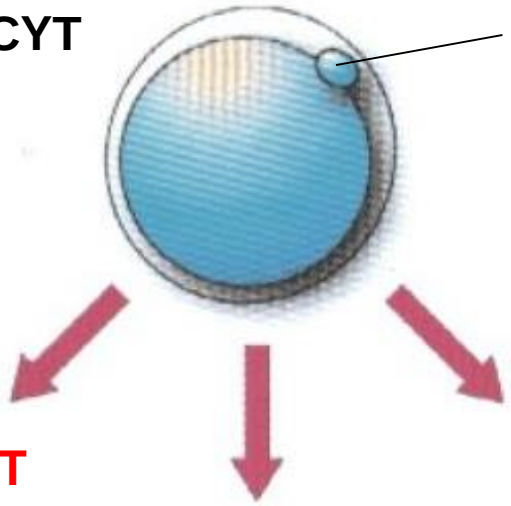
Co přináší savčí matka svému potomstvu (kromě výživy v děloze)

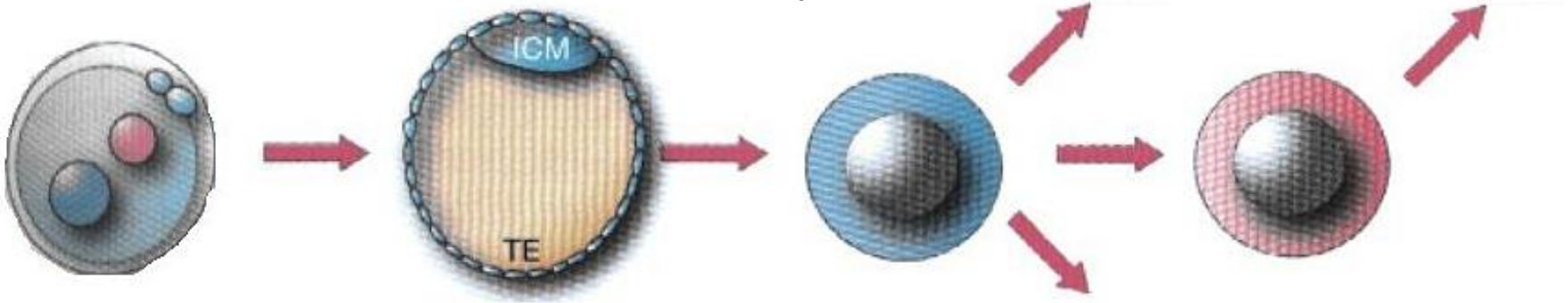


MATERNÁLNÍ DĚDIČNOST
(RNA, proteiny aj.)
jako první informace
vyvíjející se zygoty

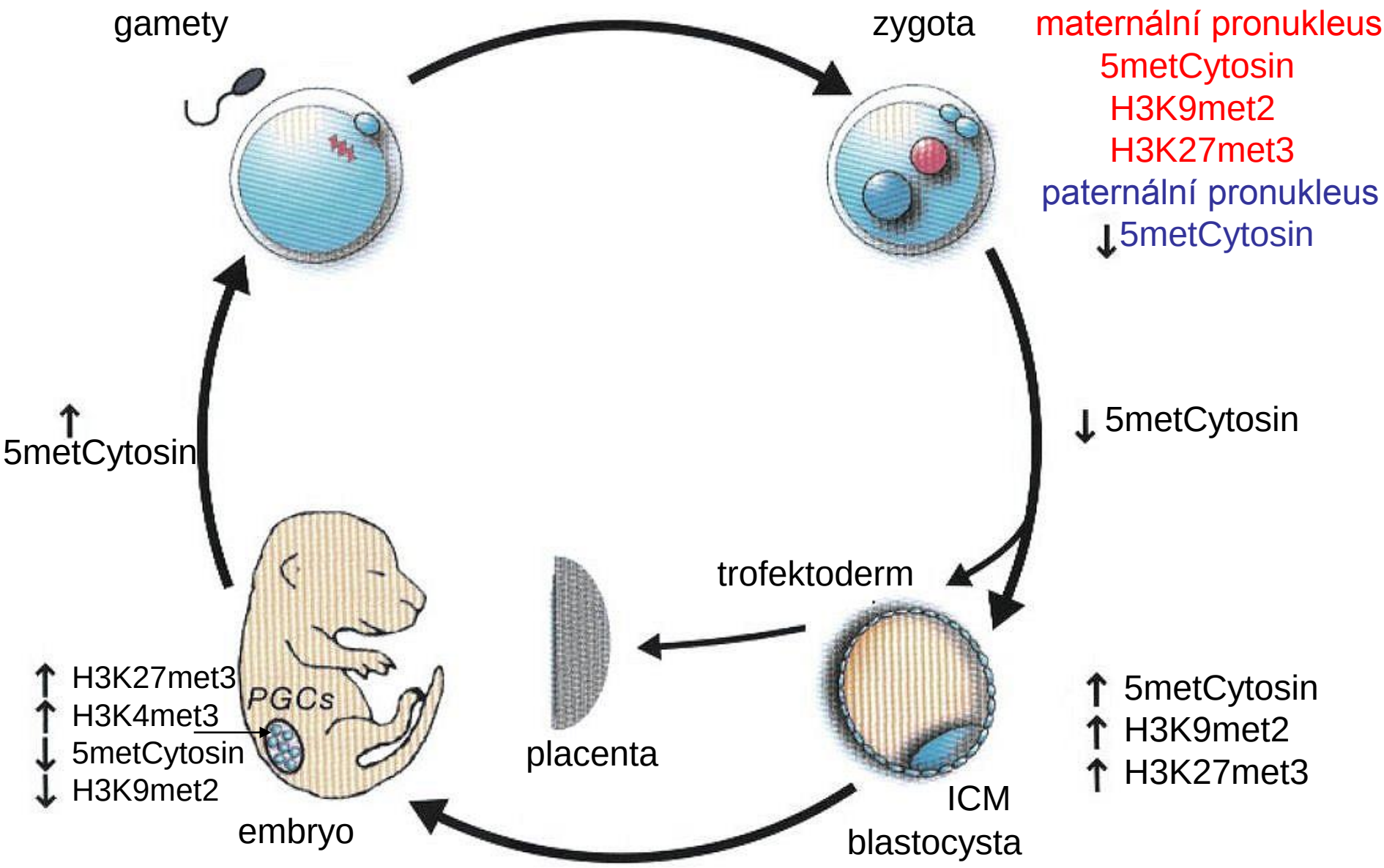
GENETICKÁ A STRUKTURNÍ INFORMACE
jaderný genom samičí gamety,
buněčné struktury (př. mitochondrie)

EPIGENETICKÁ INFORMACE
metylace DNA a modifikace
chromatinu oocytu

Raný vývoj savčího embrya



EPIGENETICKÉ REPROGRAMOVÁNÍ V PRŮBĚHU SAVČÍHO VÝVOJE



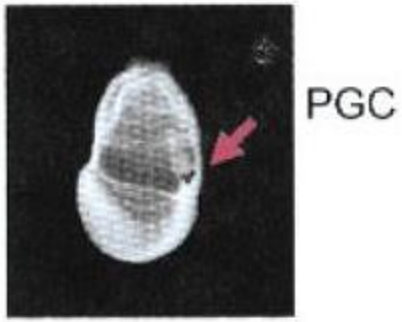
DVA MODELY INICIACE ZÁRODEČNÉ DRÁHY

Preformace = dědičnost preformovaných zárodečných buněčných determinant
(Drosophila, Caenorhabditis)

Epigeneze = specifikace buněk zárodečné dráhy, kde skupina potenciálně ekvivalentních pluripotentních buněk získá své poslání v reakci na induktivní signály, zatímco zbývající buňky se stávají somatickými (myš, člověk, rostliny)

U *D. melanogaster* jsou prekurzory zárodečných buněk pólové buňky v posteriorní části syncytia, transkripční umlčování závisí na RNA kódované genem *Pgc*

