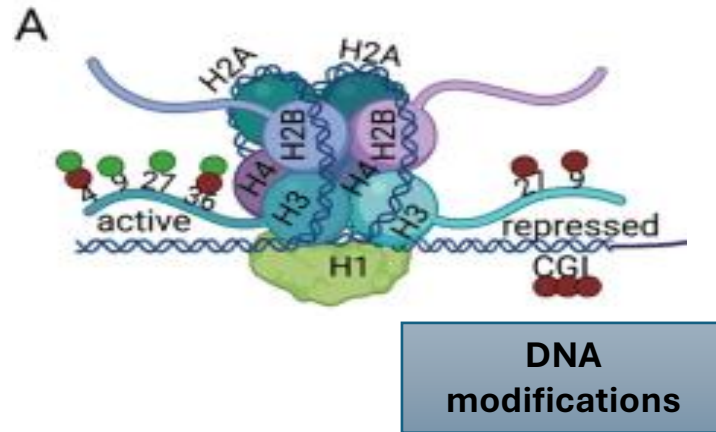


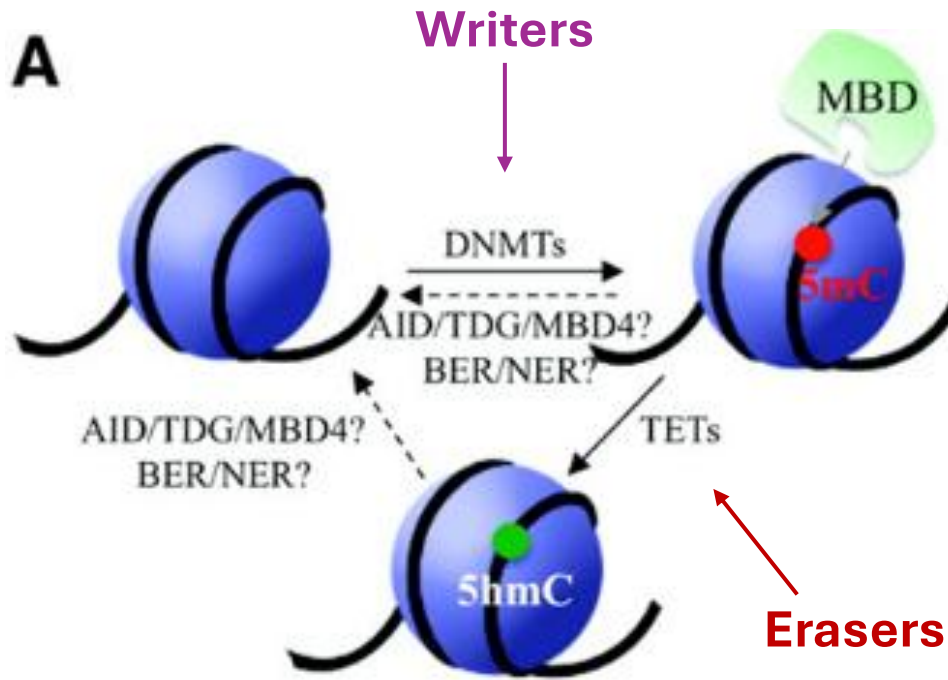
Classification of Chromatin Disorders and Episignatures

Siddharth.Banka@manchester.ac.uk

Types of DNA modifications



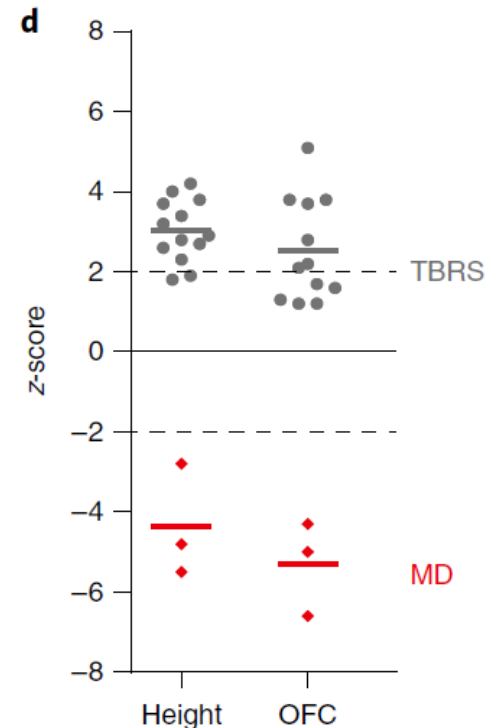
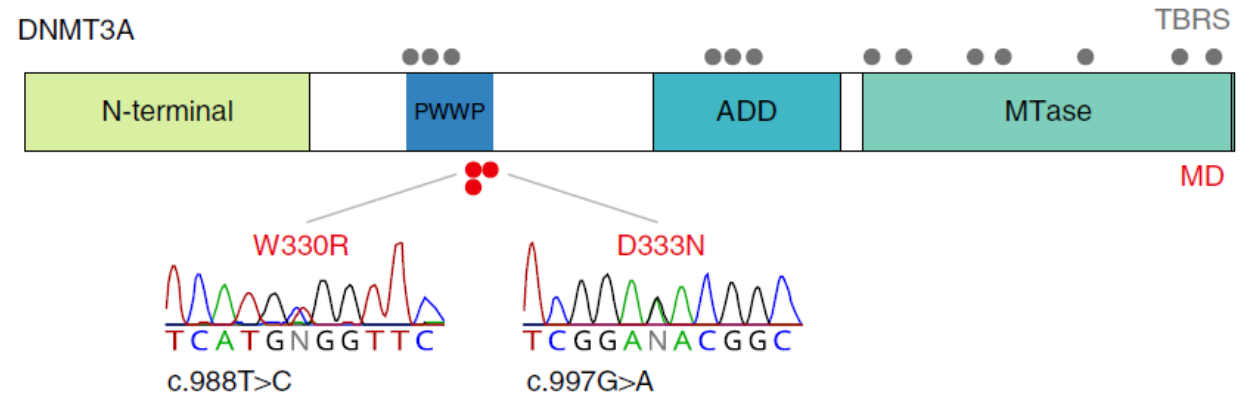
5mC DNA methylation machinery disorders



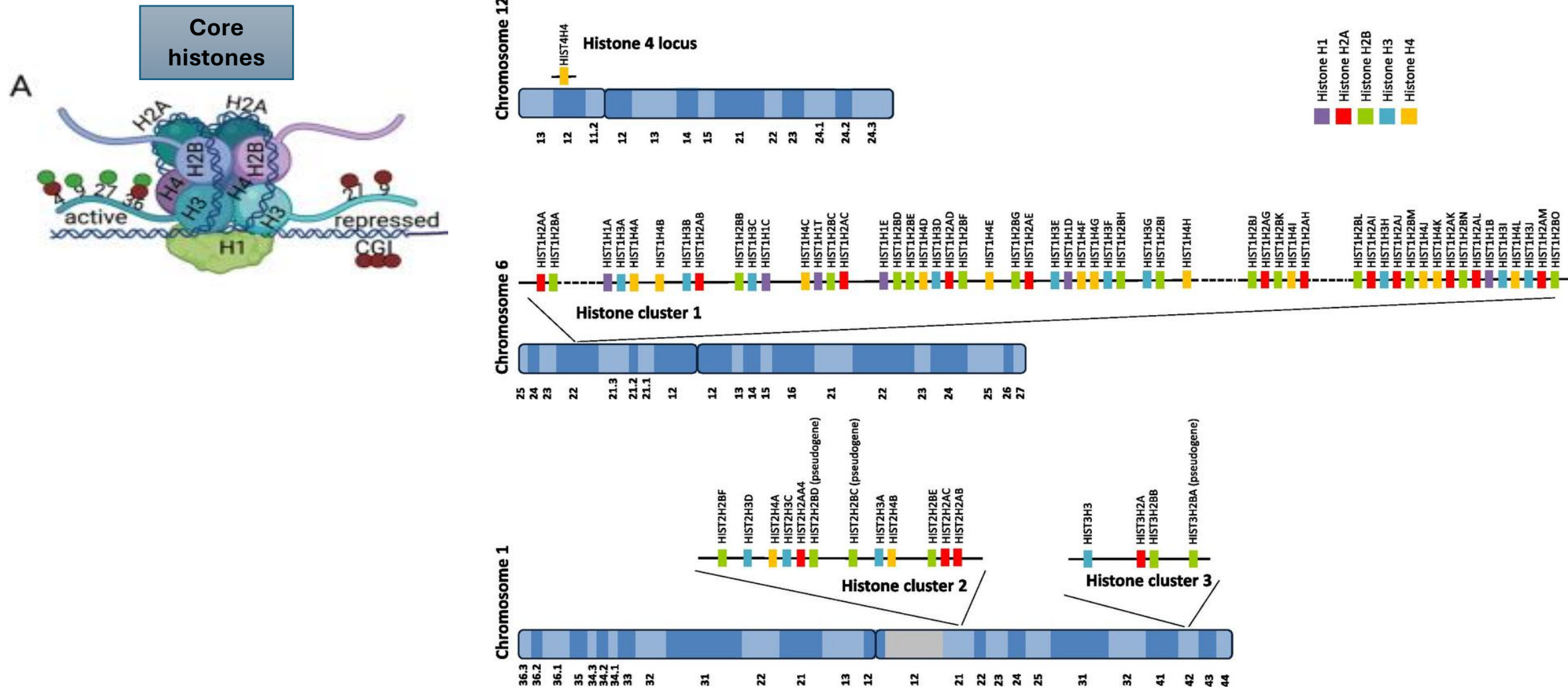
- *DNMT1*
 - AD Cerebellar ataxia, deafness, and narcolepsy
 - AD HSN 1E
- *DNMT3A*
 - **Tatton-Brown Rahman syndrome**
 - **Heyn-Sproul-Jackson syndrome**
- *DNMT3B*
 - Immunodeficiency-centromeric instability-facial anomalies syndrome type 1
 - Digenic FSHD type 4
- *TET2* - AR Immunodeficiency Type 75
- *TET3* - Beck-Fahrner syndrome

DNMT3A-related syndromes

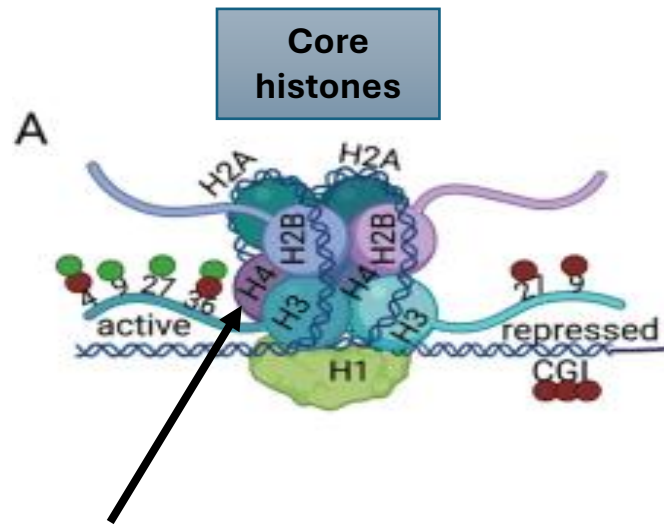
- **Tatton-Brown Rahman syndrome (LOF)**
 - ID, tall stature, macrocephaly, obesity.
 - Synophrys, straight eyebrows, horizontal or downward slanting PFs, prominent medial incisors.
 - Risk of leukaemia with variant R882H
- **Heyn-Sproul-Jackson syndrome (GOF)**
 - Microcephalic dwarfism



