McKUSICK - NATHANS
Institute of Genetic Medicine

JOHNS HOPKINS MEDICINE
THE JOHNS HOPKINS HOSPITAL

KABUKI SYNDROME 101

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THE McKUSICK-NATHANS
EPIGENETICS AND CHROMATIN CLINIC (ECC)

History

"Kabuki make-up syndrome" first described in medical literature

1981

First gene (MLL2) identified

2010

Kabuki Conference
Baltimore, MD

2015

How rare (or common) is KS?

1/32,000 to 1/87,000

people have Kabuki syndrome

Niikawa N, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: A study of 62 patients. Am J Med Genet. 1988;31:565–89.

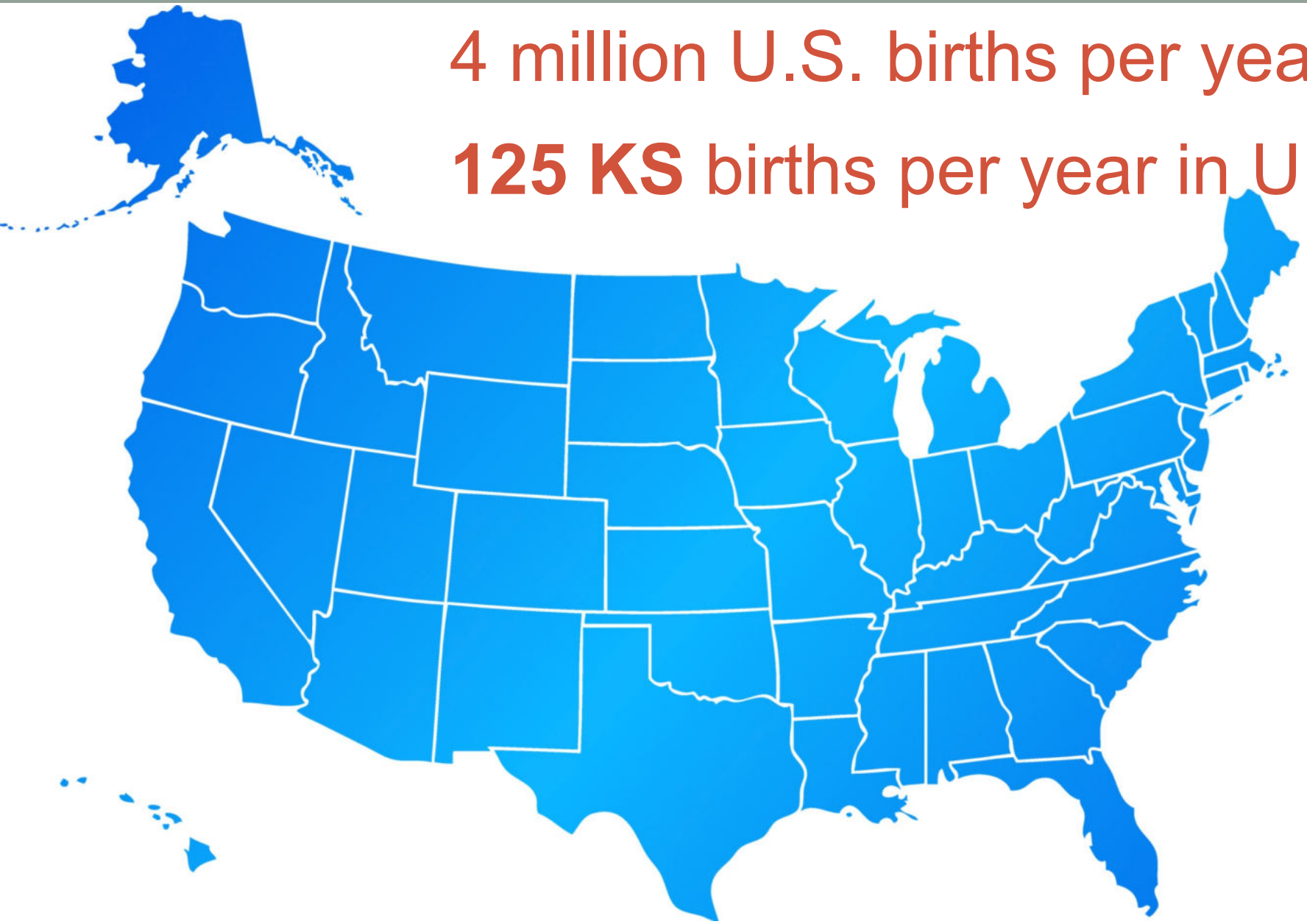
White SM, et al. Growth, behavior, and clinical findings in 27 patients with Kabuki (Niikawa-Kuroki) syndrome. Am J Med Genet A. 2004;127A:118–27.

Raven's Stadium
71,000

Camden Yards
46,000

4 million U.S. births per year

125 KS births per year in U.S.



130 million births in the world per year
350,000 birth in the world per day

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4,062 KS births in the world per year
11 KS births in the world per day

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HOW IS KS DIAGNOSED?

Clinical Diagnosis

Diagnosis based on features and medical conditions together that can be gathered in the medical office

Molecular Diagnosis

Diagnosis based on genetic testing that identifies specific gene and mutation

Facial Features

- Long palpebral fissures
- Long eye lashes
- Arched eye brows
- Thin ends of eyebrows
- Flatness of the cheeks and nose
- Large, prominent ears
- Small head size

Banka, S., et al. How genetically heterogeneous is Kabuki syndrome? MLL2 testing in 116 patients, review and analyses of mutation and phenotypic spectrum. Europ. J. Hum. Genet. 20: 381-388, 2012.