C. elegans | **D. melanogaster** | **M. musculus**



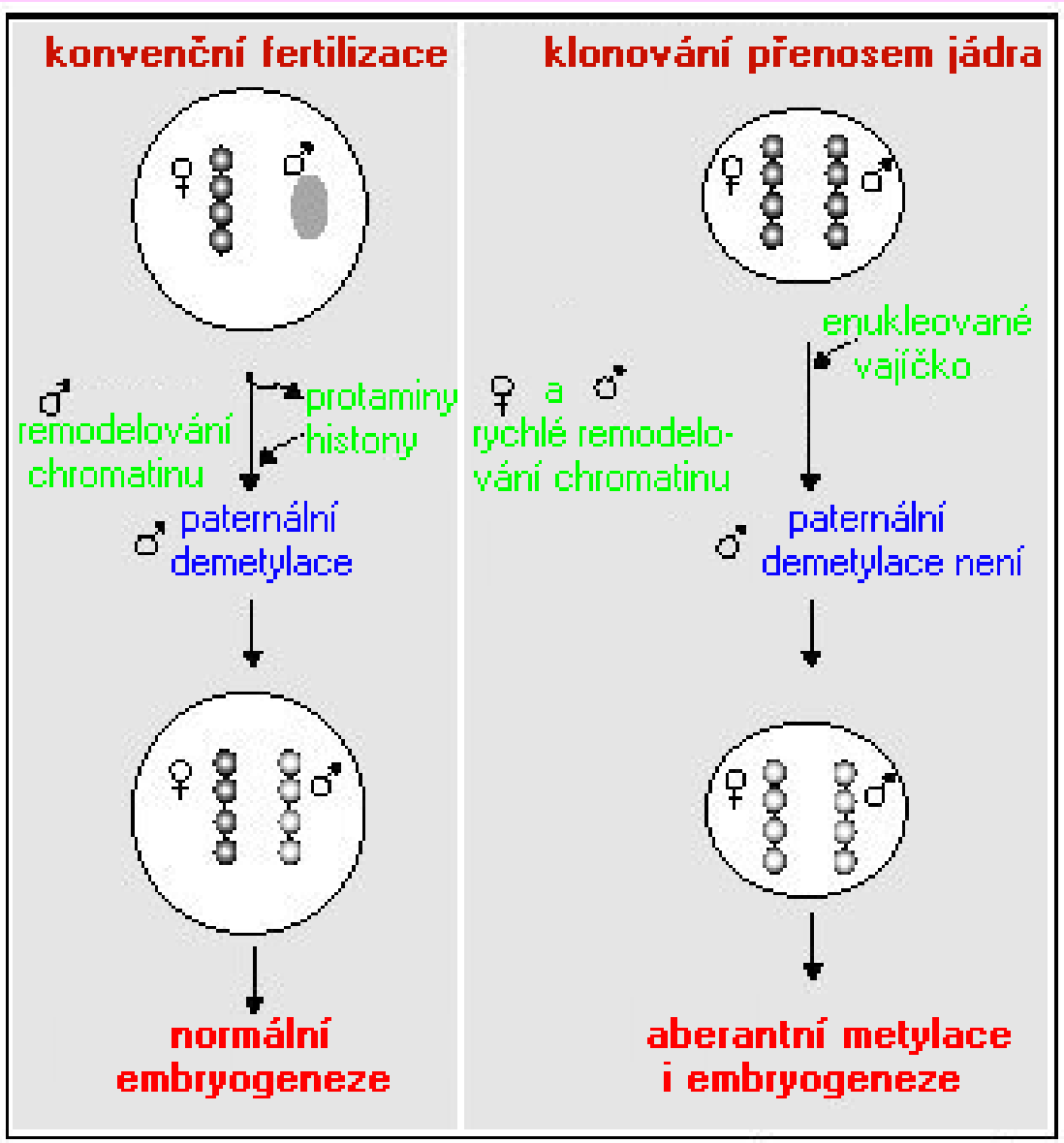
Pie-1 | *pgc: Polar granule component* | Blimp1

Zárodečná linie *C. elegans* je specifikována po prvním buněčném dělení zygoty expresí genu *Pie1* (transkripční umlčování), druhá buňka se stává somatickou.

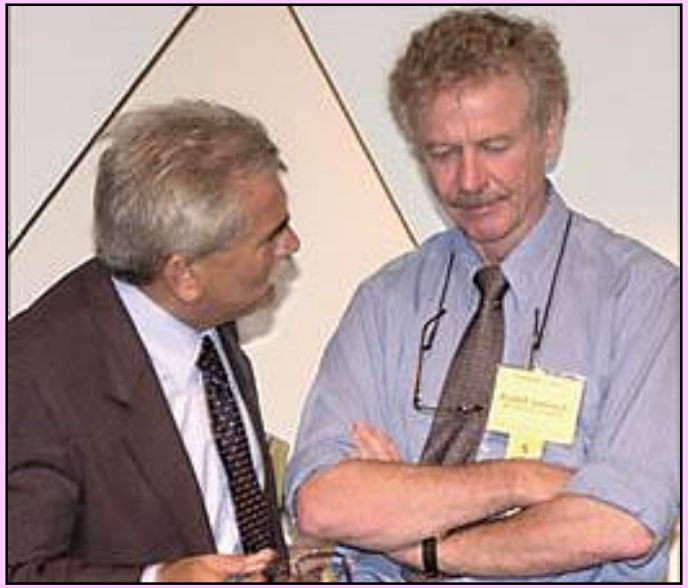
U *M. musculus* časné prekurzory zárodečných buněk vznikají po expresi genu *Blimp1*, který iniciuje transkripční umlčování v těchto buňkách.

KLONOVÁNÍ : TRANSPLANTACE JADER

Klonování savců vede k poruchám imprintingu

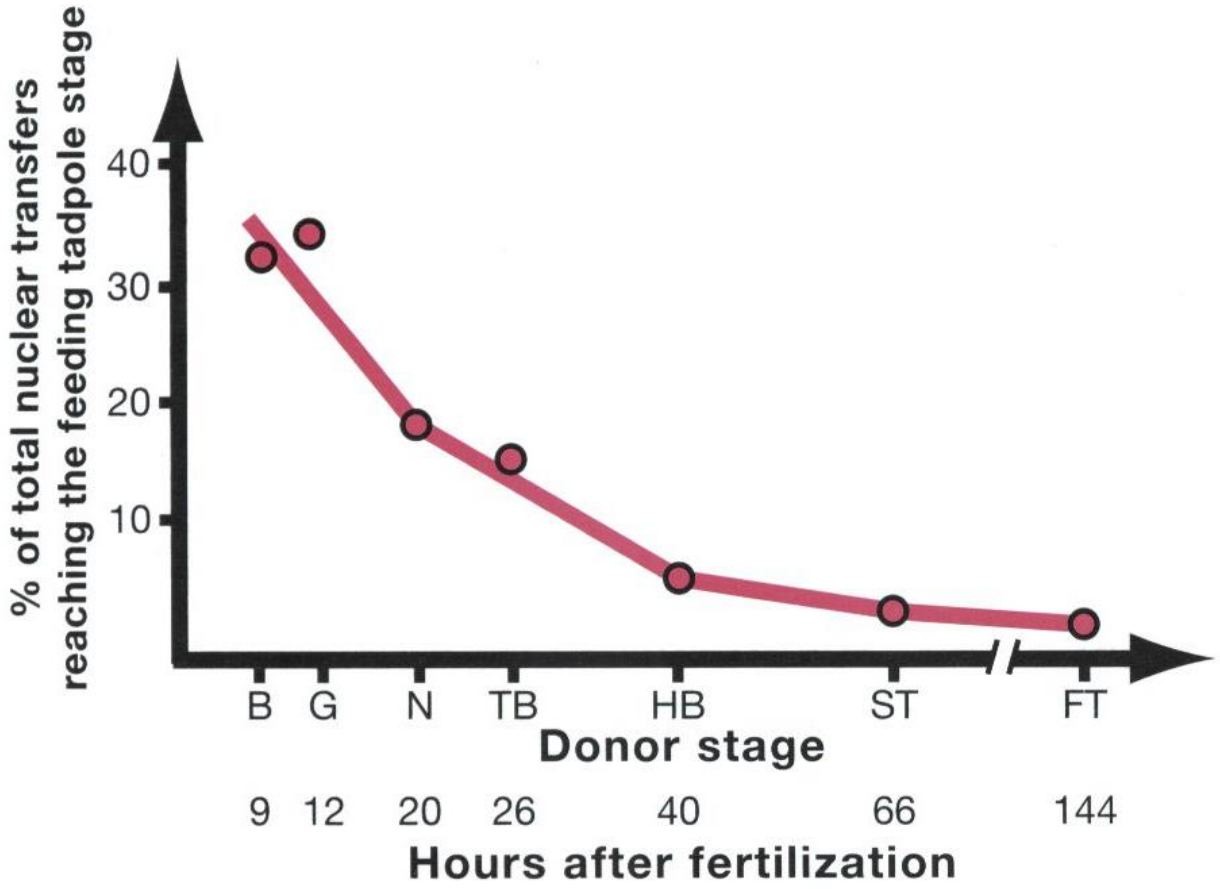


Rudolf Jaenisch
… imprinting



Severino Antinori
… klonování

„Fatherless“ Kaguya (Nature 428: 860, 2004)
vyřazení imprintovaných genů může vést k vývinu plodné myši partenogenetického původu