Core histones are transcribed by multiple gene copies

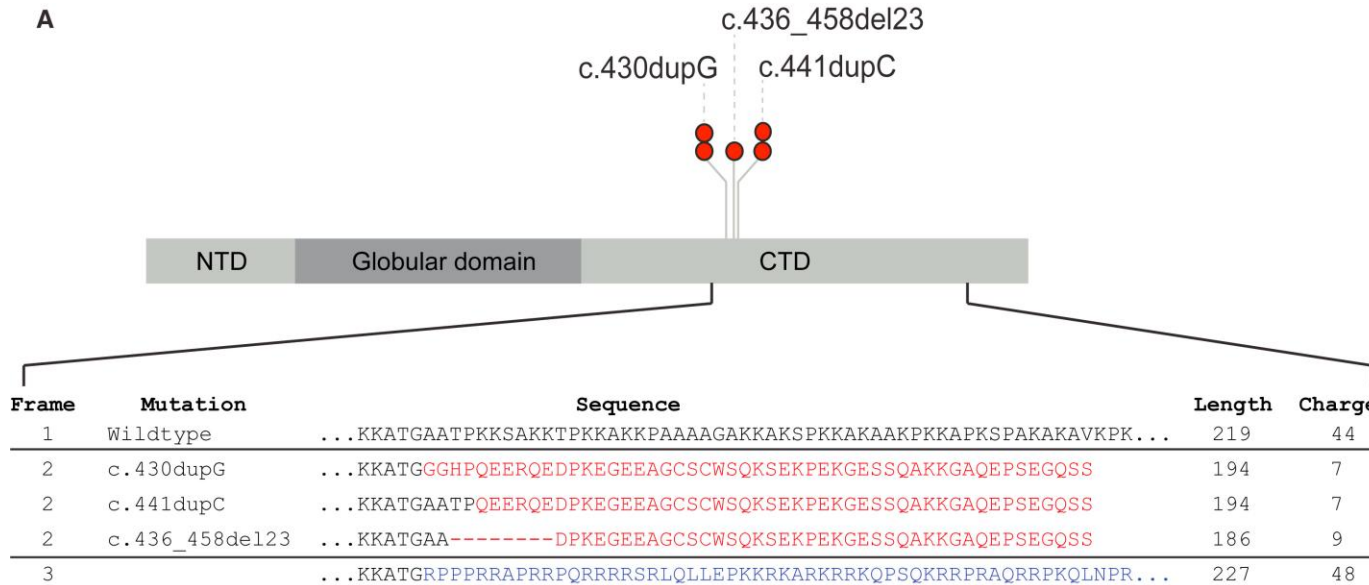


Core histones are transcribed by multiple gene copies

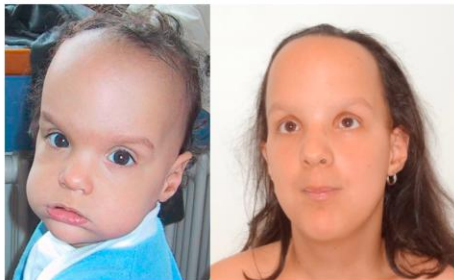


- **H1 replication dependent**
 - *HIST1H1E*-related Rahman syndrome
- **H3 replication independent**
 - *H3F3A*-related Bryant–Li–Bhoj syndrome 1
 - *H3F3B*-related Bryant–Li–Bhoj syndrome 2
- **H4 replication dependent**
 - *H4C3*-related Tessadori Bicknell van Haaften syndrome 1
 - *H4C4*-related TvBF2
 - *H4C5*-related TvBF3
 - *H4C6*-related TvBF3
 - *H4C9*-related TvBF4
 - *H4C11*-related TvBF5

HIST1H1E-related related Rahman syndrome



B COG0405



1.5 years

13 years

C COG0412



1.5 years

15.5 years

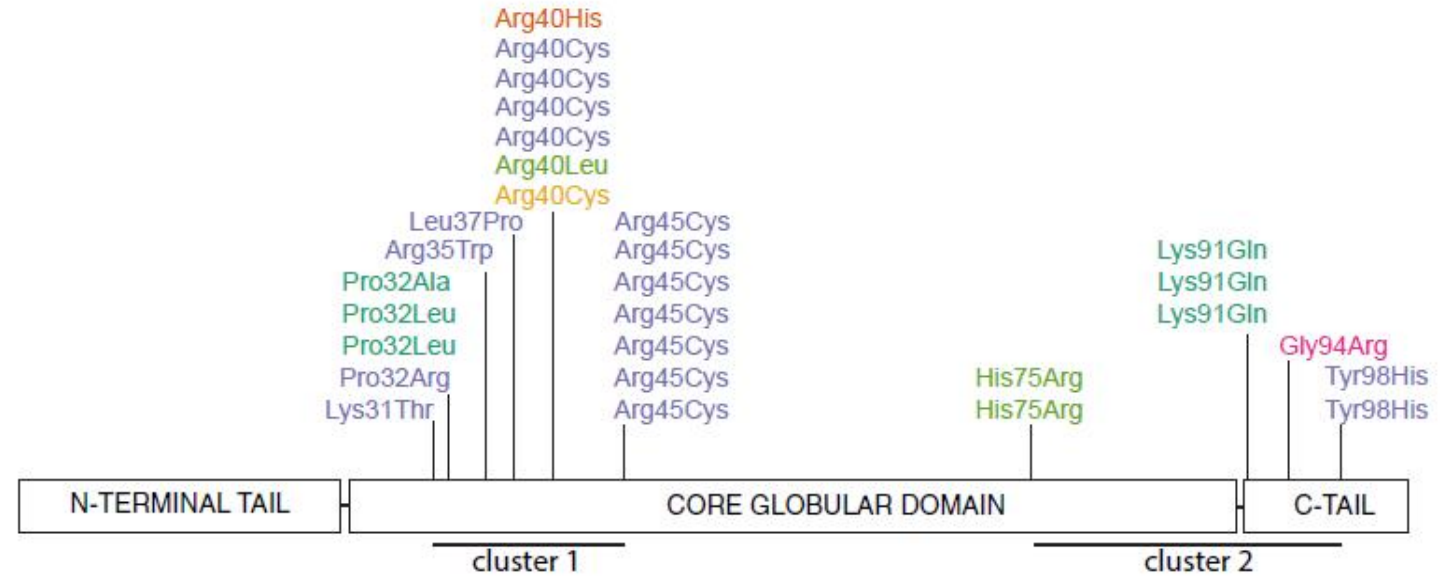
D COG1832



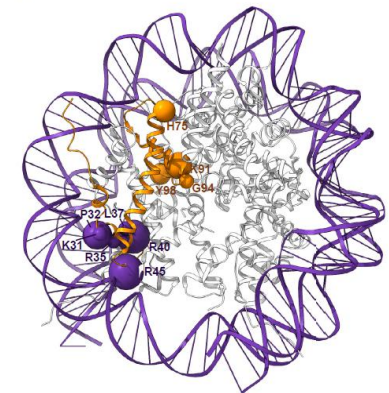
4 years

Patient Number	Incidence
Gender	
Age (years)	
Facial gestalt	100%
Intellectual disability	100%
Abnormal Brain MRI	87%
Cryptorchidism	69% ♂
Hypotonia	63%
Behavioral issues	50%
Abnormal dentition	43%
Cardiac anomalies	43%
Skeletal anomalies	40%
Hypothyroidism	25%

H4 replication dependent-related Tessadori-Bicknell-van Haaften syndromes

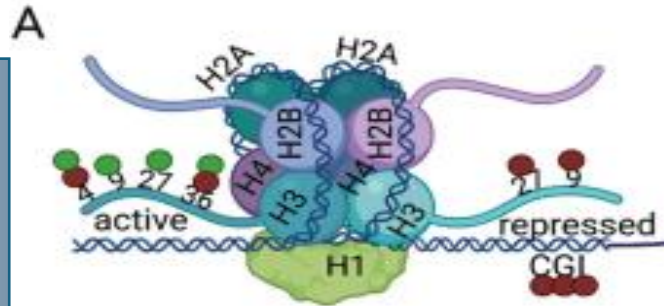


- **H4C3-related TvBF1**
- **H4C4-related TvBF**
- **H4C5-related TvBF3**
- **H4C6-related TvBF3**
- **H4C9-related TvBF4**
- **H4C11-related TvBF**

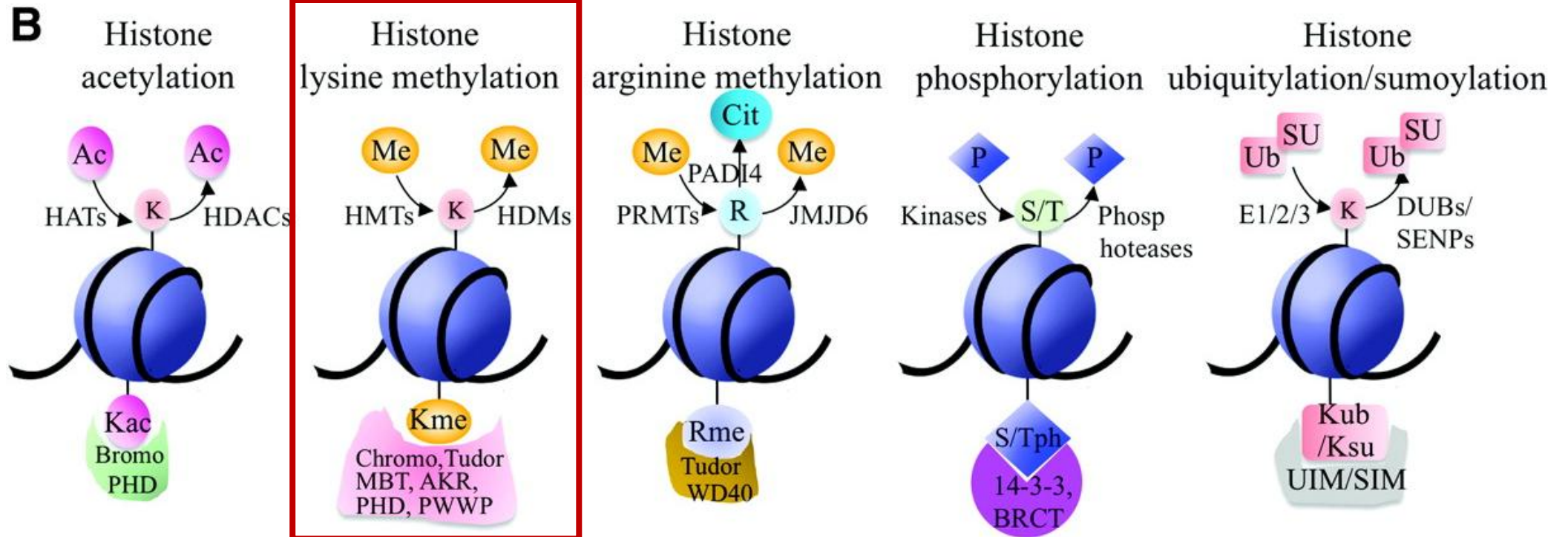


Post-translational modifications of histone tails

Histone modifications

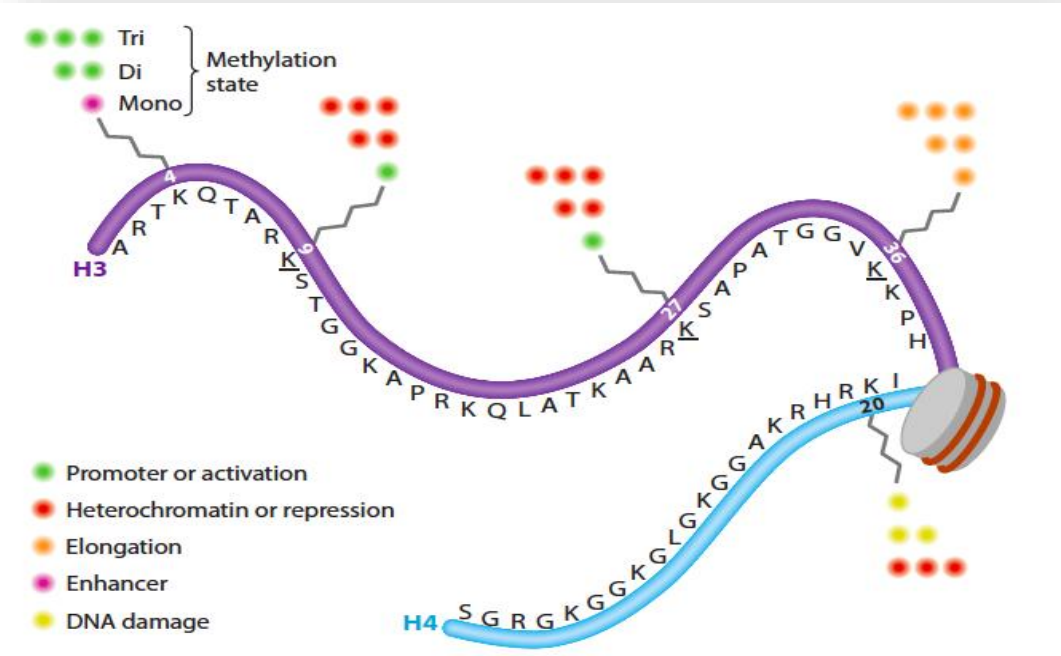
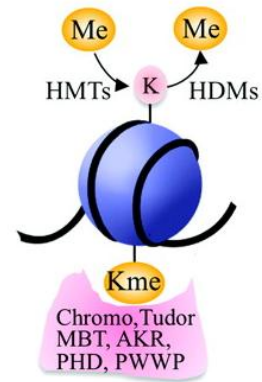


Zhou et al. Nuclear, Circulation Research. 2011;
 Plass et al. Nat Rev Genet. 2013;
 Mosammamaparast and Shi. Ann Rev Biochem 2010.