Physical Features

- Flexible joints
- Persistent fetal fat pads on fingers and toes
- Short stature

J Genet Med. 2010 Jun;7(1):37-44. Korean.

Condition	Frequency
Hypotonia	25-89%
Intellectual Disability	84-92%
Slow growth after birth	35-81%
Joint hypermobility	50-75%
Feeding Difficulties	~70%
Heart defects	40-50%
Premature breast development	7-50%
Hearing loss	40%
Seizures	10-39%
Eye problems	~33%
Cleft lip and/or cleft palate	~33%
Kidney defects	>25%
Immune dysfunction	?
Teeth abnormalities	?

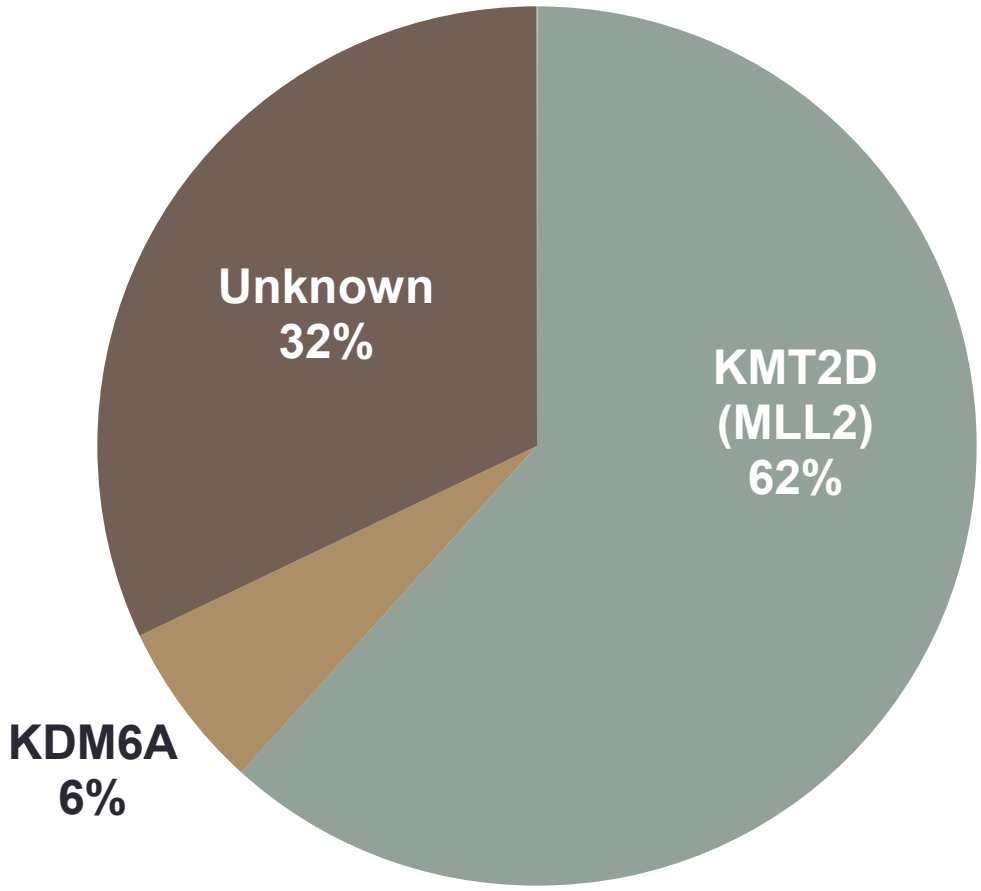
Clinical Diagnosis

Diagnosis based on features and medical conditions together that can be gathered in the medical office