The Survival of *Xenopus* Nuclear Transfer Embryos Decreases as Donor Nuclei Are Taken from More Specialized Donor Cells

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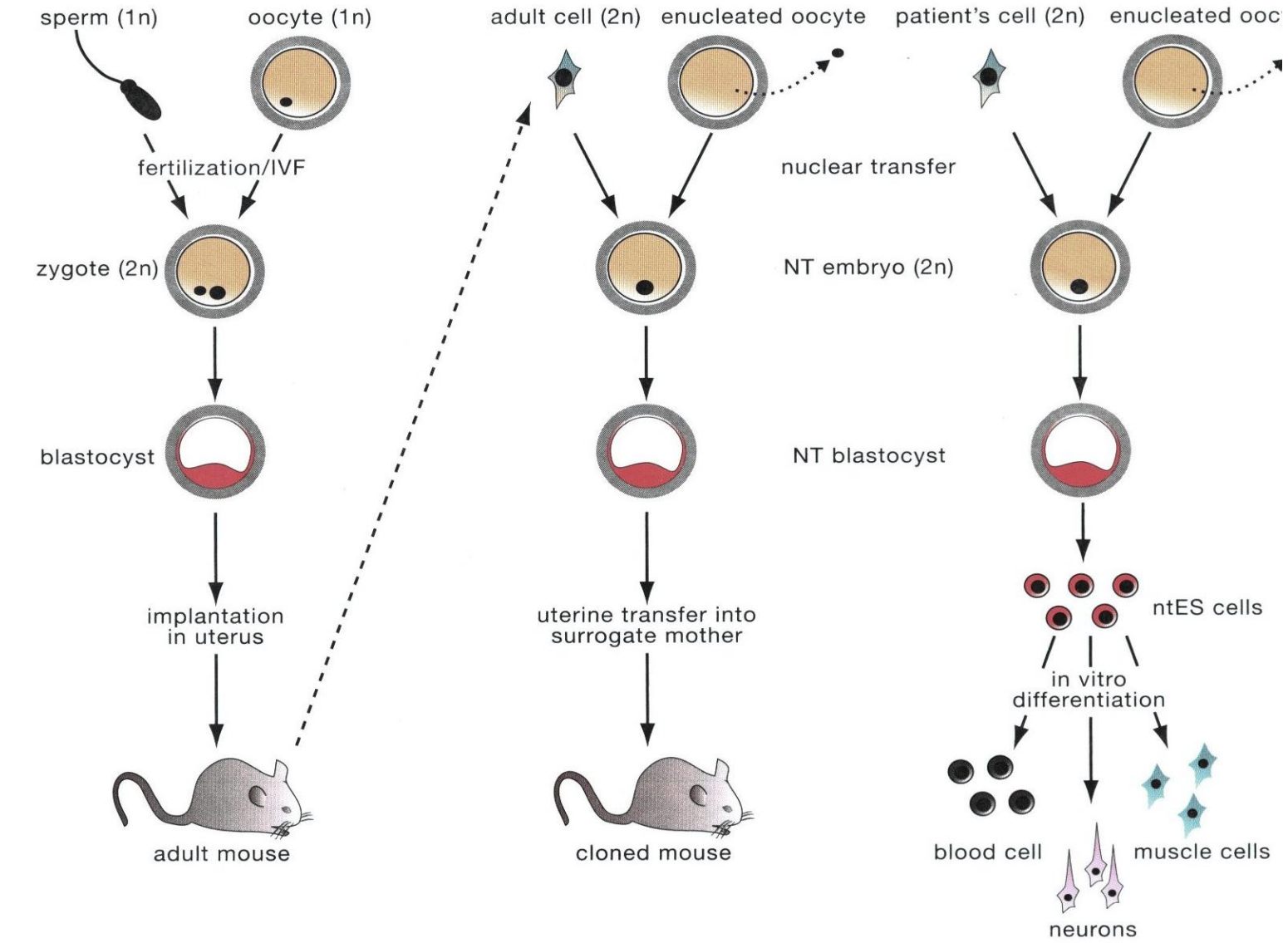
Donor stage abbreviations: (B) blastula; (G) gastrula; (N) neurula; (TB) tail bud; (HB) heart beat; (ST) swimming tadpole; (FT) feeding tadpole.

NORMÁLNÍ VÝVOJ

REPRODUKČNÍ KLONOVÁNÍ

TERAPEUTICKÉ KLONOVÁNÍ

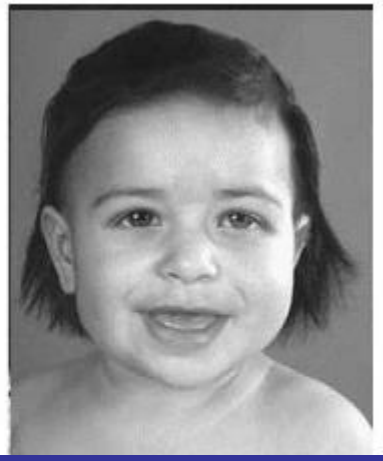


EPIGENETIKA
A LIDSKÉ CHOROBY

eckwith-Wiedemann

Parentální imprinting růstových faktorů:

převaha otce (chr11)



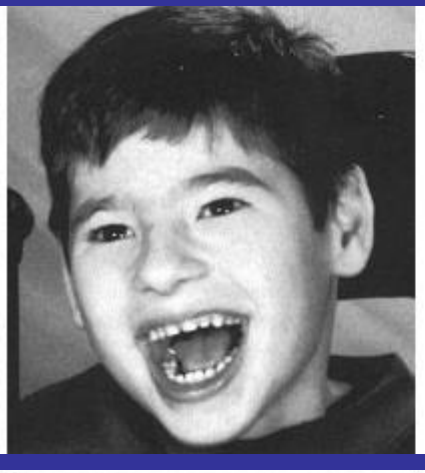
Russel-Silver

převaha matky (chr7)

Prader-Willi

Parentální imprinting genového shluku (ch15):

paternální delece



Angelman

maternální delece

Martin-Bell

X-chromosom vázané mentální retardace:

metylace CGG

Rett

mC-vazebný protein

EPIGENETIKA A LIDSKÉ CHOROBY

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- Russell-Silverův syndrom
- Angelmanův syndrom
- Prader-Williův syndrom
- Pseudohypoparatyreóza

[2] PORUCHY METYLACE DNA
- Imunodeficience ICF syndrom
- Metyléntetrahydrofolát reduktáza
- Rettův syndrom

[3] PORUCHY STRUKTURY CHROMATINU
- Schimkeho imunoskeletální dysplázie
- Rubinstein-Taybiho syndrom
- Facioscapulohumerální svalová dystrofie

[4] X-VÁZANÉ EPIGENETICKÉ PORUCHY
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- Mentální retardace vázaná na α-thalasemii
- Cofflin-Lowryho syndrom