Histone lysine methyltransferase (KMT) disorders

Histone lysine methylation

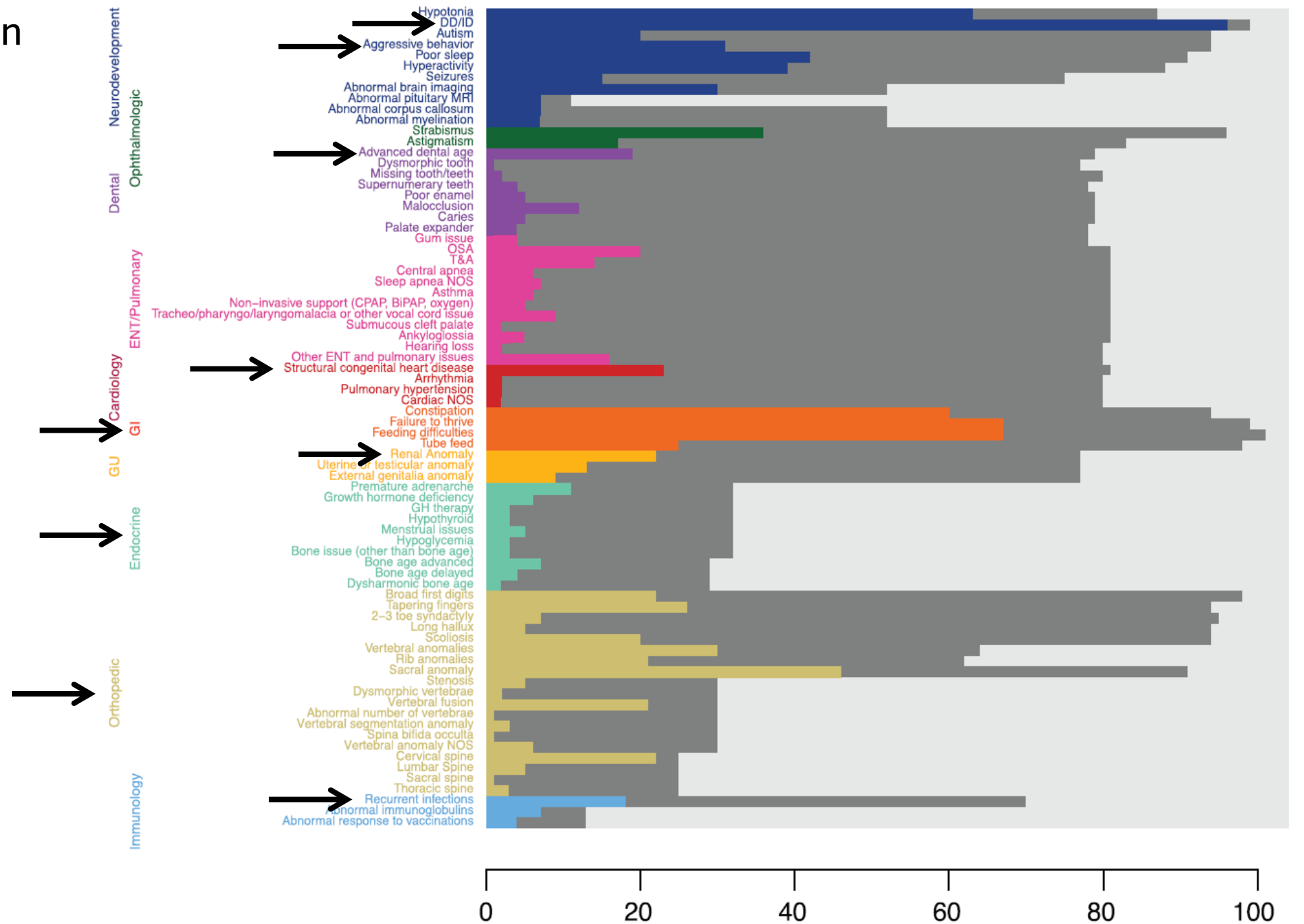


Gene	Histone Target	Associated Syndromes
<i>KMT1A</i>	H3K9	
<i>KMT1B</i>	H3K9	
<i>KMT1C</i>	H3K9	
<i>KMT1D</i>	H3K9	
<i>KMT1E</i>	H3K9	
<i>KMT1F</i>		
<i>KMT2A</i>	H3K4	Wiedemann-Steiner syndrome
<i>KMT2B</i>	H3K4	Childhood-onset dystonia 28; AD ID 68
<i>KMT2C</i>	H3K4	Kleefstra syndrome 2
<i>KMT2D</i>	H3K4	Kabuki syndrome 1; BCAHH
<i>KMT2E</i>	H3K4	O'Donnell-Luria-Rodan syndrome
<i>KMT2F</i>	H3K4	
<i>KMT2G</i>	H3K4	
<i>KMT2H</i>	H3K4	
<i>KMT3A</i>	H3K36	
<i>KMT3B / NSD1</i>	H3K36	Sotos syndrome
<i>KMT3C</i>	H3K36 (p53)	
<i>KMT4</i>	H3K79	
<i>KMT5A</i>	H4K20	
<i>KMT5B</i>	H4K20	AD ID 51
<i>KMT5C</i>		
<i>KMT6 / EZH2</i>	H3K27	Weaver syndrome
<i>KMT7</i>	H3K4	
<i>KMT8</i>	H3K9	
<i>SETD1A</i>		Early-onset epilepsy +/- DD; NDD + speech impairment + dysmorphic facies
<i>SETD1B</i>		ID with seizures and language delay
<i>SETD2</i>		AD ID70; Luscan-Lumish syndrome; Rabin-Pappas syndrome
<i>ASH1L</i>		AD ID 52
<i>EHMT1</i>		Kleefstra syndrome 1

KMT2A - Wiedemann Steiner syndrome



KMT2A - Wiedemann Steiner syndrome



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

Esther Meyer^{1,48}, Keren J Carss^{2,3,48}, Julia Rankin^{4,48}, John M E Nichols^{5,48}, Detelina Grozeva⁶, Agnel P Joseph⁷,

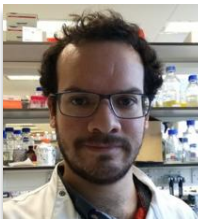


KMT2C - Kleefstra syndrome 2



DD, ID behavioral and psychiatric problems,
hypotonia, seizures and short stature.

Kleefstra et al. AJHG. 2008; Koemans et al PLoS Genetics 2017; Faundes et al. AJHG. 2018.; Rots et al. AJHG. 2024



KMTD - Kabuki syndrome 1

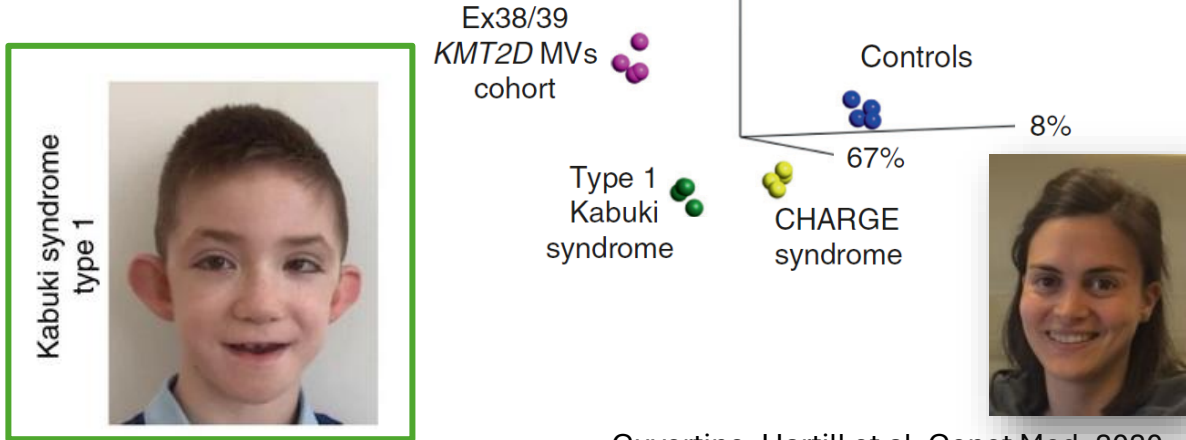
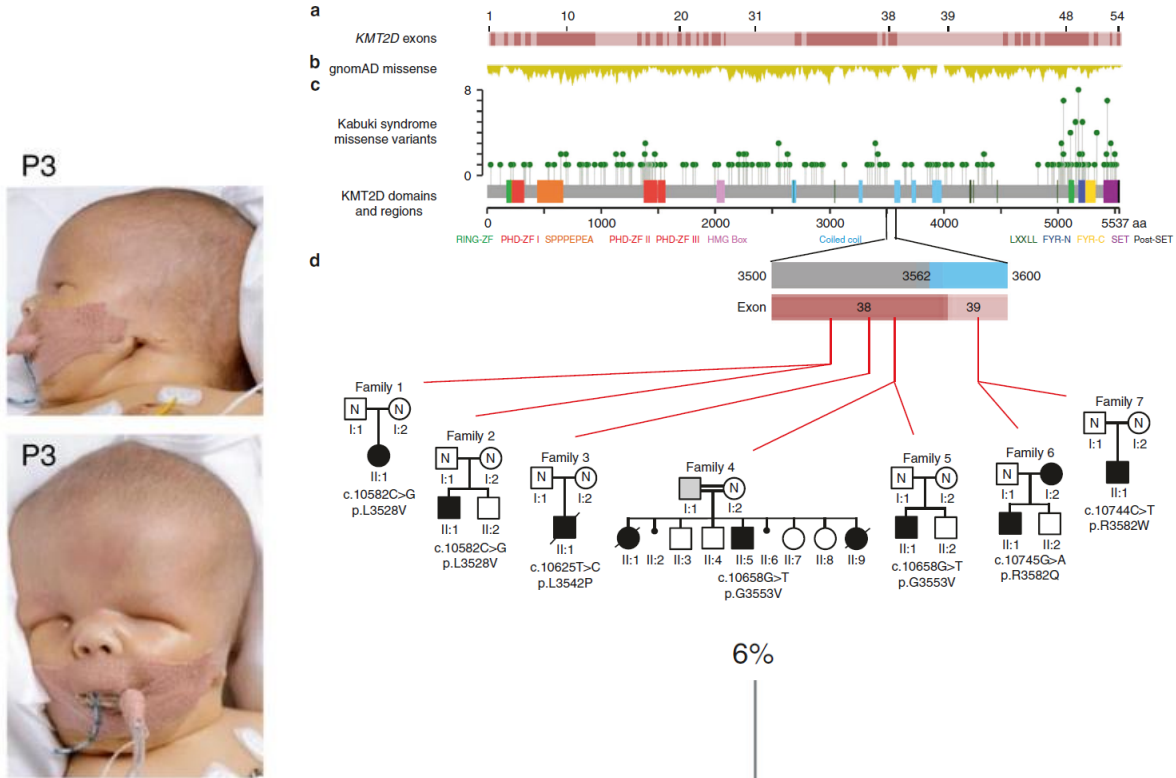
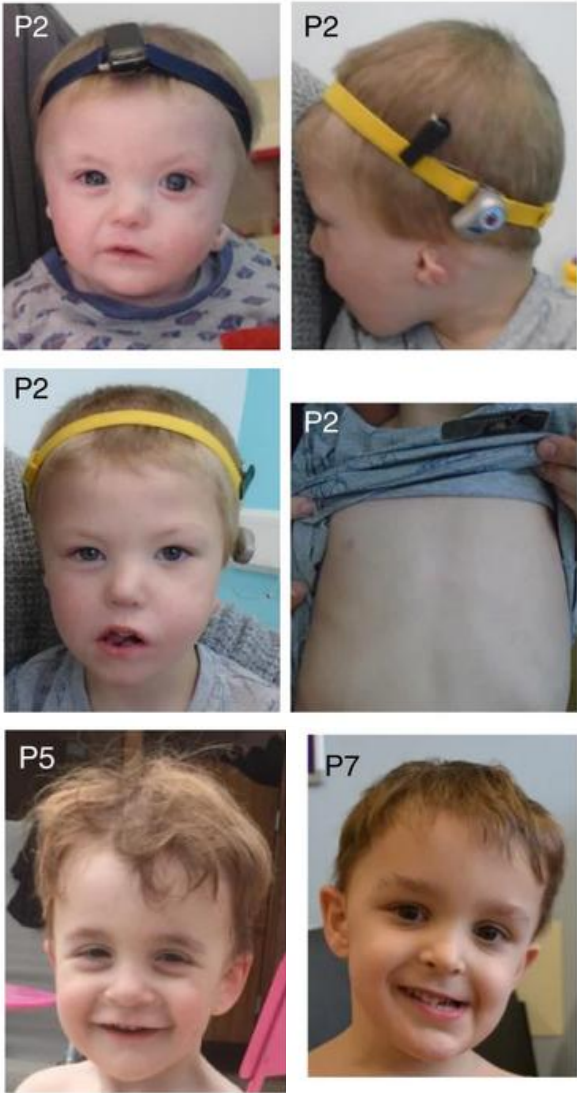
- Neonatal hypotonia and feeding difficulties
- Failure to thrive. Some need PEG, but feeding generally improves with time feeding.
- Truncal obesity from mid-late childhood
- Cleft Palate (40 to 50%)
- Cardiac defects (~40%)
- Renal abnormalities (~40%)
- Joint dislocations
- Endocrine issues
- Immunodeficiency
- Autoimmune complications