Molecular Diagnosis

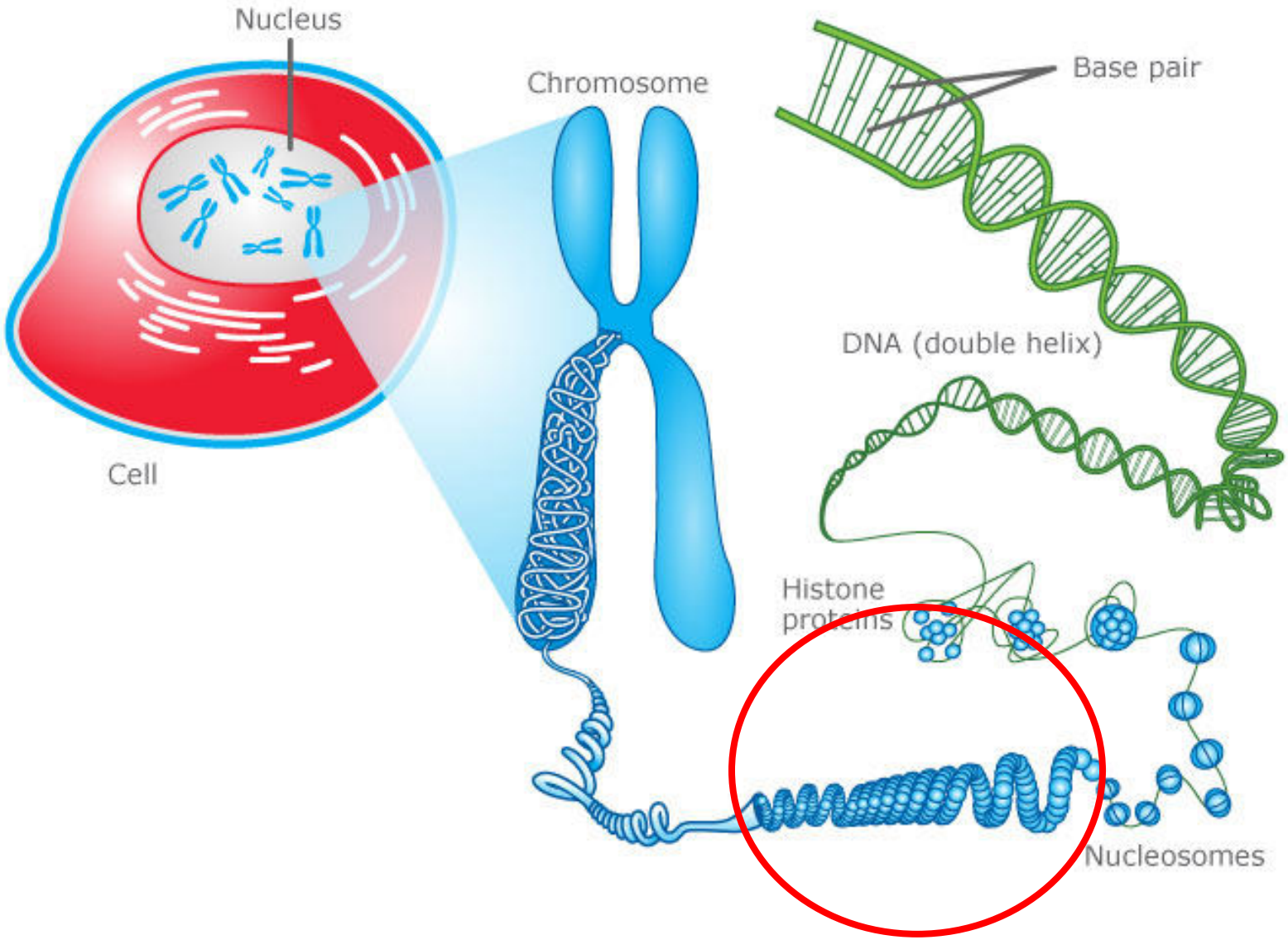
Diagnosis based on genetic testing thatidentifies specific gene and mutation

Molecular Diagnosis



•Miyake, N, et. Al. MLL2 and KDM6A mutations in patients with Kabuki syndrome. Am. J. Med. Genet. 161A: 2234-2243, 2013.
•Banka, S., et al.How genetically heterogeneous is Kabuki syndrome? MLL2 testing in 116 patients, review and analyses of mutation and phenotypic spectrum. Europ. J. Hum. Genet. 20: 381-388, 2012.
•Hannibal, M. C., et al. Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. Am. J. Med. Genet. 155A: 1511-1516, 2011.

HOW DO THESE GENES CAUSE KS?