[5] NÁDOROVÉ BUJENÍ
- Wilmsův renální tumor

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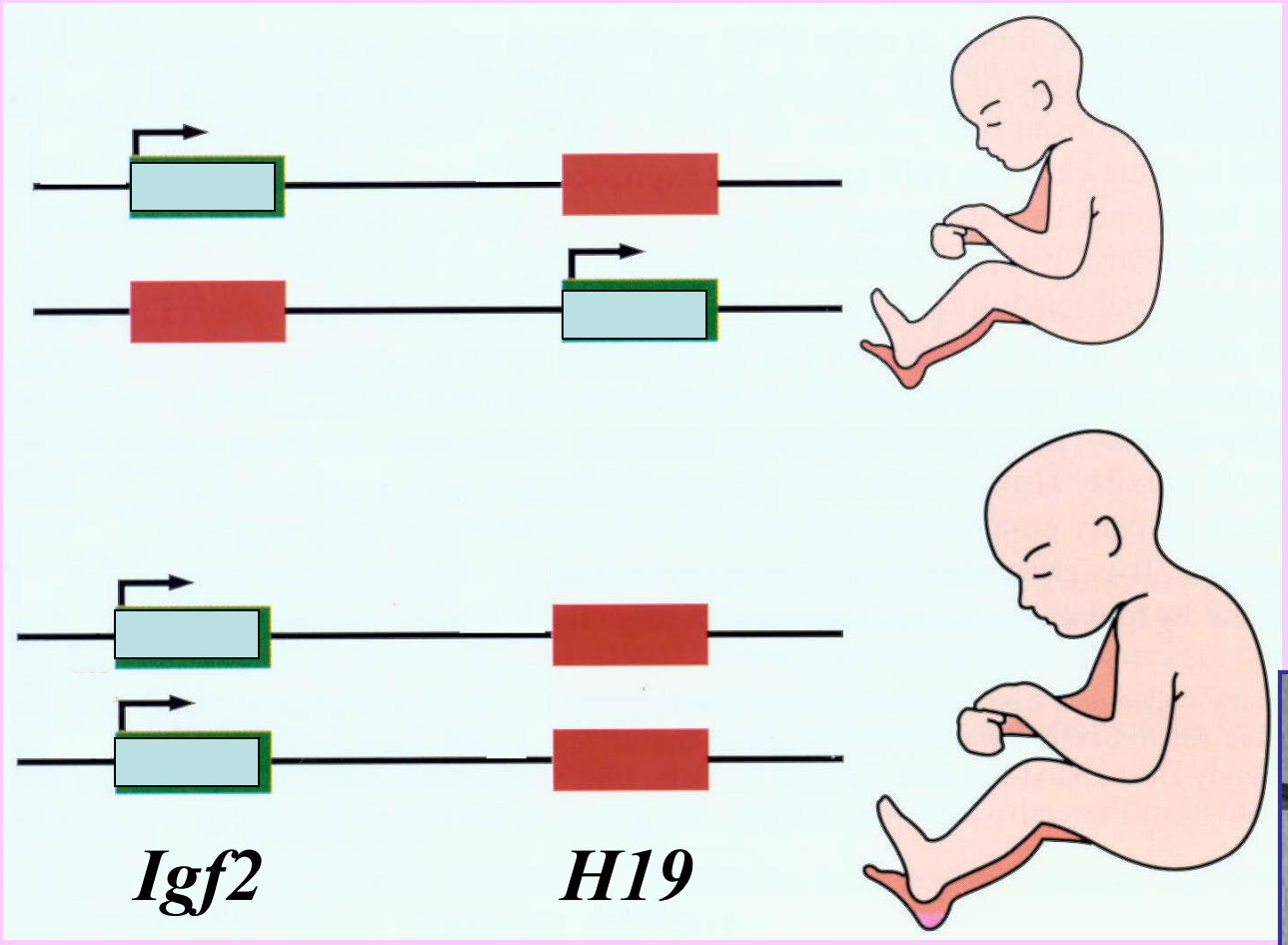
Chybný imprint P-alely (insulinový růstový faktor) či M-alely (růst suprimující H19-RNA) vede k Beckwith-Wiedemannově syndromu (aneb příběh Otesánka)

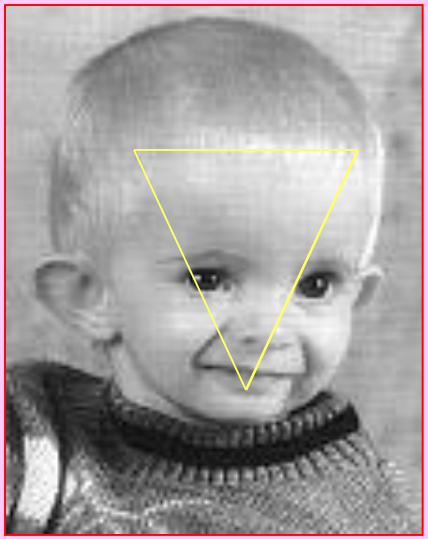


normál

BWS

(J. B. Beckwith 1963, H. R. Wiedemann 1964)

Russell-Silverův syndrom :
maternální disomie chromosomu 7



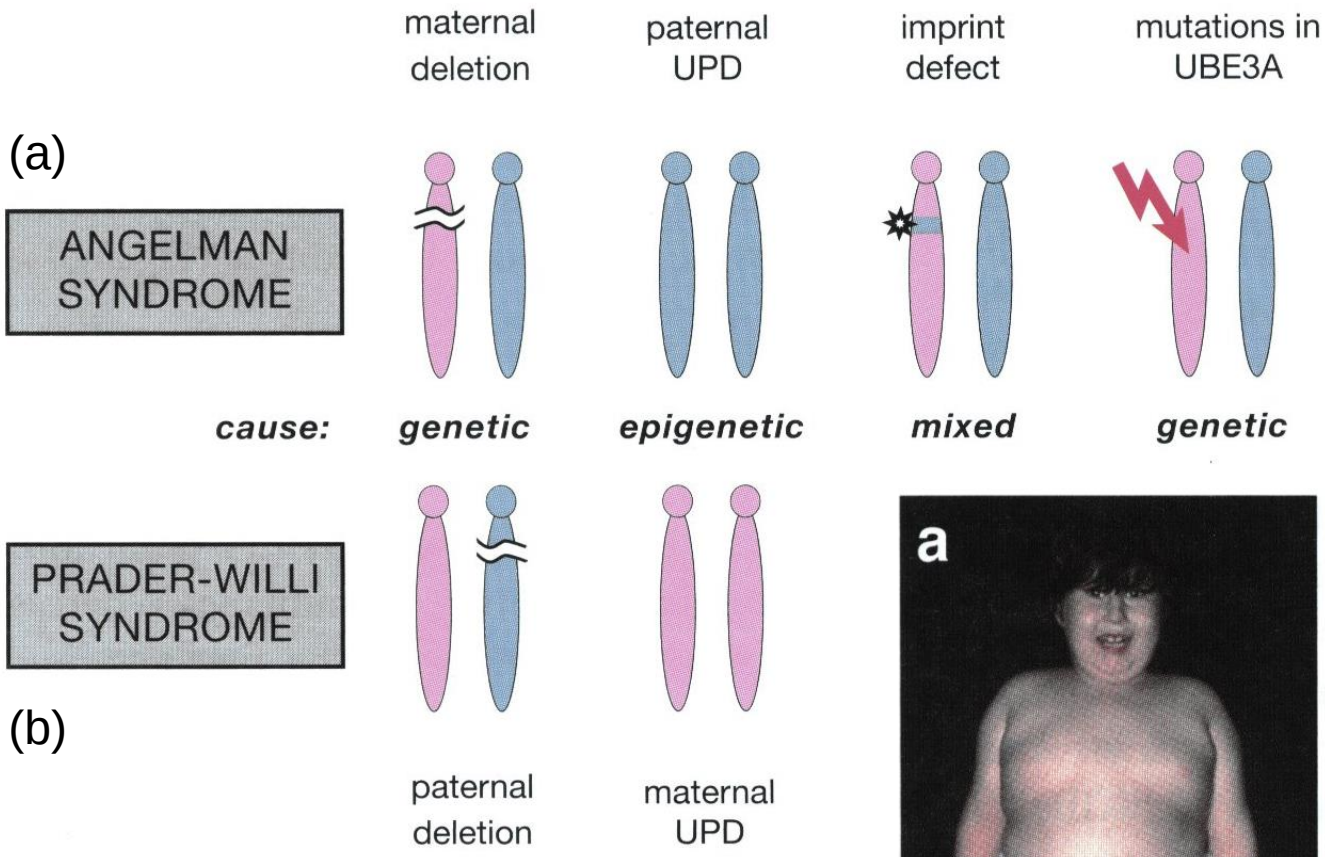
- růstová retardace *in utero*
- postnatální růstová deficience
- asymetrický dwarfismus

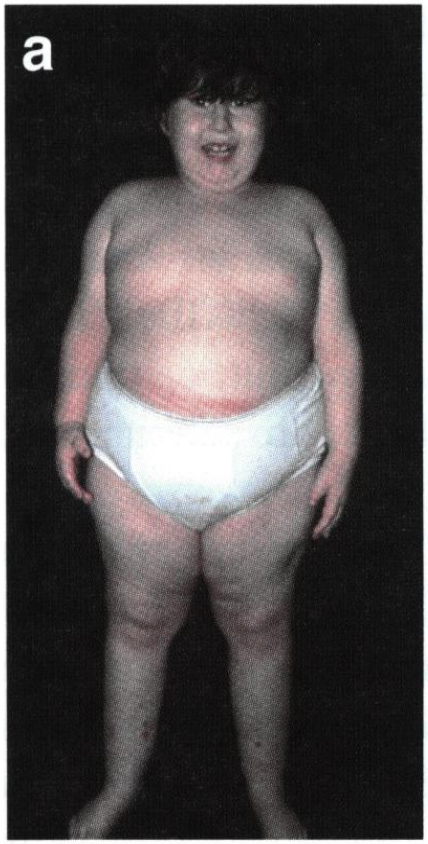
POTLAČUJE MATKA VÝVIN SVÝCH DĚTÍ ?