KS1 has an allelic disorder: *KMT2D*-related BCAHH

Feature	Ex38/39 <i>KMT2D</i> MVs	Type 1 Kabuki syndrome
Branchial sinus/ neck pits	7/9 (78%)	Not reported or extremely rare
Hearing loss	8/9 (89%)	Common
External ear abnormalities	6/9 (67%) (small, hypoplastic, or absent)	Common (usually prominent and simple)
Structural abnormality of eye	2/9 (22%)	Rare
Abnormality of lacrimal ducts	7/9 (78%)	Rare
Choanal atresia	7/9 (78%)	Rare
Cleft lip/palate	0	Common
Athelia/ hypoplastic nipples	6/9 (67%)	Not reported (prominent breasts are common)
Congenital heart disease	3/9 (33%)	Common
Renal structural abnormality	0	Common
Seizures	0	Common
Intellectual disability	0	Common
Feeding difficulties	5/9 (44%)	Common
Short stature	5/9 (56%)	Common
Thyroid abnormality/ hypothyroidism	6/9 (67%)	Rare
Abnormality of immune system/ recurrent infections	4/9 (44%)	Common

Ex38/39 *KMT2D* MVs cohort



***EHMT1* - Kleefstra syndrome (9q34 del)**

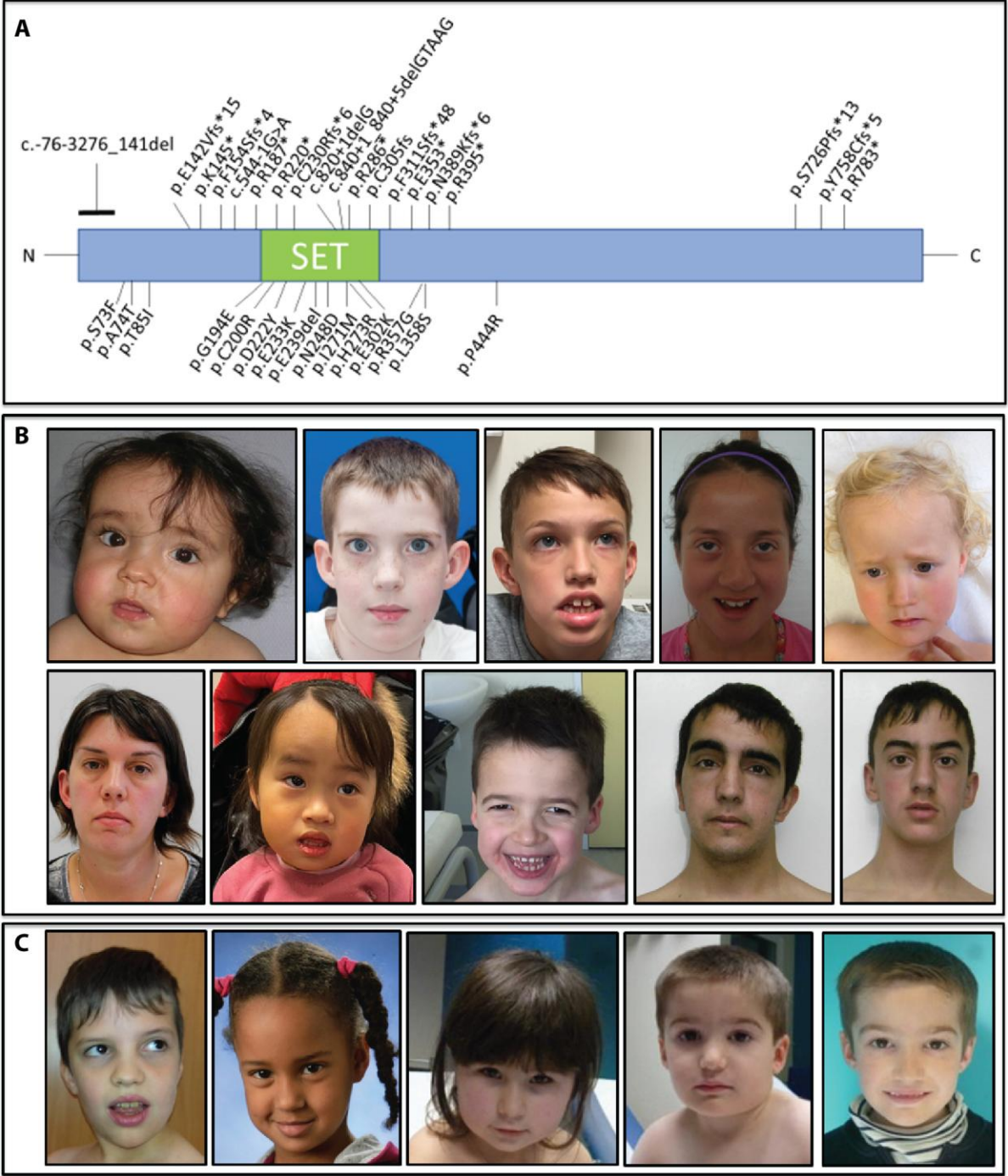
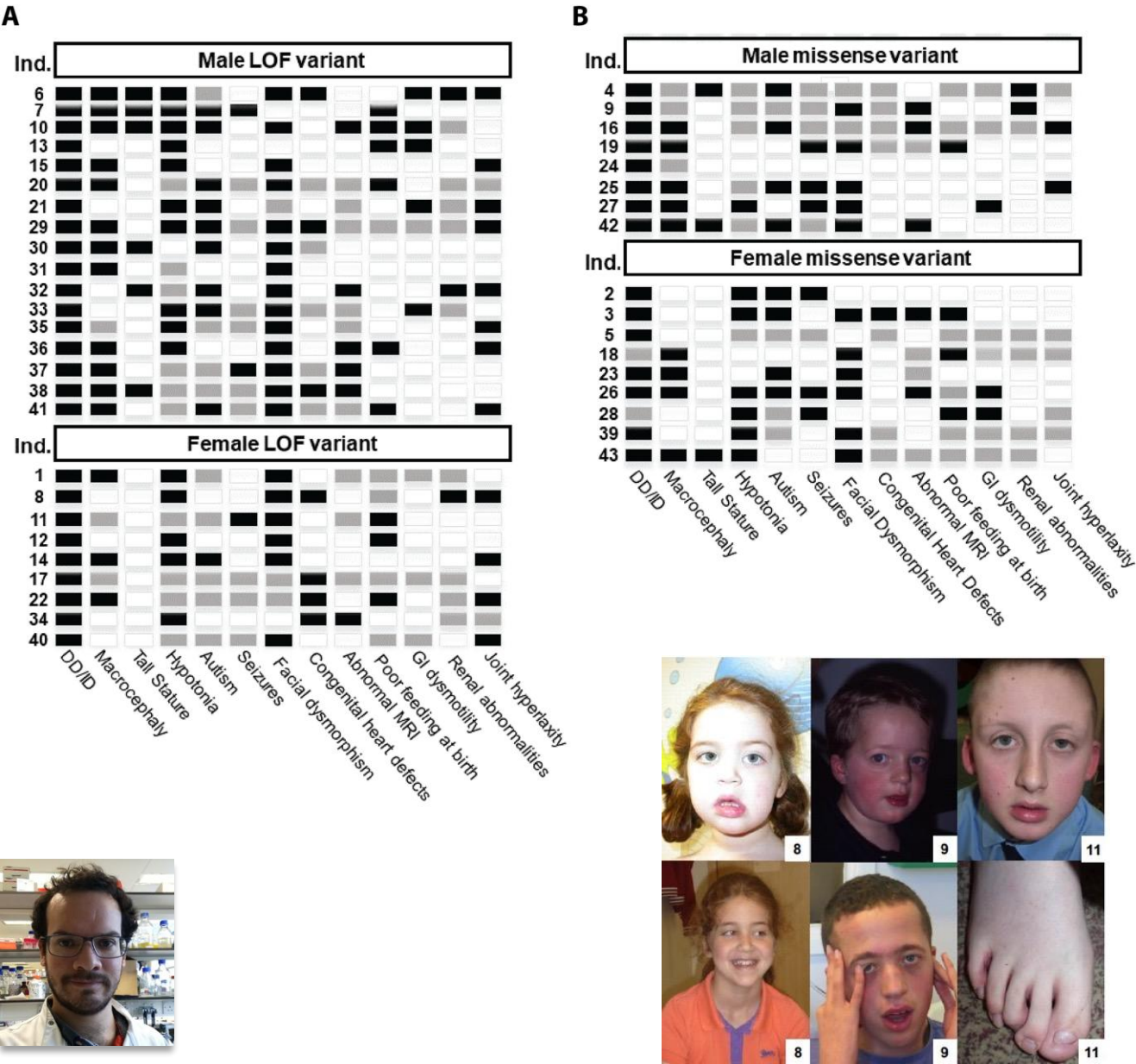
- Moderate to severe ID
- Severe speech delay
- Motor delay and childhood hypotonia
- Epilepsy / febrile seizures
- Autism spectrum disorder
- Mood and psychotic disorders)
- Extreme apathy or catatonic(-like) features post puberty
- Nonspecific brain abnormalities: structural defects (corpus callosum hypoplasia), cortical hypoplasia, or white matter defects
- Hypermetropia and hearing loss (sensorineural and/or conductive)
- Heart defects, renal/urologic defects, genital defects in males.
- Severe infections (respiratory)



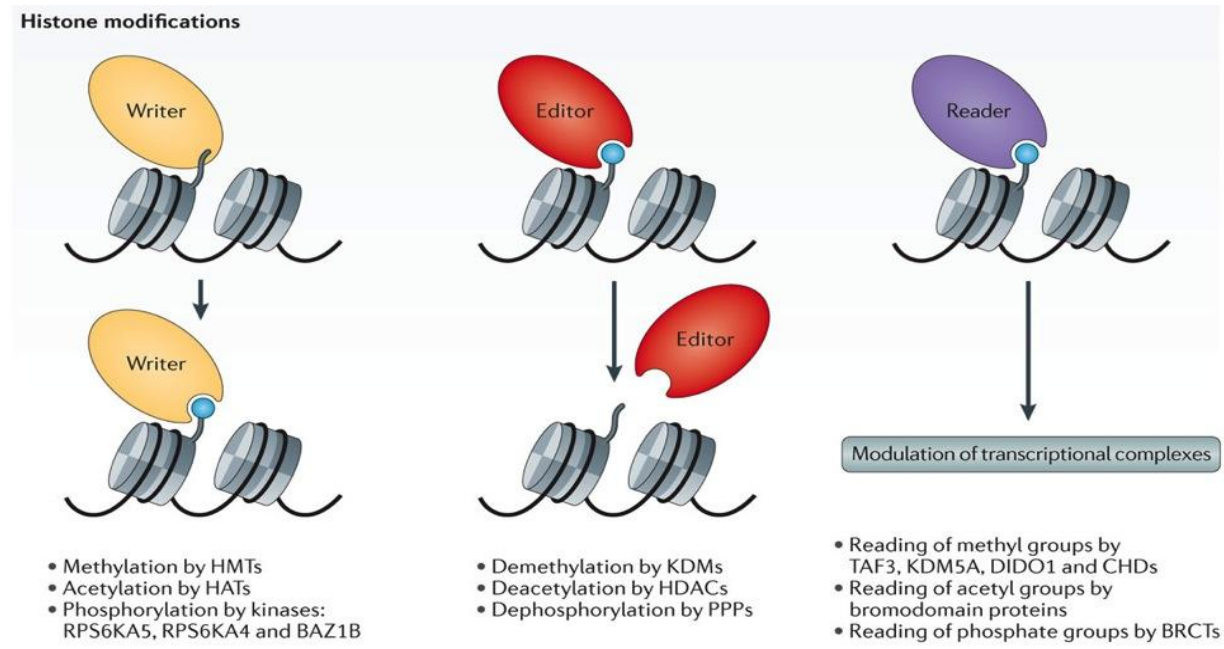
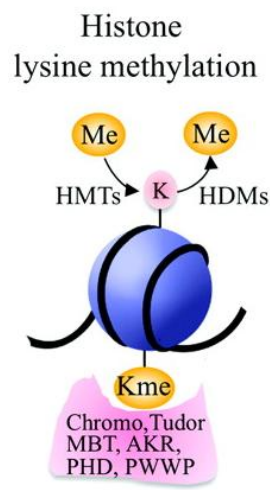