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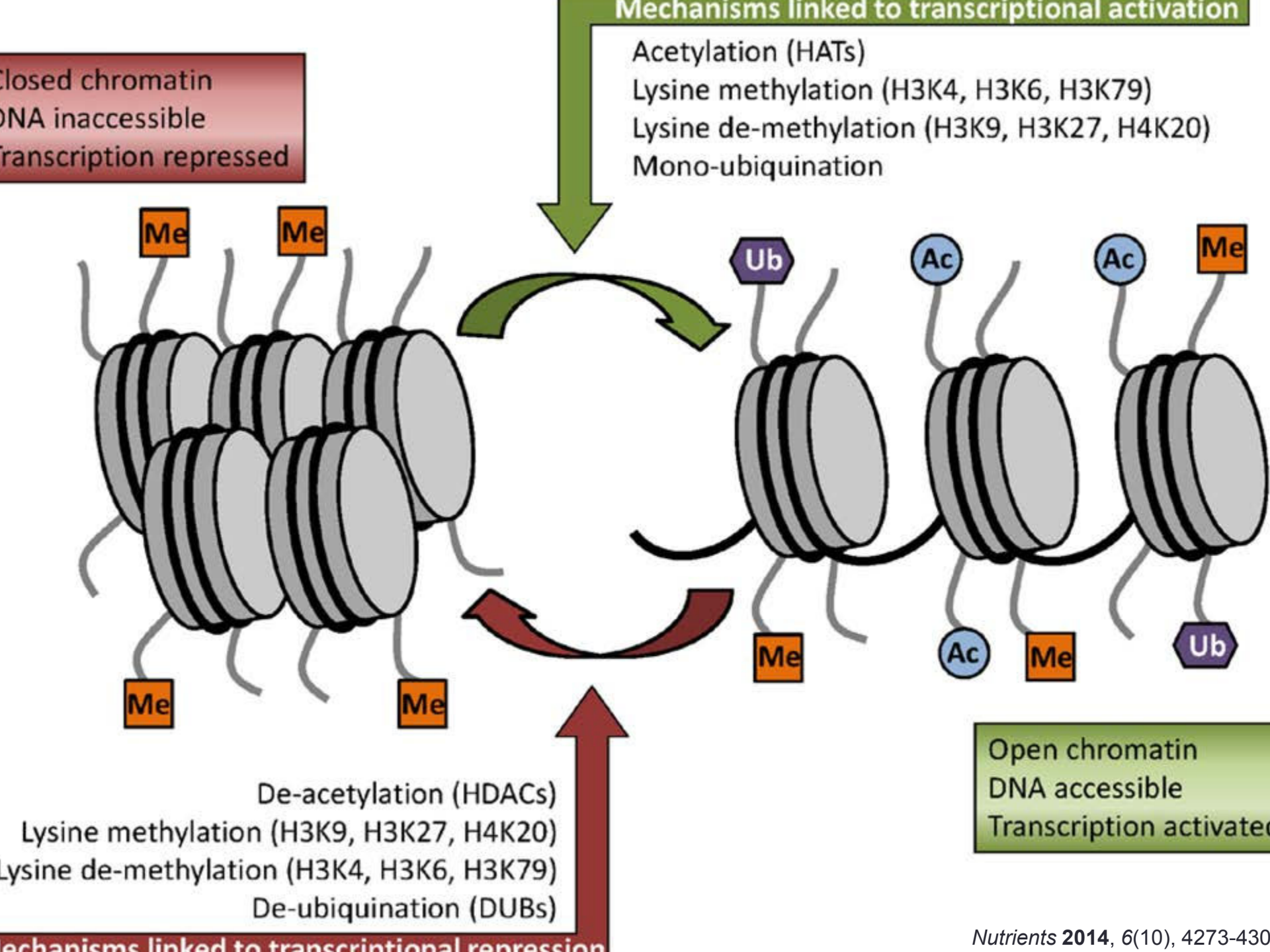
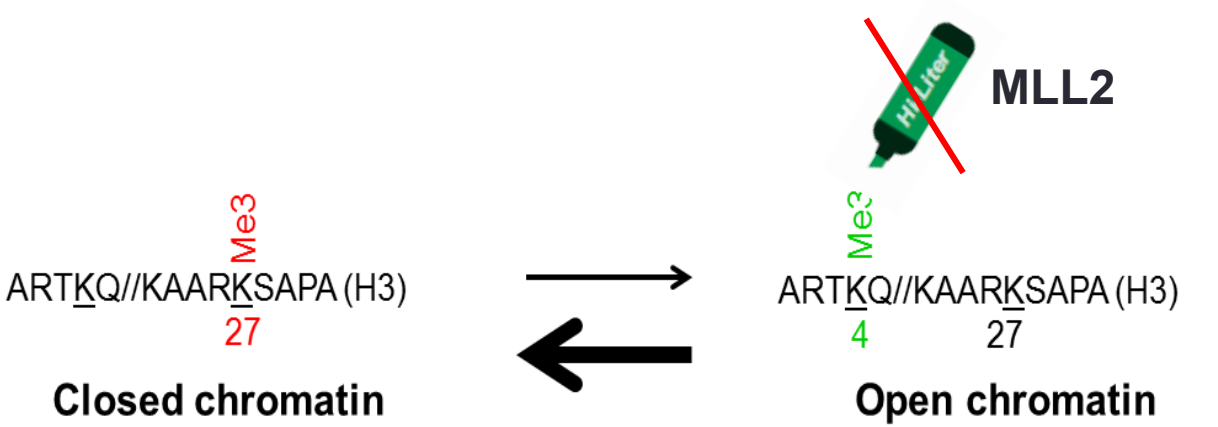


Nutrients **2014**, *6*(10), 4273-430

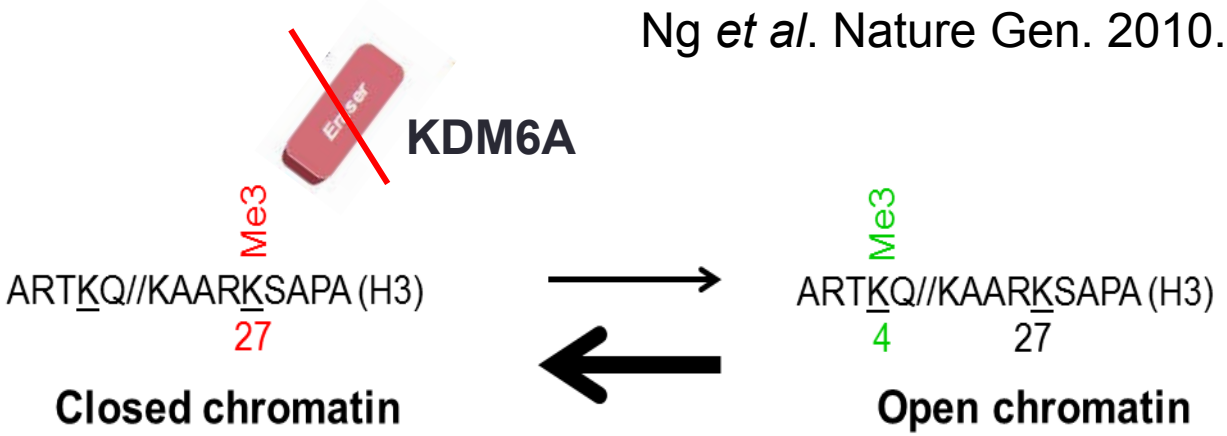
Epigenetic machinery: the genome's “highlighter”

- Epigenetic marks are modifications of DNA or associated proteins, other than the DNA sequence itself, that are heritable through cell division (mitosis)
- Reversible and affected by the environment.
- Multiple genes involved in creating “highlighting” marks while other genes “erase”

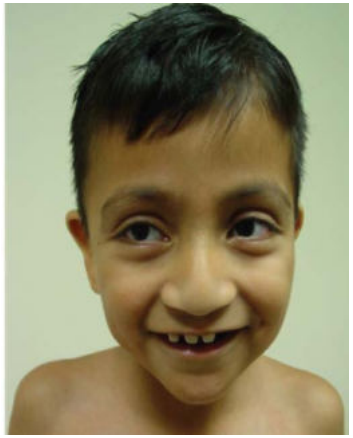
Kabuki syndrome: An imbalance of open and closed chromatin?