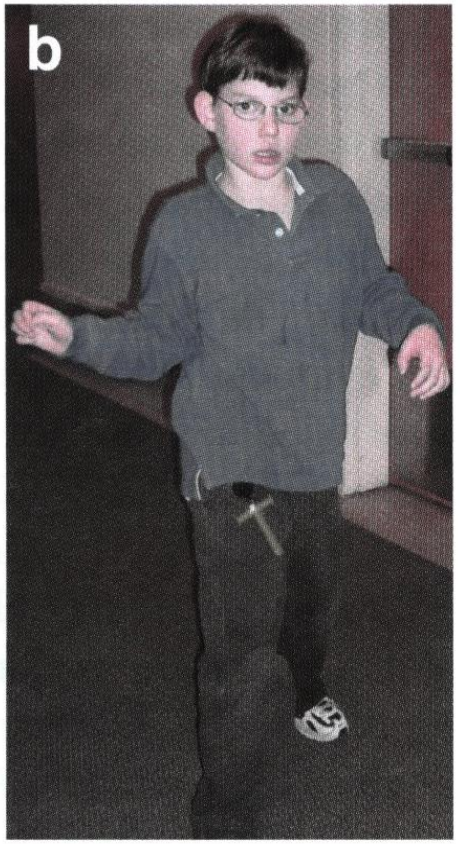
aneb příběh Palečka

David Haig … teorie parentálního konfliktu

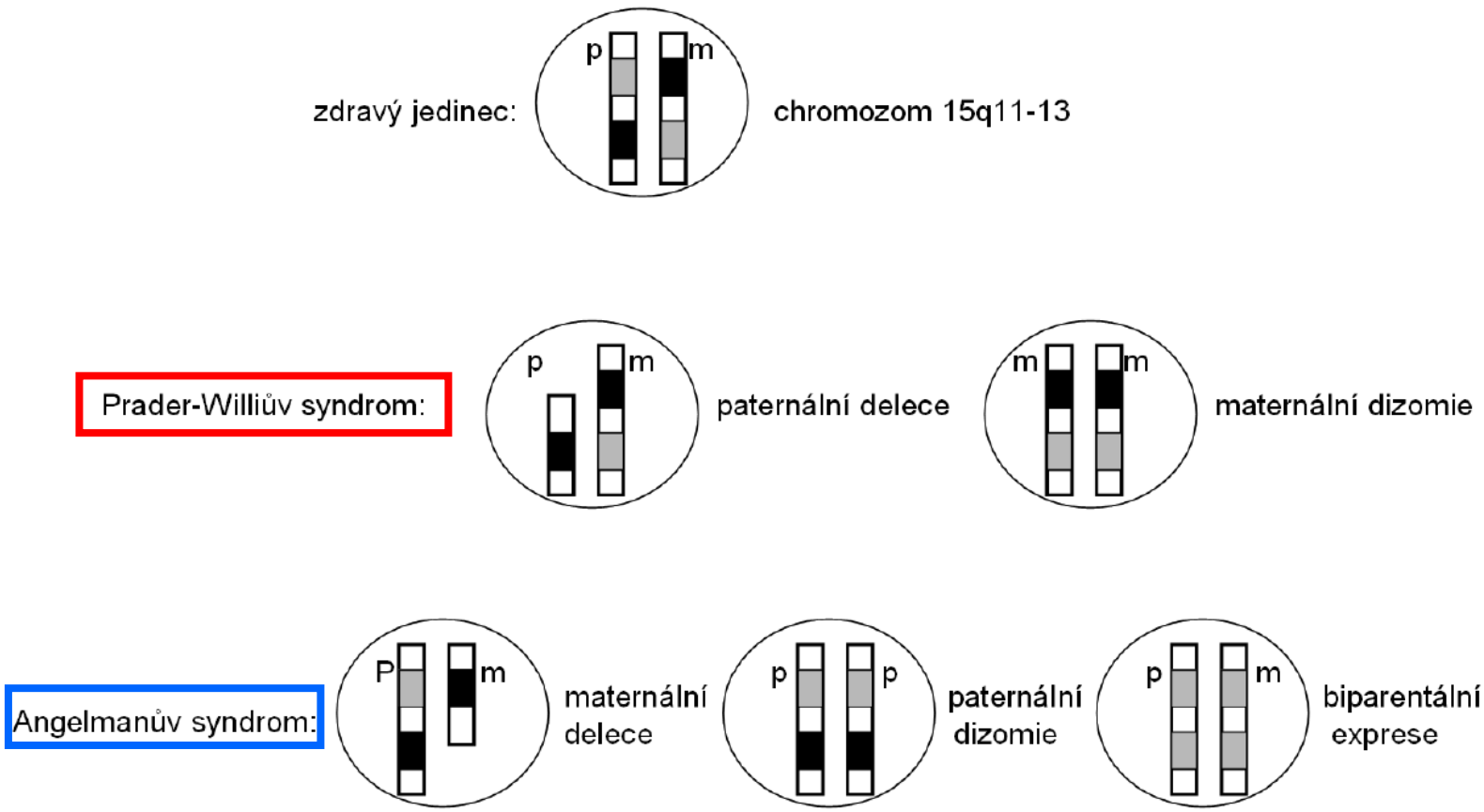
(A. Russell 1954, H. K. Silver 1953)







Angelmanův a Prader-Williův syndrom mohou být způsobeny genetickými nebo epigenetickými poruchami dvou imprintovaných genových shluků p11-13 na chromozomu 15



Prader-Williův a Angelmanův syndrom jsou komplexní neurovegetativní choroby, které souvisejí s imprintingem genového shluku (jsou naznačeny vždy dva lokusy) na chromozomu 15. Aktivní (světlé symboly) a imprintované (tmavé symboly) alely se nacházejí na paternálním (p) i maternálním (m) chromozomu. Nejčastější příčinou lehčího PW syndromu jsou delece na paternálním chromozomu a maternální dizomie. Těžší AS je obvykle způsoben maternální delecí, paternální dizomií nebo biparentální expresí.

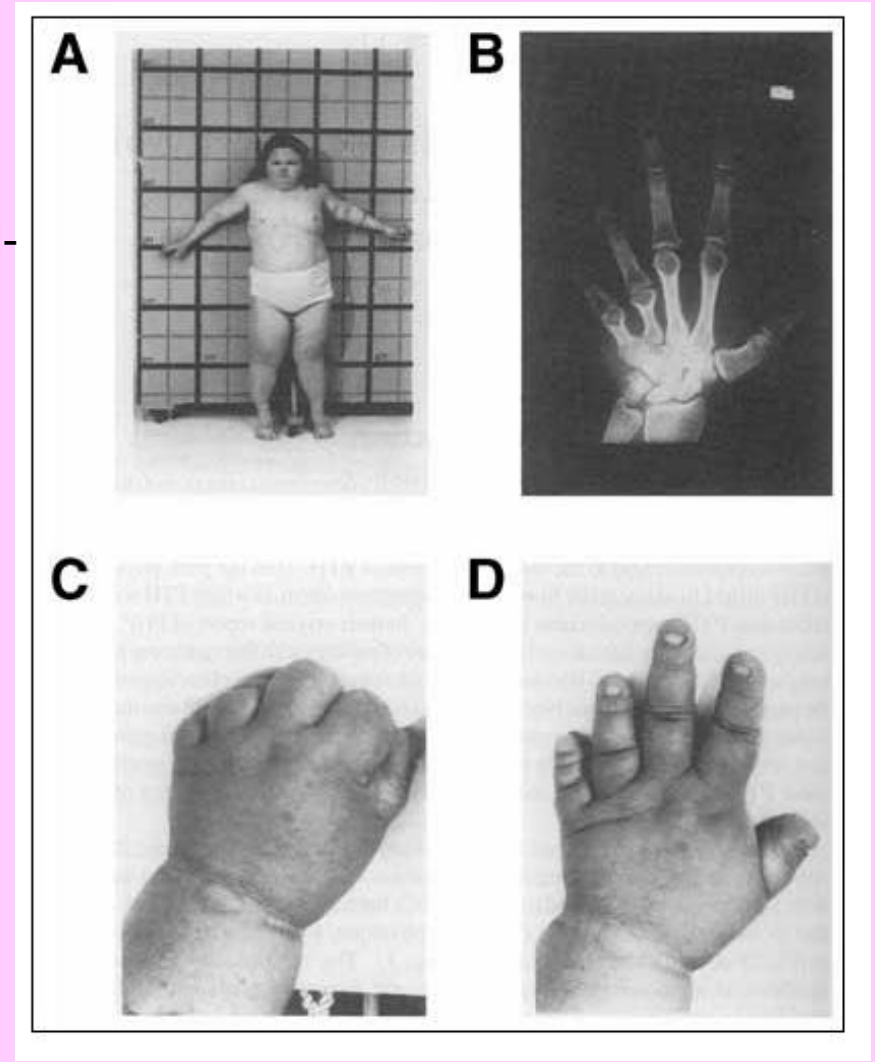
Pseudohypoparatyreóza (PHP)

Porucha funkce parathyroidního hormonu (příštítných tělísek), vede ke změně metabolismu vápníku a fosfátu, řada vývojových defektů.