	Soto (<i>NSD1</i>)	Weaver (<i>EZH2</i>)	Luscan Lumish (<i>SETD2</i>)
Overgrowth phenotype	Not all are tall. 20% only macrocephaly. 10% neither tall nor macrocephalic	All are tall (height above 8SD +). 50% are macrocephalic	Normal birth parameters. Overgrowth from mid-childhood. Macrocephaly. Final height is normal
ID	Normal (2%) - Mild (30%) – Moderate (50%) - Severe (20%)	Normal (20%) - Mild (45%) - Moderate (30%) – Severe (5%)	Mild ID. Speech delay. Normal motor development
Other differences	Congenital heart diseases Scoliosis Renal anomalies Seizures	Connective tissue phenotype Umbilical hernia Deep set nails and camptodactyly Hoarse voice	Behavioural issues

KMT5B-related AD ID 51



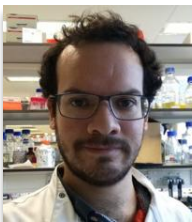
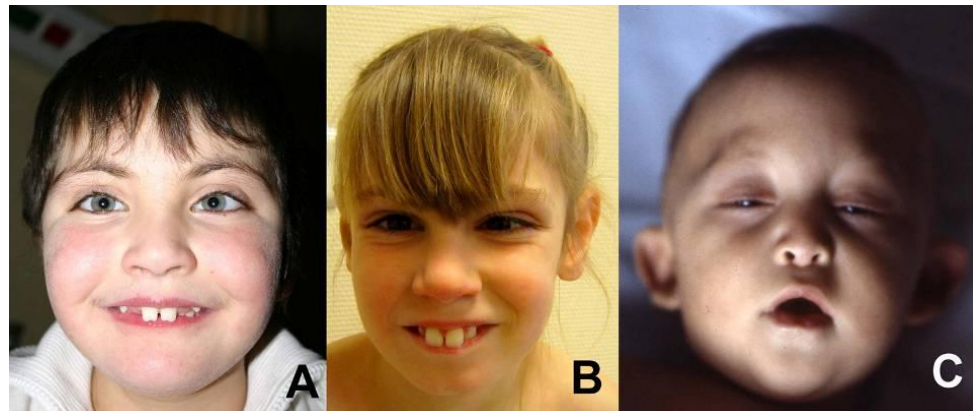
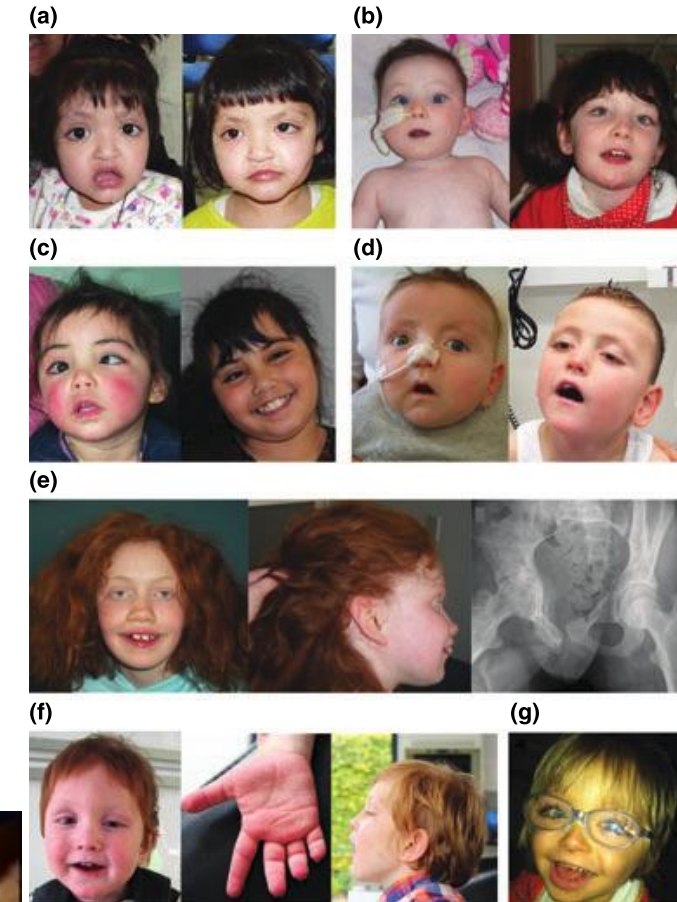
Histone lysine demethylase (KDM) disorders

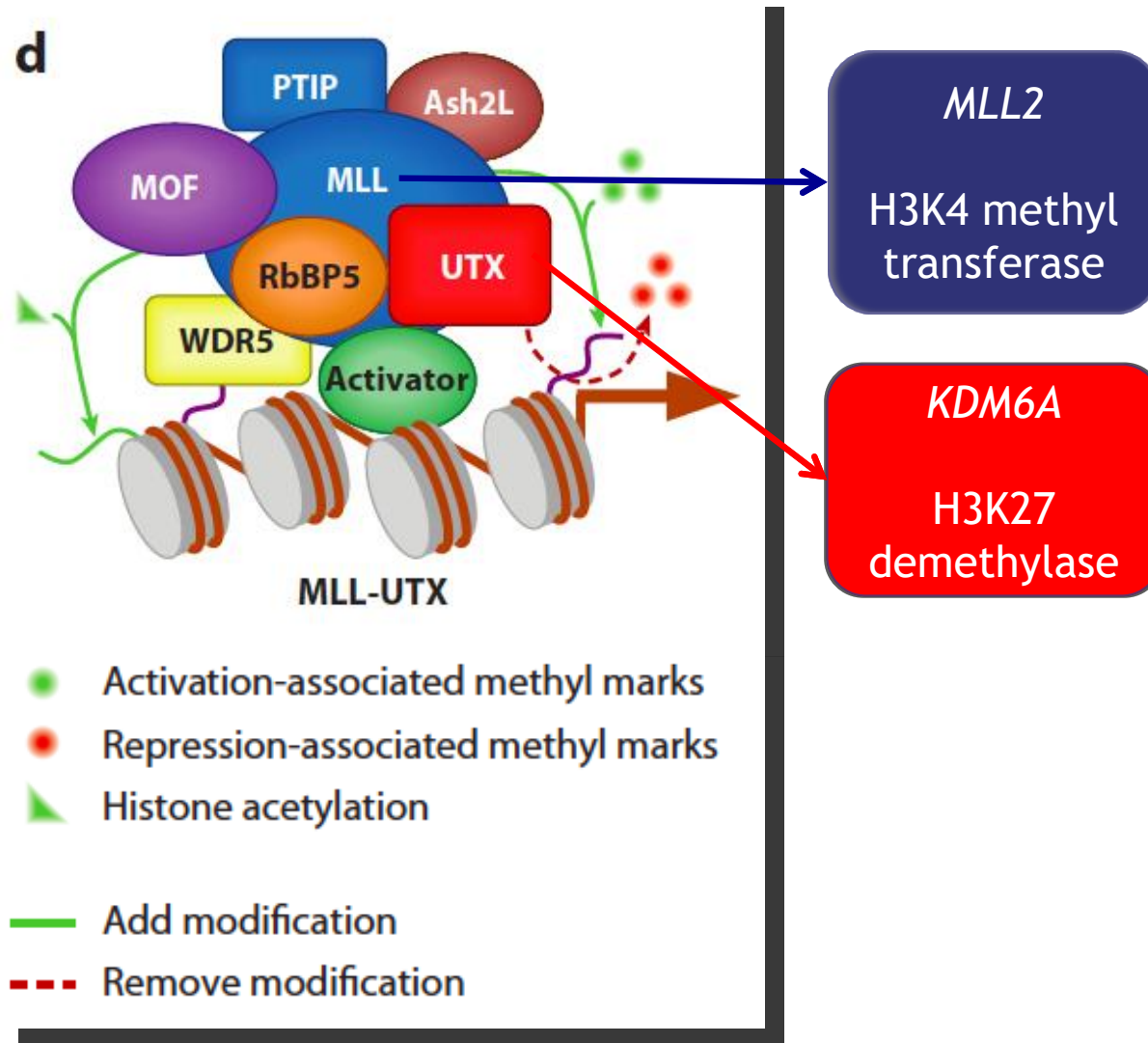


Gene	Substrate Specificity	Associated Syndromes
<i>KDM1A</i>	H3K4me1/2, H3K9me1/2	Cleft palate, psychomotor retardation, and distinctive facial features
<i>KDM2</i>	H3K36me1/2	
<i>KDM2A</i>	H3K36me1/2	
<i>KDM2B</i>	H3K36me1/2	
<i>KDM3A</i>	H3K9me1/2	
<i>KDM3B</i>	H3K9me	Diets-Jongmans syndrome
<i>KDM4</i>	H3K9/K36me2/3	
<i>KDM4A</i>	H3K9/K36me2/3	
<i>KDM4B</i>	H3K9/H3K36me2/3	AD ID 65
<i>KDM4C</i>	H3K9/K36me2/3	
<i>KDM4D</i>	H3K9me2/3	
<i>KDM5</i>	H3K4me2/3	
<i>KDM5A</i>	H3K4me2/3	El Hayek-Chahrour syndrome
<i>KDM5B</i>	H3K4me1/2/3	AR ID 65
<i>KDM5C</i>	H3K4me2/3	X-linked Claes-Jensen syndrome
<i>KDM5D</i>	H3K4me2/3	
<i>KDM6A</i>	H3K27me2/3	Kabuki syndrome 2
<i>KDM6B</i>	H3K27me2/3	Stolerman syndrome

KDM6A – X-linked Kabuki syndrome 2

- Male v Female
- Hyperinsulnism
- Prominent incisors
- Big toes

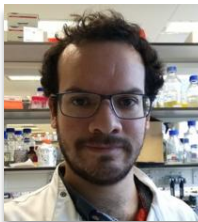




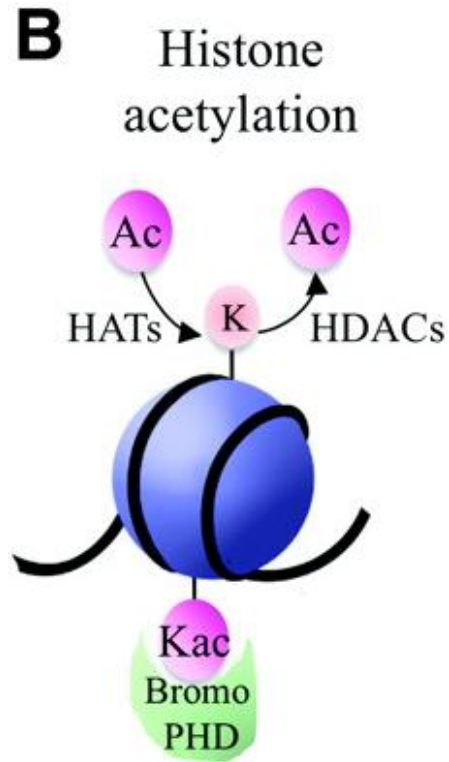
MLL2 belongs to the human SET-domain protein methyltransferase superfamily and is a histone H3 lysine 4 (H3K4)-specific methyltransferase (KMT2D)

***KDM5B* mutations causes an autosomal recessive dysmorphic disorder**

- Moderate to severe DD and ID
- Neonatal feeding difficulties
- Gait abnormalities
- Agenesis of corpus callosum
- Camptodactyly
- Atrial septal defect



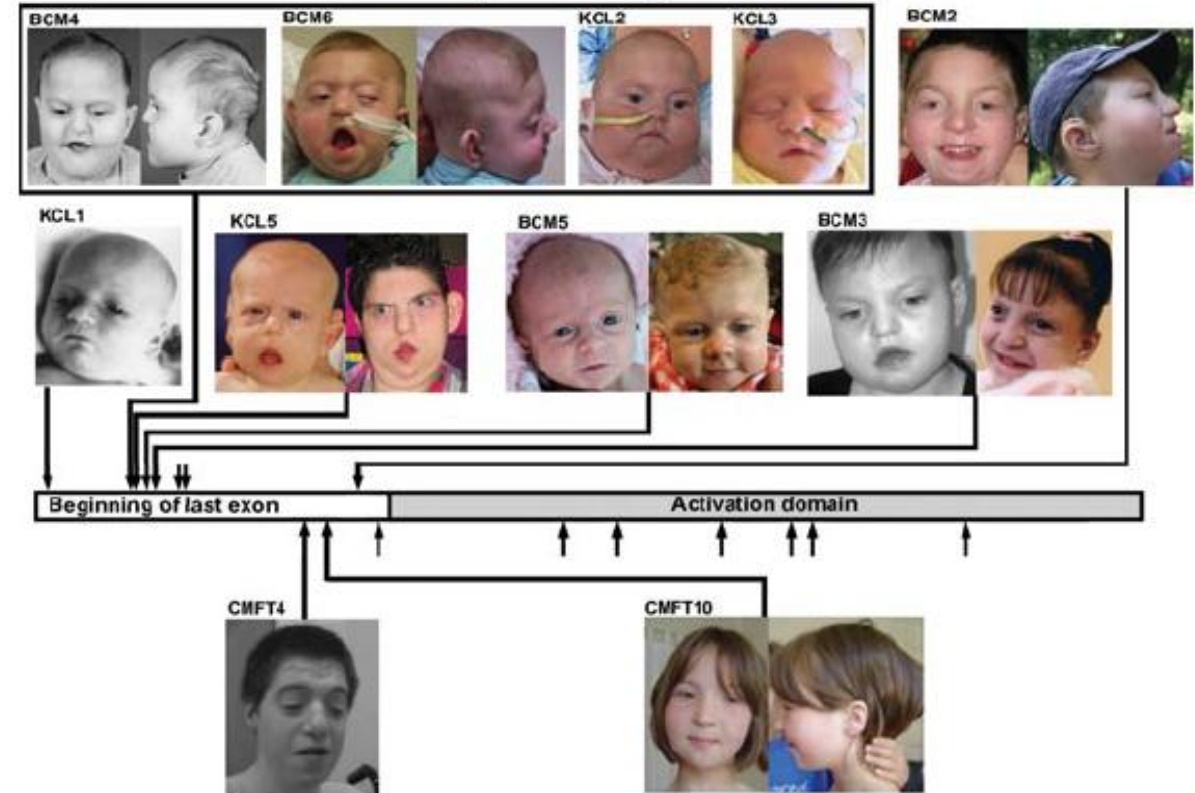
***CREBBP* and *EP300* related disorders**