Ng *et al*. Nature Gen. 2010.

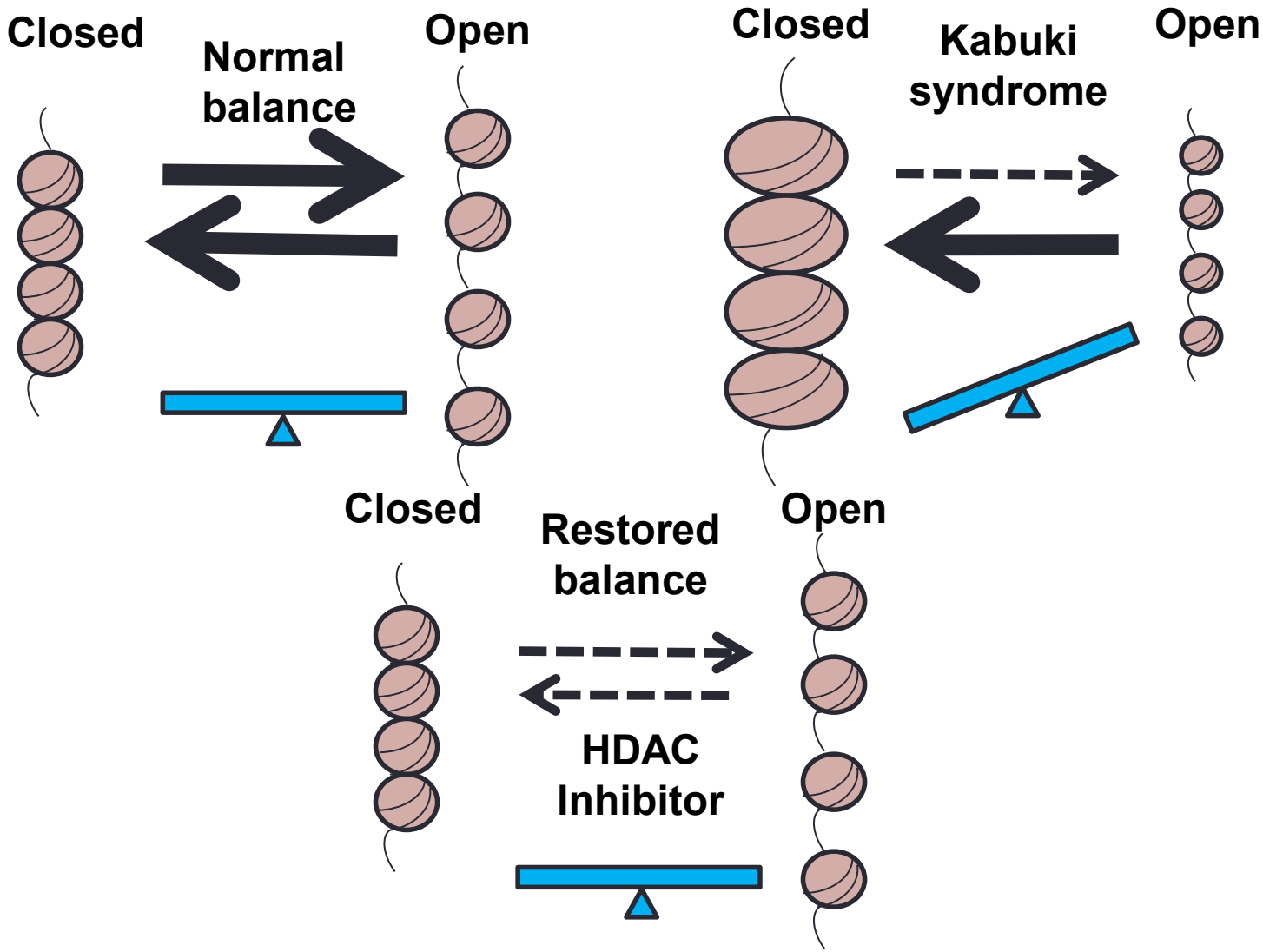


Lederer *et al*. Am. J. Hum Genet. 2012.