Odpovědný je gen *GNAS1* (guanin-nukleotid-vazebný protein) má tři alternativní exony, které jsou sestřihovány do různých exonů tvořících odlišné transkripty.

<u>Odlišná metylace v okolí těchto exonů vede k exkluzivní expresi maternální alely</u> jednoho exonu a dvou paternálních exonů.

Syndrom choroby může být způsoben poruchou imprintingu - např. uniparentální disomií, *de novo* metylací, …



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- Wilmsův renální tumor

ICF syndrome

From Wikipedia, the free encyclopedia

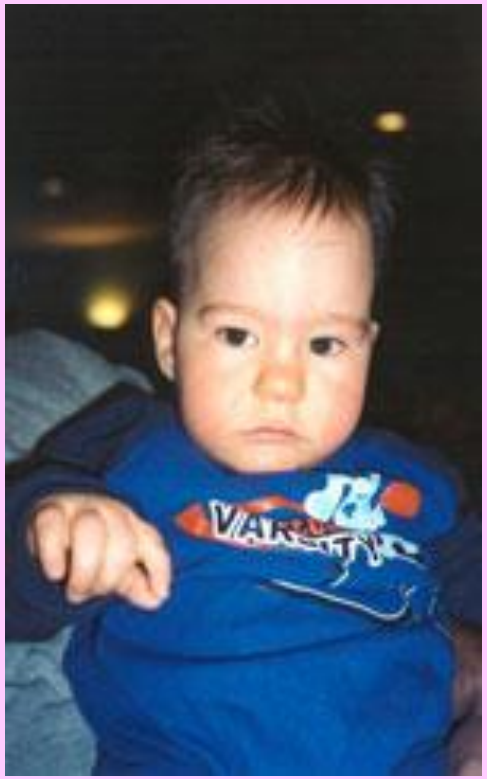
ICF syndrome (or **Immunodeficiency, centromere instability and facial anomalies syndrome**) is a very rare autosomal recessive immune disorder.

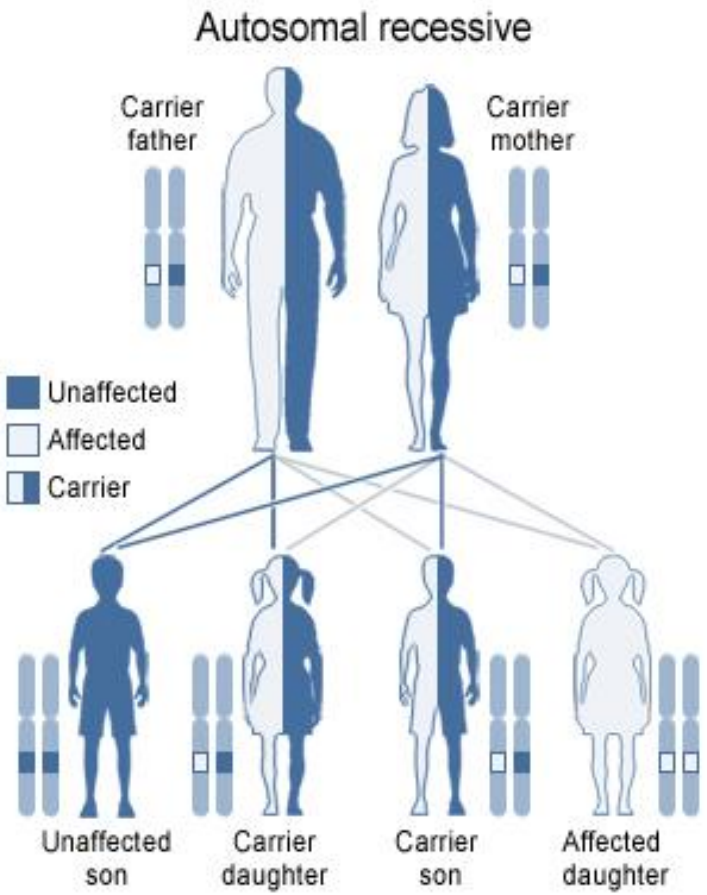
Genetics

ICF syndrome can be caused by a mutation in the DNA-methyltransferase-3b (Dnmt3b) gene.[1]

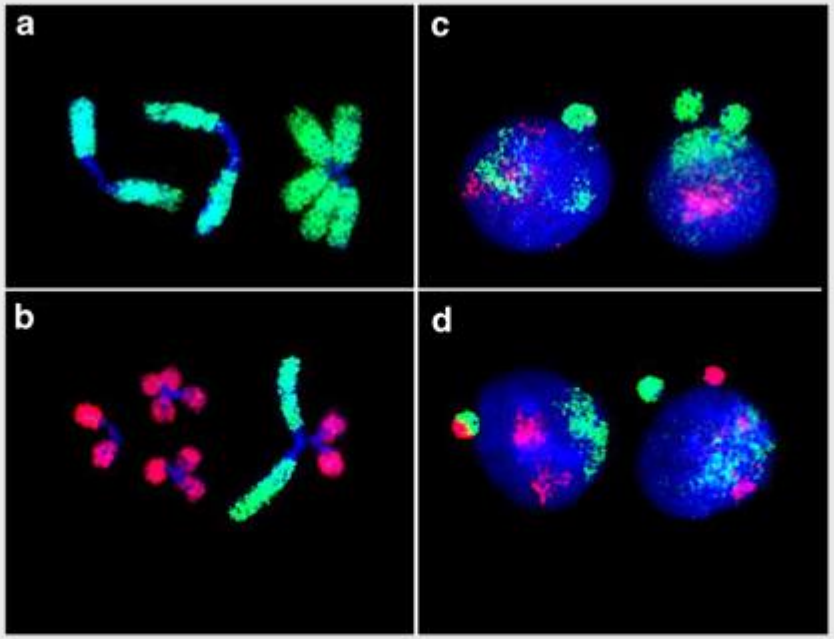
Presentation

It is characterized by variable reductions in serum immunoglobulin levels which cause most ICF patients to succumb to infectious diseases before adulthood. ICF syndr
patients exhibit facial anomalies which include hypertelorism, low-set ears, epicanthal folds and macroglossia.





ICF



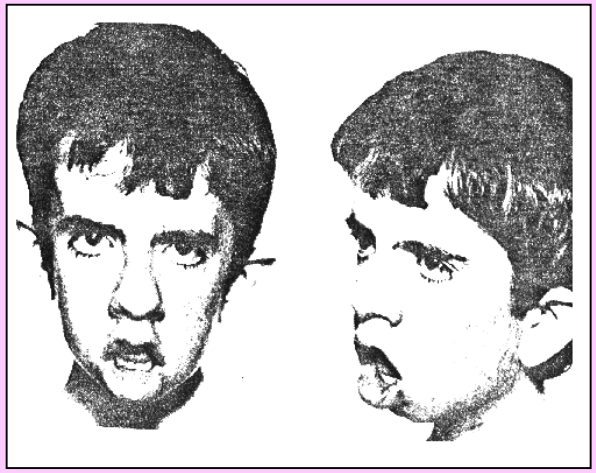
Chromosomal abnormalities in metaphasic and interphasic cells of ICF patients: dual-color FISH was performed with chromosome 1 (green) and chromosome 16 (red) paint probes. Chromosomes and nuclei are counterstained with DAPI (blue). (**a**) and (**c**) show chromosomal abnormalities and micronuclei involving specifically chromosome 1, as frequently observed in the ICF1 and 1CF3 cell lines. (**b**) and (**d**) show chromosomal abnormalities and micronuclei involving both chromosomes 1 and 16, as frequently observed in the ICF2 cell line.