- **Rubinstein Tabi syndrome Types 1 and 2 (LOF)**
 - ID, growth retardation, obesity, microcephaly, hypertrichosis.
 - High arched eyebrows, long eyelashes, down-slanting PFs, convex nasal ridge, low-hanging columella, typical smile.
 - Broad thumbs and halluces
- **Menke Hennekam syndromes Types 1 and 2 (MV in parts of exons 30 and 31)**
 - ID, Feeding issues, hearing impairments, contractures and many more.
 - At least three domain specific MKHK subtypes exist (MKHK-ZZ, MKHK-TAZ2, and MKHK-ID4)

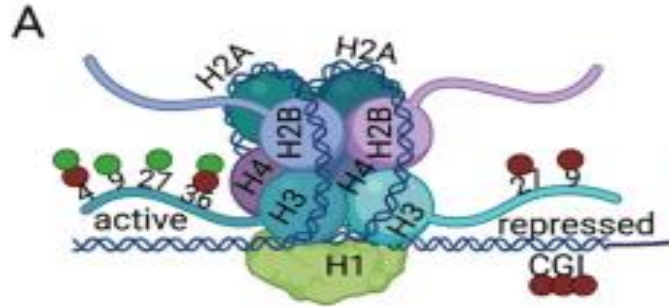


SBBYSS

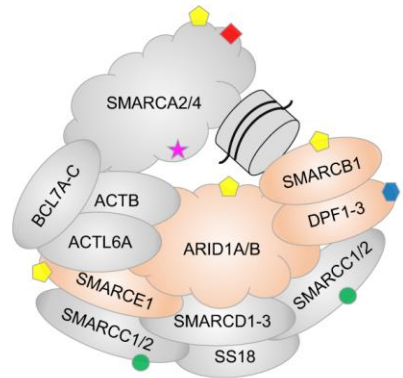


Gannon et al. EJHG 2015.
Campeau et al. Hum Mutat. 2012.

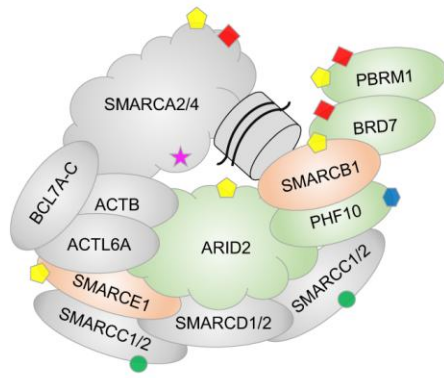
Nucleosome sliding



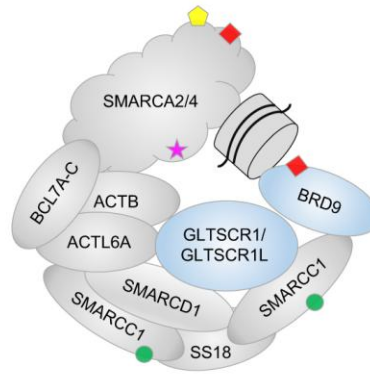
★ ATPase domain ◆ DNA-binding domain ◆ Bromodomain ● Chromodomain ◆ PHD-finger domain



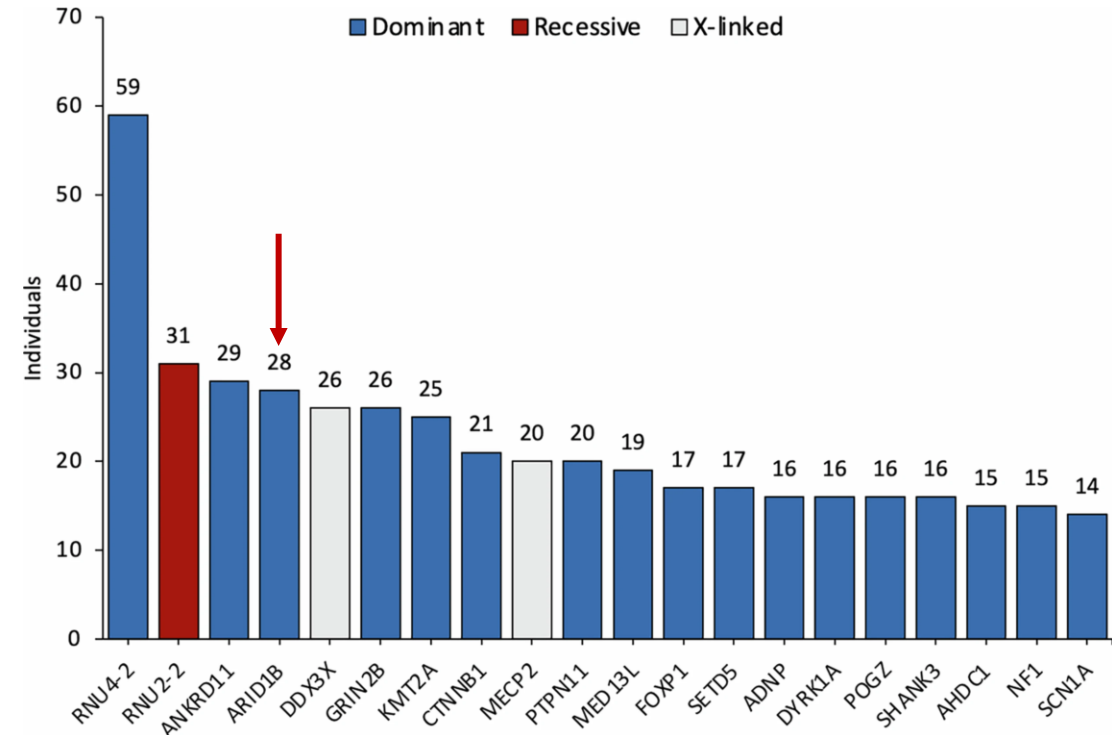
canonical BAF



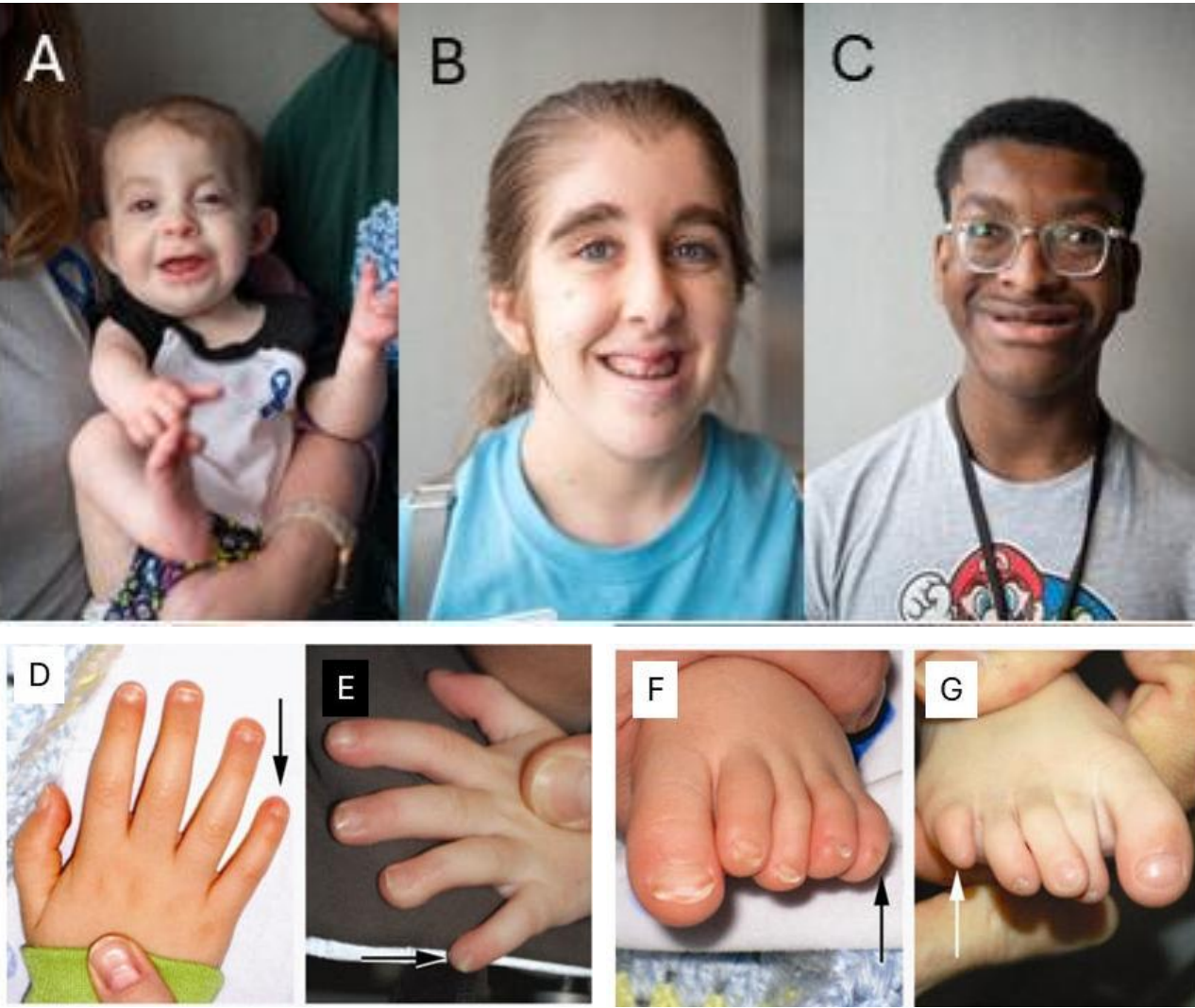
PBAF



non-canonical BAF (ncBAF/GBAF)

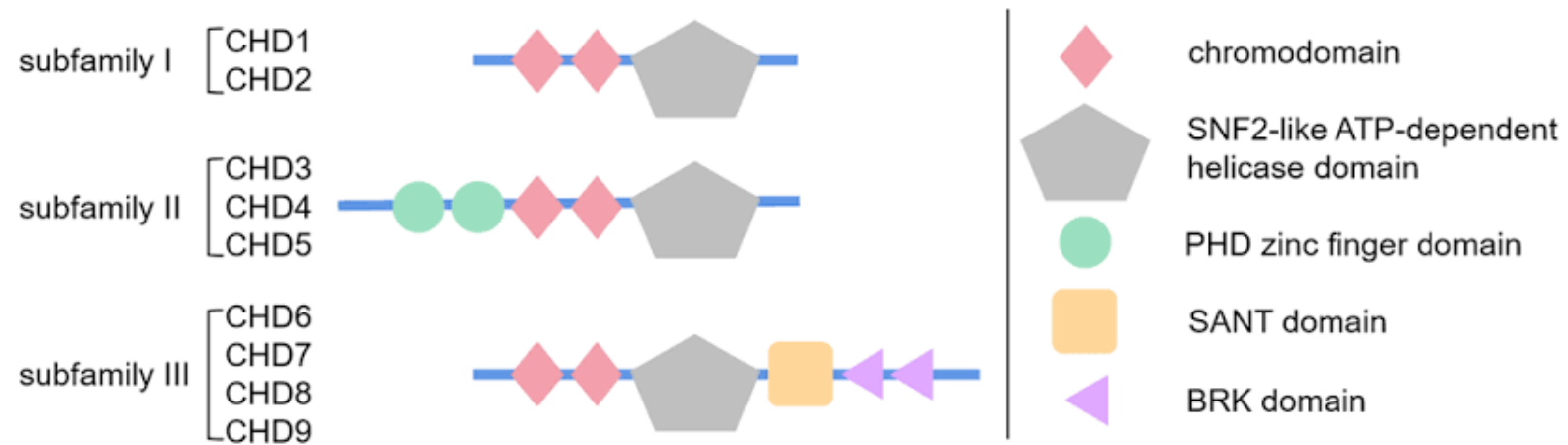
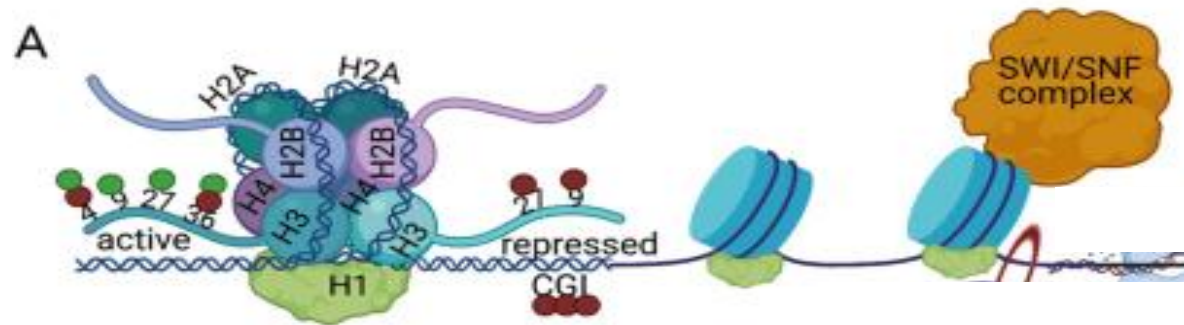