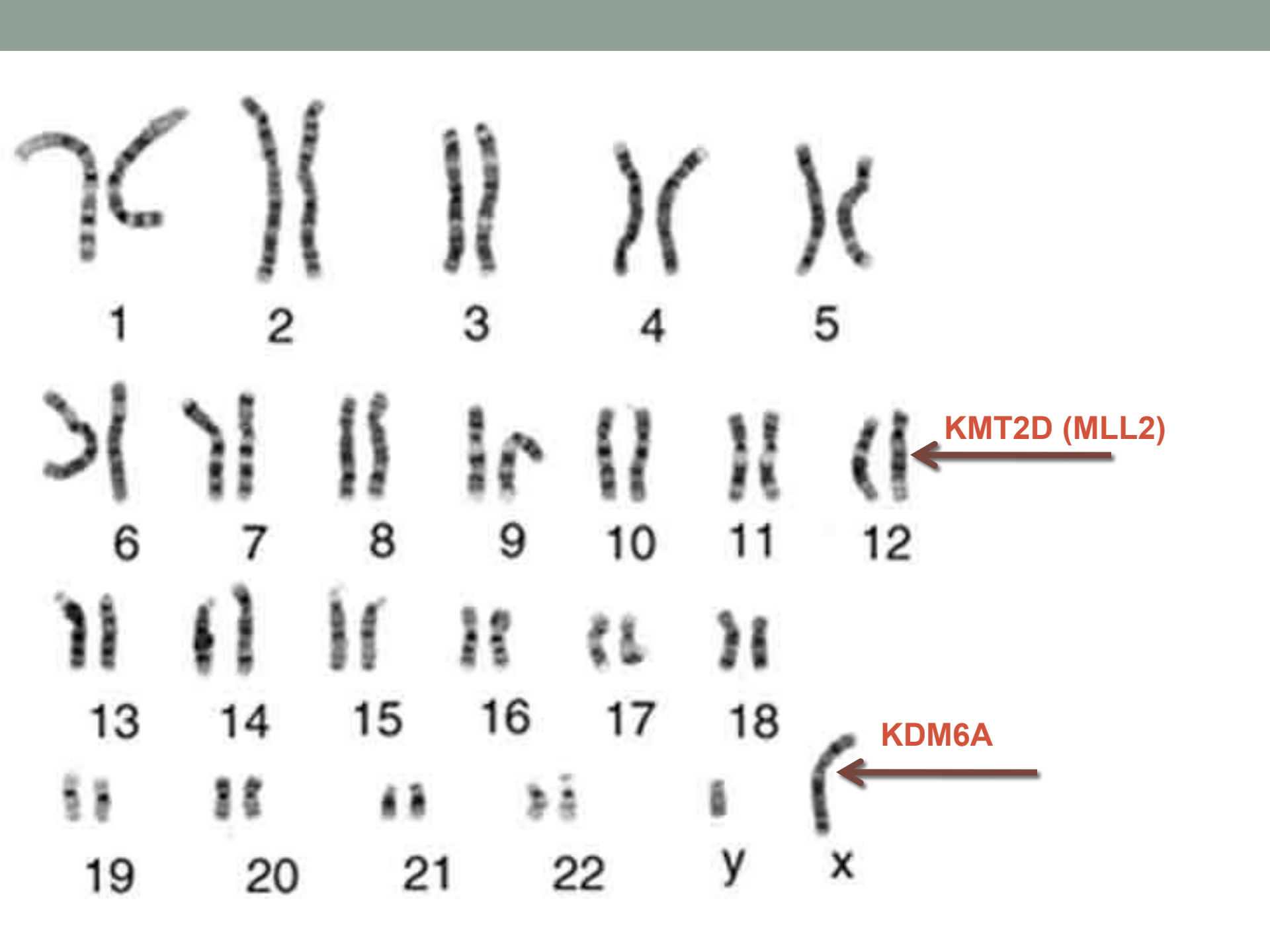


Adam MP *et al*. Clin. Genet. 2005

Kabuki syndrome (KS): A treatable cause of intellectual disability?



INHERITANCE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KMT2D (MLL2)
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KDM6A
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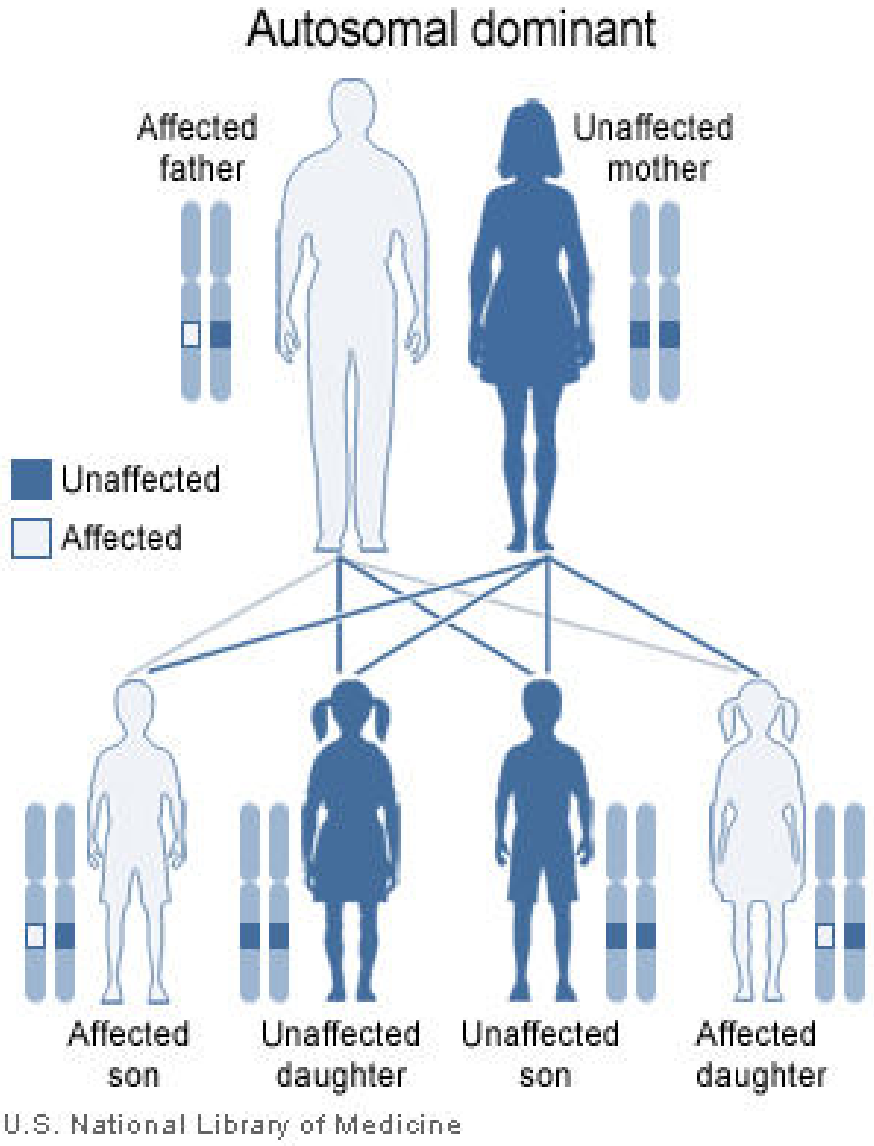
y
x