- imunodeficience, karyologická nestabilita centromer, kraniofaciální defekty, psychomotorické retardace

- mutace metyltransferázového genu *Dnmt3b* vede k hypometylaci subcentromerických repeticí (heterochromatinu) na chromozomu 1, 9 a 16

- není jasné, proč ztráta funkce široce exprimované *de novo* metyltransferázy ovlivňuje specifické repetitivní DNA sekvence

Metyléntetrahydrofolát reduktáza (MTHFR) a mentální retardace



- zásadní reakce v metylačním metabolismu: přenos metylové skupiny z metyléntetrahydrofolátu přes homocystein a metionin, konečným donorem metylové skupiny pro všechny metyltransferázy je S-adenosyl metionin (SAM)

- deficience MTHFR způsobuje vzácnou autosomálně-recesivní mentální poruchu

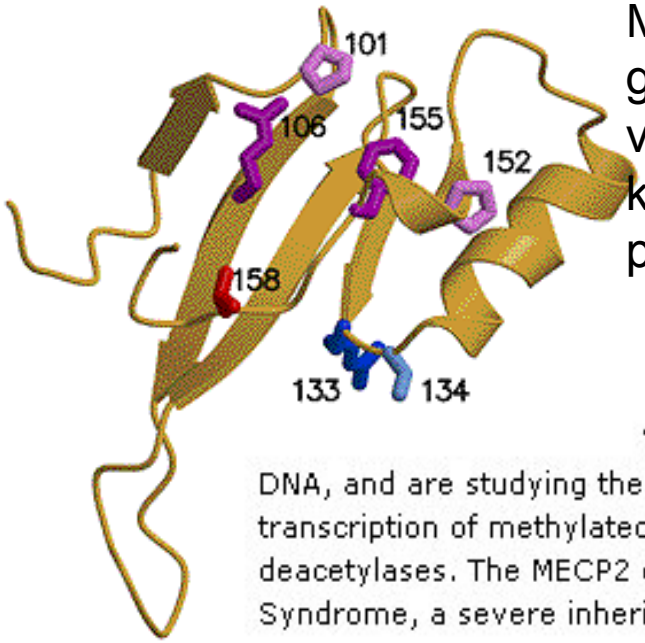
- gen MTHFR je polymorfní, může se projevit i nízká folátová dieta, následkem mohou být i projevy Angelmanova syndromu

METYLACE DNA, CHROMOSOM X a RETTŮV SYNDROM

It is now known that RS can occur in males, but is usually lethal, causing miscarriage, stillbirth or early death.

First described by Dr. Andreas Rett, RS received worldwide recognition following a paper by Dr. Bengt Hagberg and colleagues in 1983.

http://www.rettangels.org/



Mutace v X-vázaném genu kódujícím mC-vazebný protein vede k těžké mentálně-fyzické poruše

We have identified proteins that mediate repression by binding to methylated DNA, and are studying their biology. The founding member of the family is MeCP2, which represses transcription of methylated genes by recruitment of a corepressor complex that contains histone deacetylases. The MECP2 gene is clinically important as mutations within it are the primary cause of Rett Syndrome, a severe inherited neurological disorder that affects girls.

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Schimkeho imunoskeletální dysplázie (Schimke immuno-osseous dysplasia, SIOD)

- autosomálně recesivní komplexní syndrom charakteristický dysplázií páteře a konců dlouhých kostí, růstovou retardací, poruchy ledvin a imunity

- SIOD je způsobena mutací genu *SMARCAL1* (SW1/SNF2, aktin-dependentní regulátor chromatinu), který kóduje protein regulující transkripční aktivitu prostřednictvím remodelování chromatinu

Schimkeho immunoskeletální dysplázie

SMARCAL1

From Wikipedia, the free encyclopedia

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1, also known as **SMARCAL1**, is a human gene.[1]

The protein encoded by this gene is a member of the SWI/SNF family of proteins. Members of this family have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. The encoded protein shows sequence similarity to the E. coli RNA polymerase-binding protein HepA. Mutations in this gene are a cause of Schimke immunoosseous dysplasia (SIOD), an autosomal recessive disorder with the diagnostic features of spondyloepiphyseal dysplasia, renal dysfunction, and T-cell immunodeficiency.[1]

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1

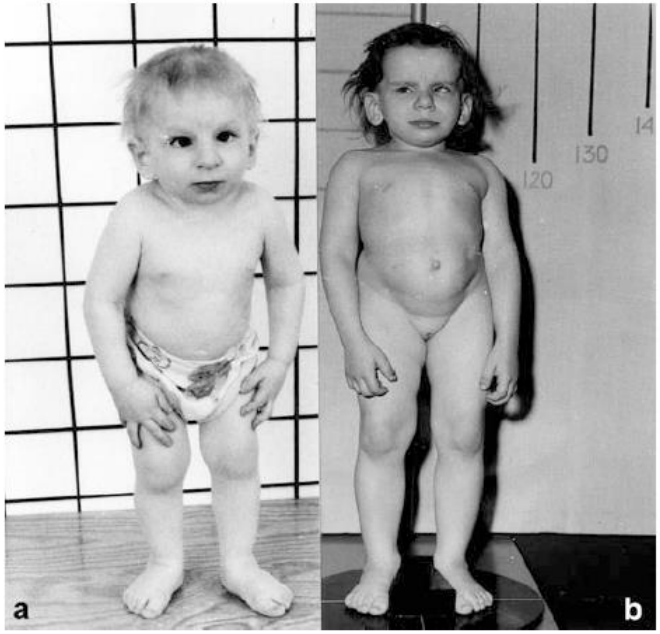


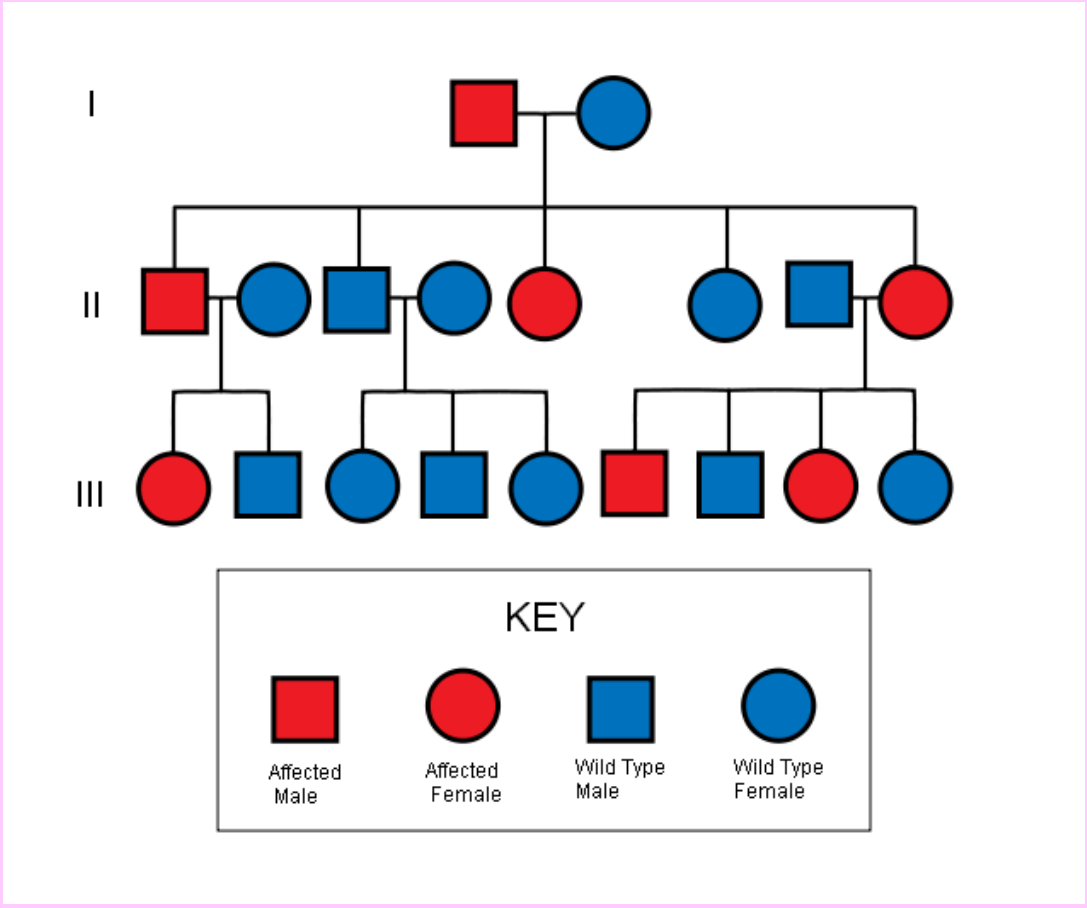
Fig. 1a, b Clinical photographs. **a** Case 1. Note the peculiar face with broad depressed nasal bridge, bulbous tip of nose and weak fine hair. The patient has a short trunk and neck, long extremities and large hands and feet. **b** Case 2. Note the wide nose with a bulbous tip, low-set large ears and fine weak hair. The patient has a barrel chest, short neck and relatively long extremities with large hands and feet

Schimke immuno-osseous dysplasia (SIOD). SIOD is characterised by growth retardation, renal failure, spondylo-epiphyseal dysplasia, specific phenotype and defective cellular immunity. These two children demonstrated a bone dysplasia with characteristic radiographic appearances. We postulate that SIOD should be considered in all cases of growth failure with an unclassifiable bone dysplasia. Repeated urine tests for proteinuria could be helpful in reaching the correct diagnosis.