BAFopathies



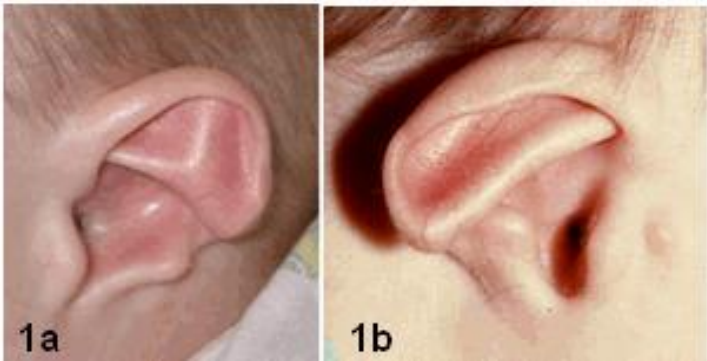
Disease / Syndrome	Associated Gene(s)	Description
Coffin–Siris Syndrome (CSS)	<i>ARID1A</i> , <i>ARID1B</i> , <i>ARID2</i> , <i>DPF2</i> , <i>SOX4</i> , <i>SOX11</i> , <i>SMARCA4</i> , <i>SMARCB1</i> , <i>SMARCC2</i> , <i>SMARCD1</i> , <i>SMARCE1</i> , <i>SOX11</i>	Characterised by developmental delay, intellectual disability, coarse facial features, and hypoplasia of the fifth fingernail/toe or distal phalanges.
Nicolaides–Baraitser Syndrome (NCBRS)	<i>SMARCA2</i>	Phenotypically overlaps with CSS but stands out due to a distinct facial gestalt, sparse hair, short stature, and prominent interphalangeal joints.
SMARCC1-Associated Developmental Dysgenesis Syndrome (SaDDS)	<i>SMARCC1</i>	A recently defined BAFopathy characterised by cerebral ventriculomegaly, aqueductal stenosis, developmental delay, and structural cardiac defects.

Nucleosome sliding and Reading of histone modifications



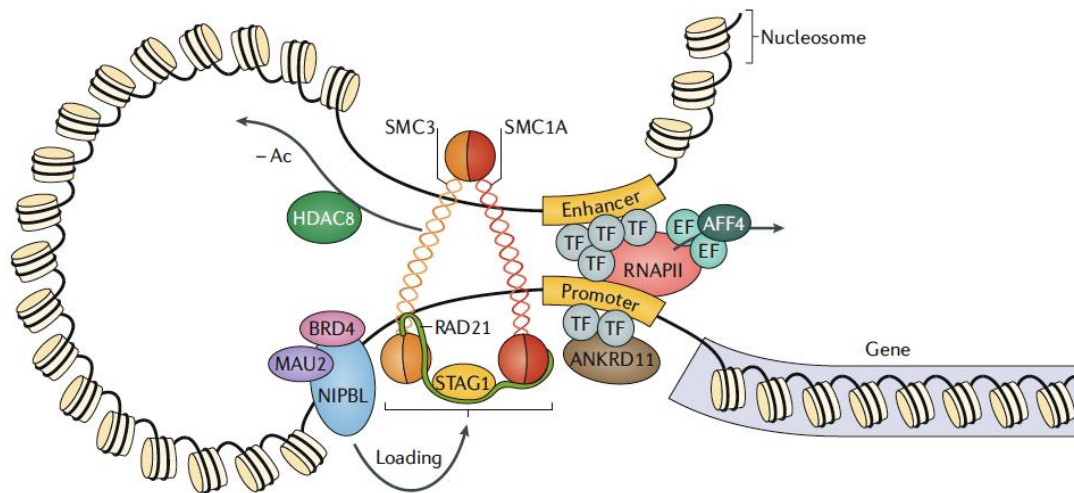
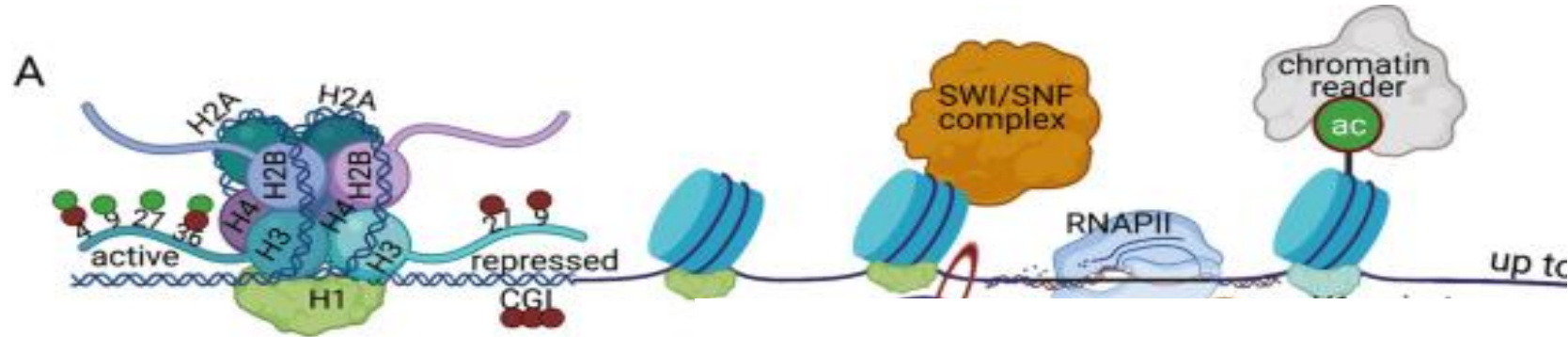
Some more recognisable chromatinopathies

Gene	Human Disorder	Key Clinical Features
<i>CHD1</i>	Pilarowski-Bjornsson Syndrome	DD/ID, ASD, and apraxia.
<i>CHD2</i>	CHD2-Related Neurodevelopmental Disorders	DD/ID, ASD, Epileptic encephalopathy.
<i>CHD3</i>	Snijders Blok-Campeau Syndrome	DD/ID, macrocephaly and distinctive facial features.
<i>CHD4</i>	Sifrim-Hitz-Weiss Syndrome	DD/ID, congenital heart defects, macrocephaly, and skeletal anomalies.
<i>CHD7</i>	CHARGE Syndrome	Coloboma, Heart defects, Atresia of the choanae, Retardation of growth/development, Genital abnormalities, and Ear anomalies/deafness.
<i>CHD8</i>	Autism Spectrum Disorder (Syndromic)	DD/ID, ASD, macrocephaly, distinct facial features

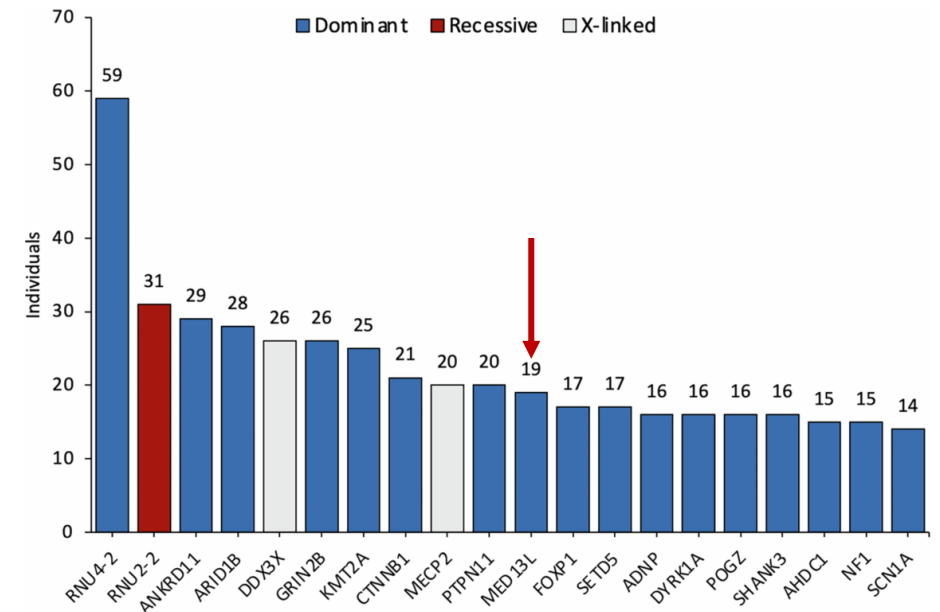
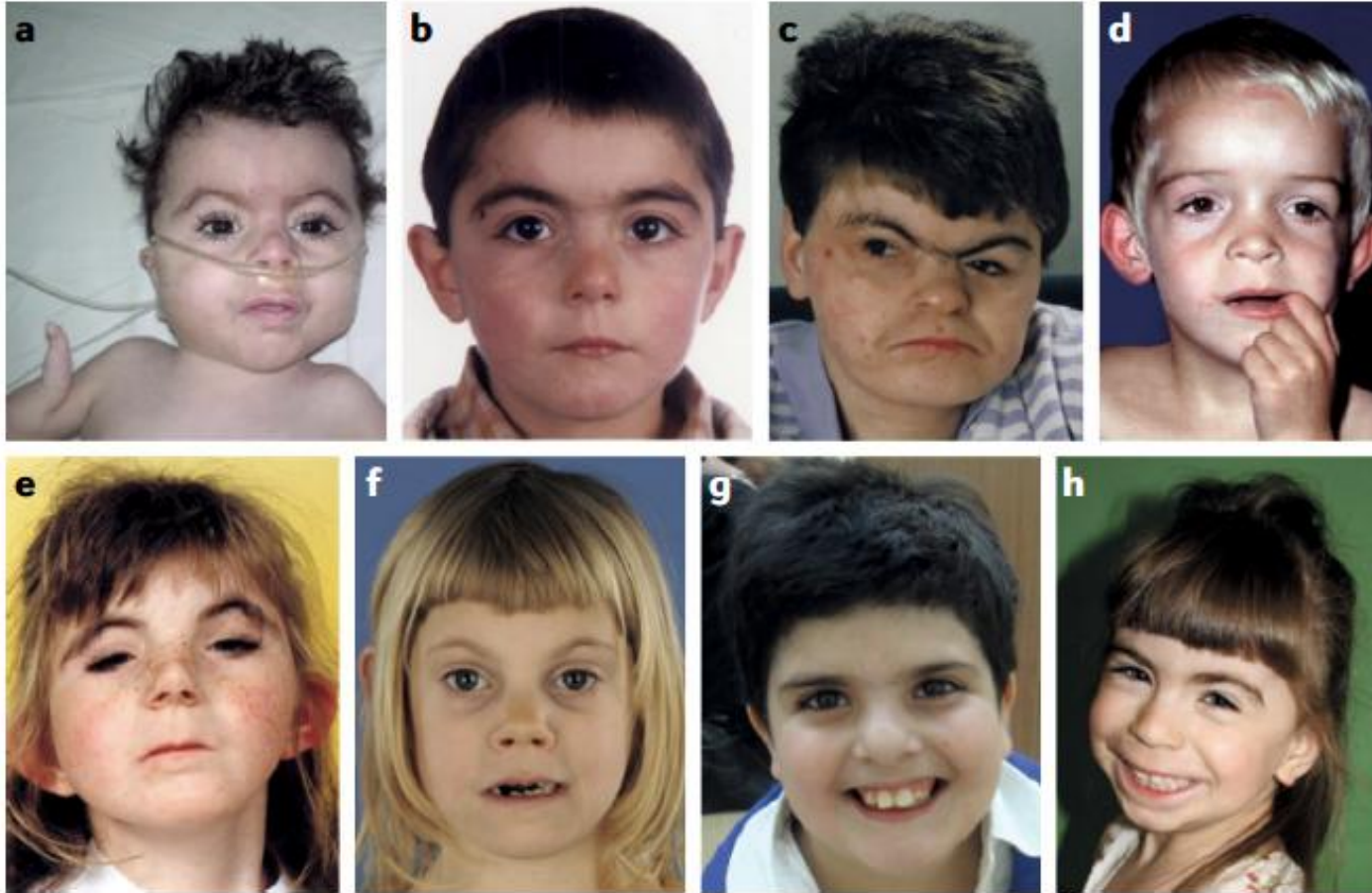