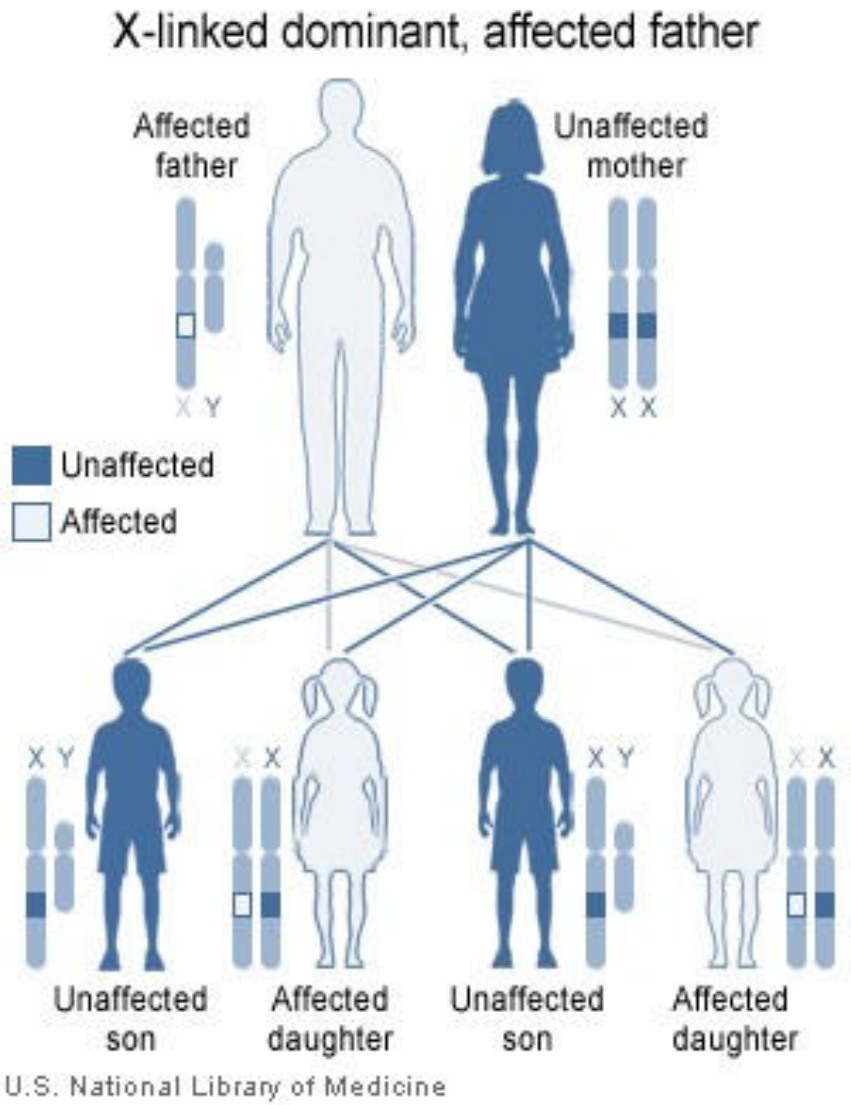
KMT2D (MLL2)

- Autosomal dominant
- Most cases de novo (new)
- If you have KS, 50% chance to have a child with KS