Molly Godfrey

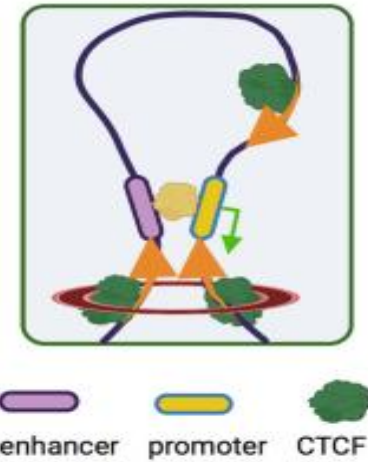
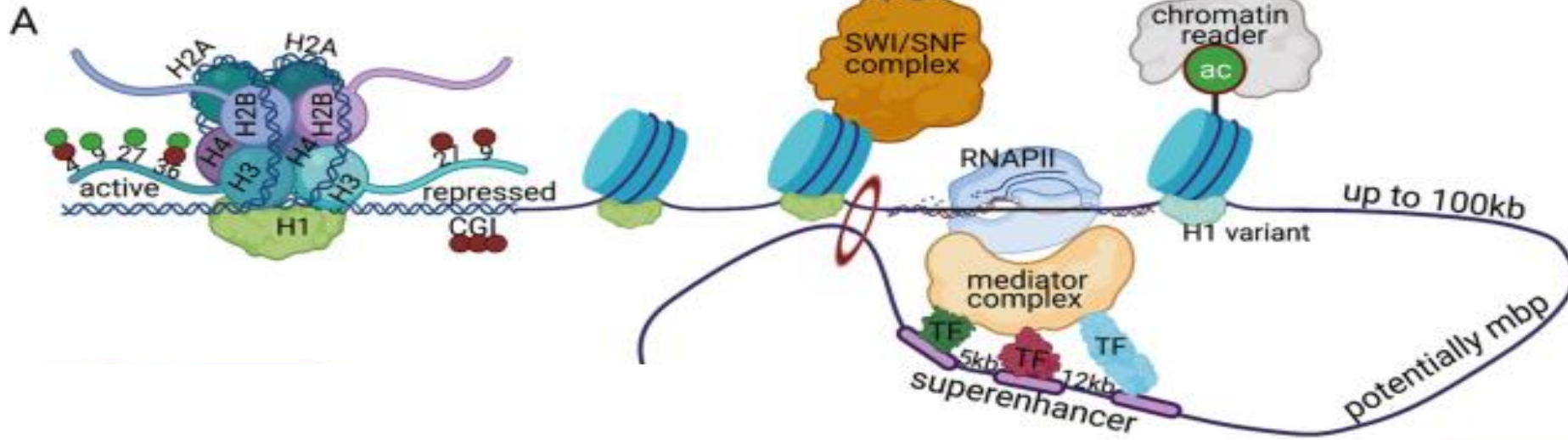
Looping and transcription



Cohesinopathies and mediator complex disorders



Chromatin organisation



KBG syndrome

- DD/ID
- ADHD, ASD
- Macrodonia (particularly of the upper central incisors)
- Facial dysmorphism
- Het LOF *ANKRD11* variants

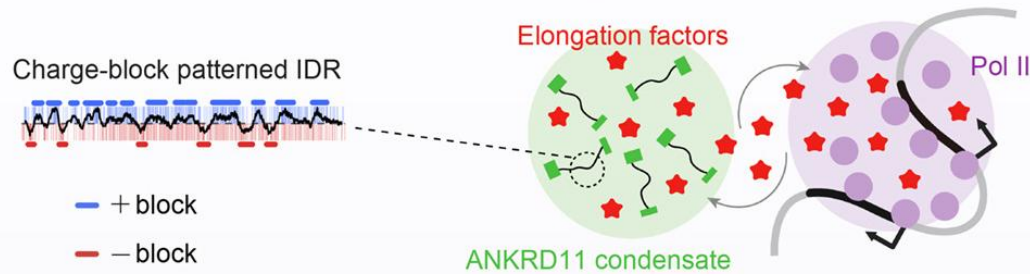


Figure 1. Macrodonia of permanent upper central incisors, dental pits, and prominent mamelons

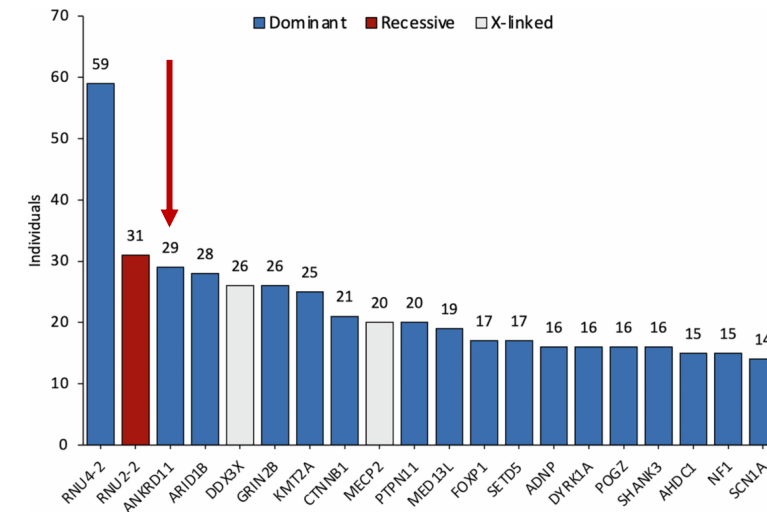
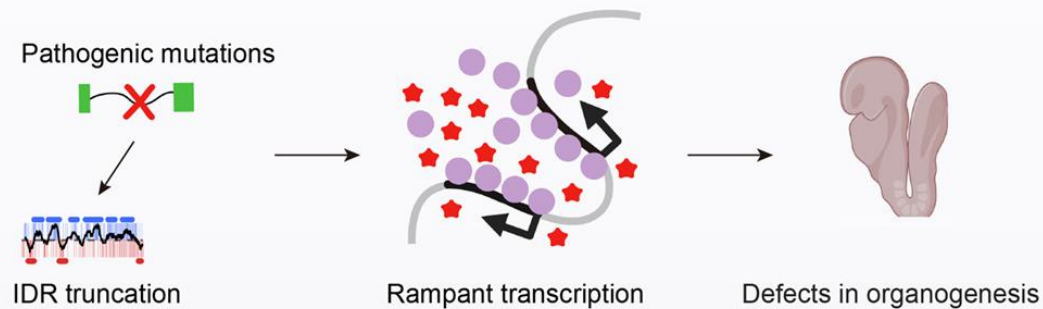


Figure 2. Triangular face, synphrys, prominent nasal bridge, anteverted nares, long philtrum, and thin vermilion of the upper lip in two affected males

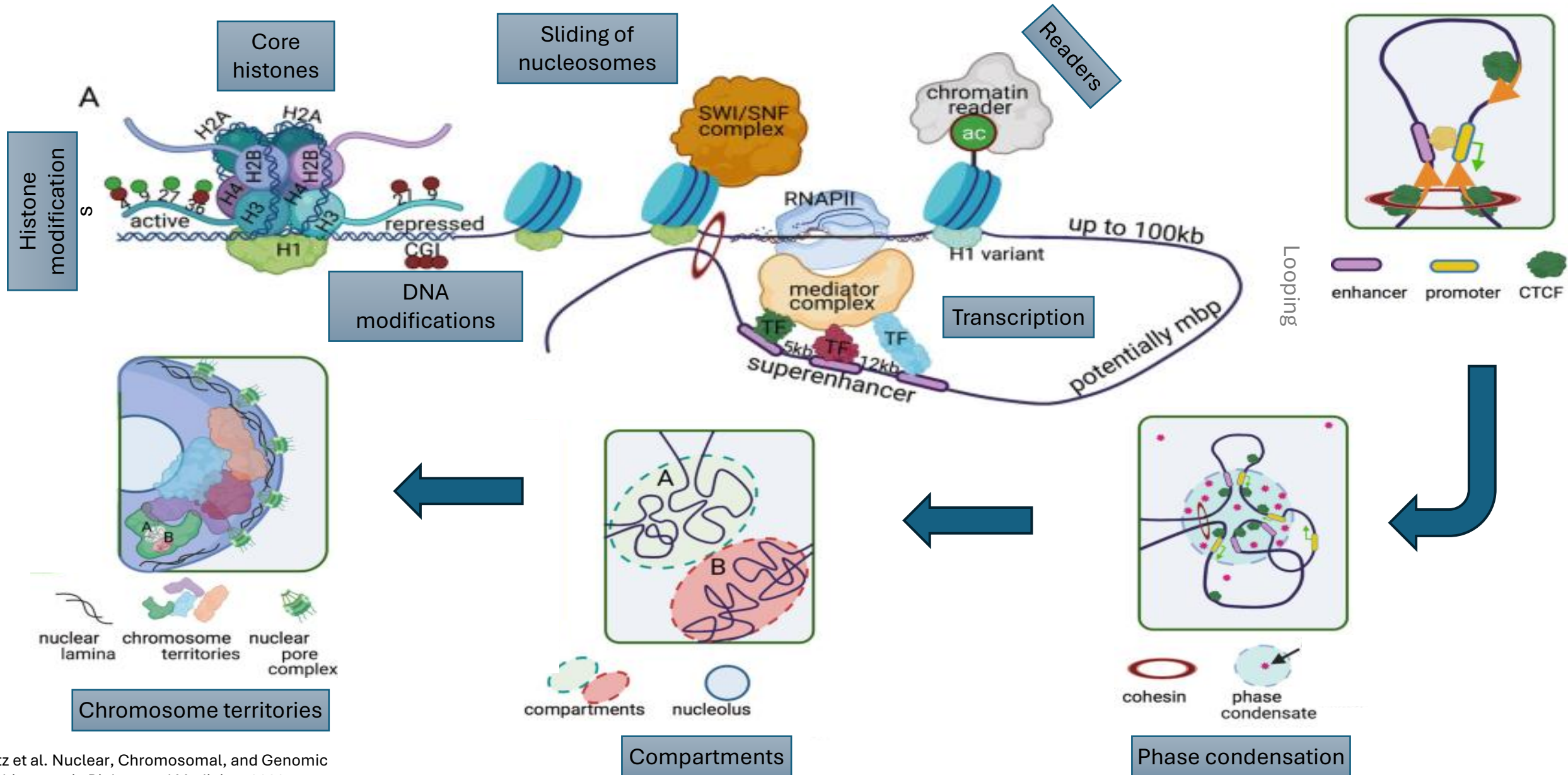
ANKRD11 condensates restrict Pol II elongation



Dysregulated hypertranscription in multi-organ disorders



Chromatin organisation



Rare Disease Research UK.

Epigenomics of Rare Disorders - EpiGenRare

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EpiGenRare Network is community of like-minded academics, healthcare professionals and representatives from industry and patient support groups that aims to address the many remaining challenges in understanding, diagnosing and treating epigenetic rare disorders.

1st EpiGenRare Conference – 26th March 2025

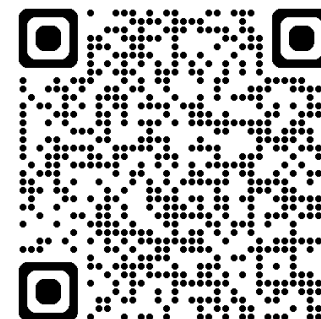


Welcome to the European Human Genetics Conference
Hybrid Conference
Gothenburg, Sweden
JUNE 13–16, 2026

**EpiGenRare Symposium; Episignatures
workshop**



**Would you like to join
EpiGenRare Network?**



Take home messages

- Variation in genes encoding components of the chromatin machinery are important for rare diseases.
- Several chromatinopathies are characterised by CNS phenotypes, growth issues, congenital anomalies and dysmorphism.
- Classification of chromatinopathies suggests clinical and mechanistic convergence.
- Better mechanistic understanding may lead to improved therapy options.