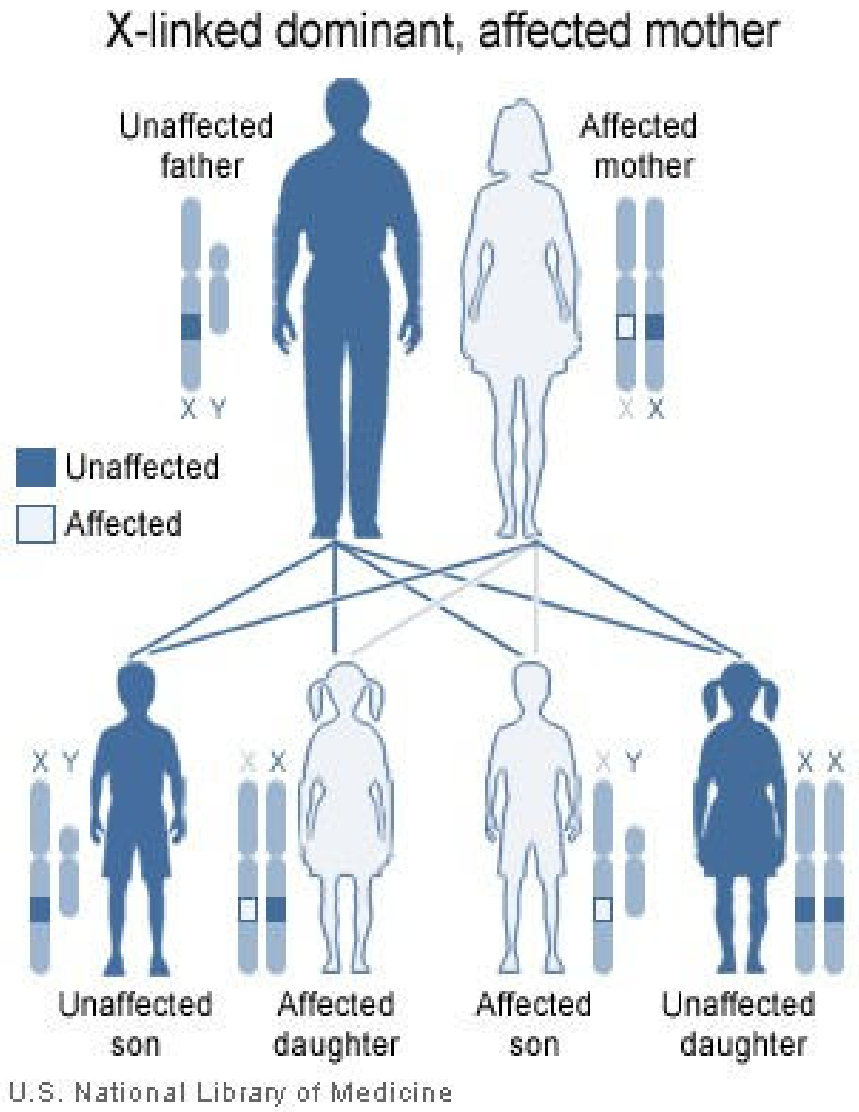
KDM6A

- X-linked (dominant)
- If father has KS,
  - All daughters will have KS
  - Sons will NOT have KS



KDM6A

- X-linked (dominant)
- If mother has KS,
  - 50% for both sons and daughters to have KS



OUR CLINIC

Epigenetics & Chromatin Clinic

Johns Hopkins
McKusick-Nathans Institute
of Genetic Medicine

Mission Statement

1) To *diagnose* and provide optimal *care* for individuals with either classical epigenetic disorders or disorders of the epigenetic machinery.

2) To *learn* from our patients some fundamental truths about epigenetics with the hope that this additional knowledge will lead to *therapeutic development* for our patients in the future.

3) To *educate* health providers, patients, and families about epigenetics and the disorders of the epigenetic machinery.

Contact Us

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Visit our website:
https://igm.jhmi.edu/ecc-clinic

Ideas:

1. Build expertise;

2. Learn from patients and families;

3. Educate health professional about Kabuki syndrome and related disorders

What have we learned?

Clinical Recommendations

- Ears: frequent ear infections -> hearing loss -> decreased language milestones
  - **ECC Clinic:** Frequent hearing checks by audiology, aggressive management of ear infections
- Muscular: neonatal hypotonia ->often improves in toddler years, but may make child look worse off early in life
  - **ECC Clinic**: physical therapy helpful
- Immunological: immune dysregulation; this can present at ANY time in life as immune dysregulation or as an autoimmune disorder:
  - **ECC Clinic:** Immune function studies and titers for vaccinations
    - At JHH we collaborate with immunologist (Dr. Lederman)

Clinical Recommendations 2

- Heart: many different types of CHD; some of these unusual such as coarctation (need to visualize aortic arch)
  - **ECC Clinic:** echocardiogram with specific views of aortic arch
    - JHH work with Dr. Dietz group to evaluate
- Kidneys: many different anatomical defects; need to be uncovered because of infectious risks
  - **ECC Clinic:** renal ultrasound
- Intellectual disability: there are strengths and weaknesses; some patients have overcome these nicely and some have minimal weaknesses
  - **ECC Clinic:** Neuropsychological testing after a certain age
    - We need to map these in general and in individuals (Dr. Vaurio at KKI)

Clinical Recommendations 3

- Hips: congenital hip disolocation; appears to be a relatively common; maybe secondary to low tone in utero
  - **ECC Clinic:** Needs to be ruled-out in babies and young children
    - Our clinic works with Dr. Sponsellor to evaluate and treat
- Eyes: many different anatomical defects
  - **ECC Clinic:** yearly eye exams
    - JHH refers to Wilmer Eye Institute
- Spine: scoliosis
  - ECC Clinic: spine x-rays; if scoliosis present, refer to orthopedics
    - Our clinic works with Dr. Sponsellor to evaluate and treat
- Feeding problems: Look for cleft, look for reflux.

Thank you!

- To the patients for their patience
- To the families for their dedication
- To Dr. Bjornsson and Dr. Fahrner for their knowledge and commitment
- Dana Levinson- organizer extraordinaire!

THE MCKUSICK-NATHANS
EPIGENETICS AND CHROMATIN CLINIC (ECC)

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