Rubinstein-Taybi syndrom (RSTS): autosomální dominance

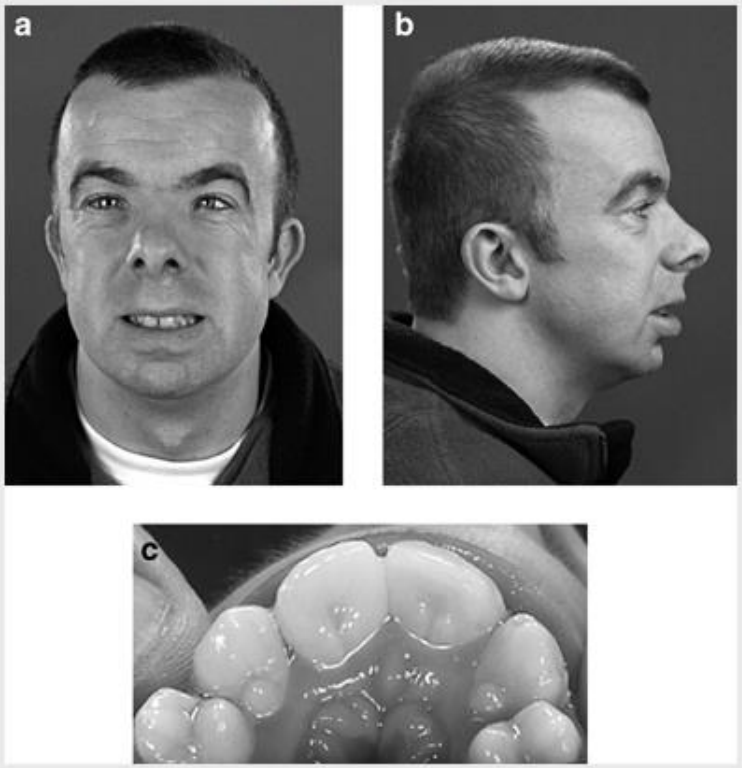
- způsoben haploinsufficiencí (mutace v heterozygotním stavu) funkce genu - CREB-vazebného proteinu (regulátor fetálního růstu a vývoje), haploinsuffience vede k poklesu aktivity histon-acetyltransferáz (HAT)

- u myši tento defekt může být revertován aplikací inhibitorů histon-deacetyláz (HDAC)



INTRACELULÁRNÍ SIGNALIZACE V MOZKU

CREB = transkripční faktor cAMP-response binding protein, souvisí s HAT aktivitou, heterozygotní mutace vede k mentální retardaci: **RUBINSTEIN-TAYBI syndrom**



(**a**, **b**) Face in RSTS. Note classical features in molecularly proven patient. (**c**) Talon cusps in RSTS. The presence of talon cusps is a strong indicator that the diagnosis RSTS in a patient with only partial features of RSTS is right.

Facioscapulohumerální dystrofie (FSHD)

-autosomálně dominantní svalová dystrofie obličeje, ramen a paží

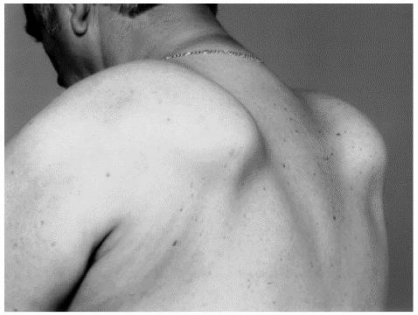


Figure 2. "Winging of the scapula" caused by weakness of the shoulder muscles

- lokus *FSHD* je v subtelomerické oblasti chromosomu 4 poblíž repetice s polymorfními 3,3kb GC bohatými repeticemi

- kontrakce těchto repeticí způsobuje stav vedoucí ke zvýšené transkripci přilehlých genů

- změna chromatinového stavu subtelomerické oblasti chromosomu 4 může vést ke změně exprese genů i syndromu choroby

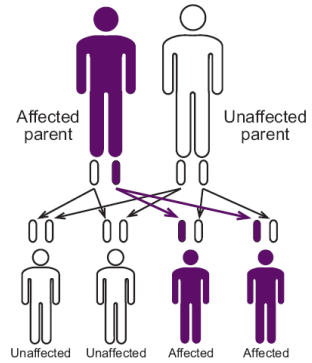


Figure 4. Diagram of autosomal dominant inheritance. Each child has a 50% chance of inheriting FSHD from an affected parent.

EPIGENETIKA A LIDSKÉ CHOROBY

[1] PORUCHY IMPRINTINGU
- Beckwith-Wiedemannův syndrom
- Russell-Silverův syndrom
- Angelmanův syndrom
- Prader-Williův syndrom
- Pseudohypoparatyreóza

[2] PORUCHY METYLACE DNA
- Imunodeficience ICF syndrom
- Metyléntetrahydrofolát reduktáza
- Rettův syndrom

[3] PORUCHY STRUKTURY CHROMATINU
- Schimkeho imunoskeletální dysplázie
- Rubinstein-Taybiho syndrom
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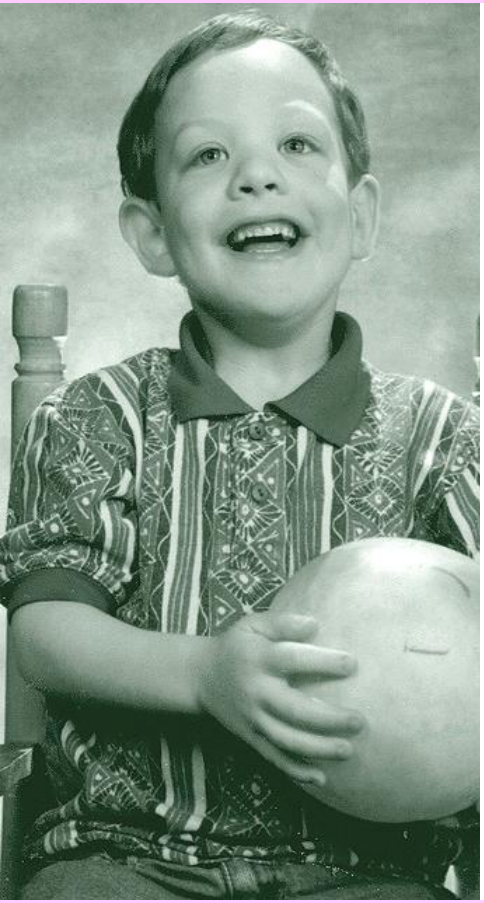
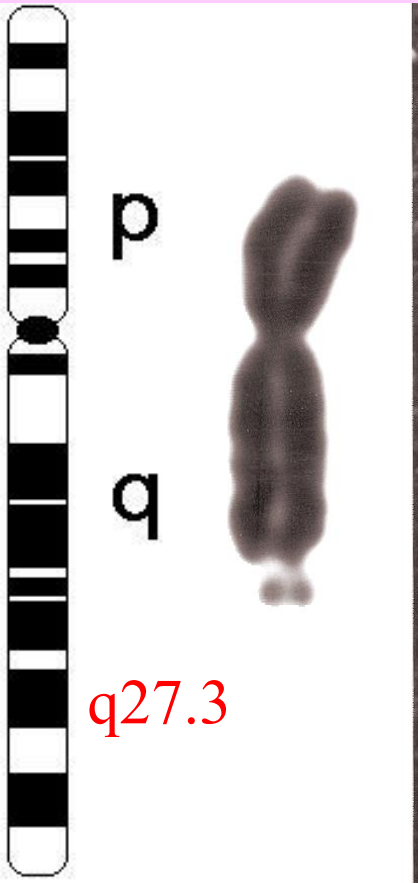
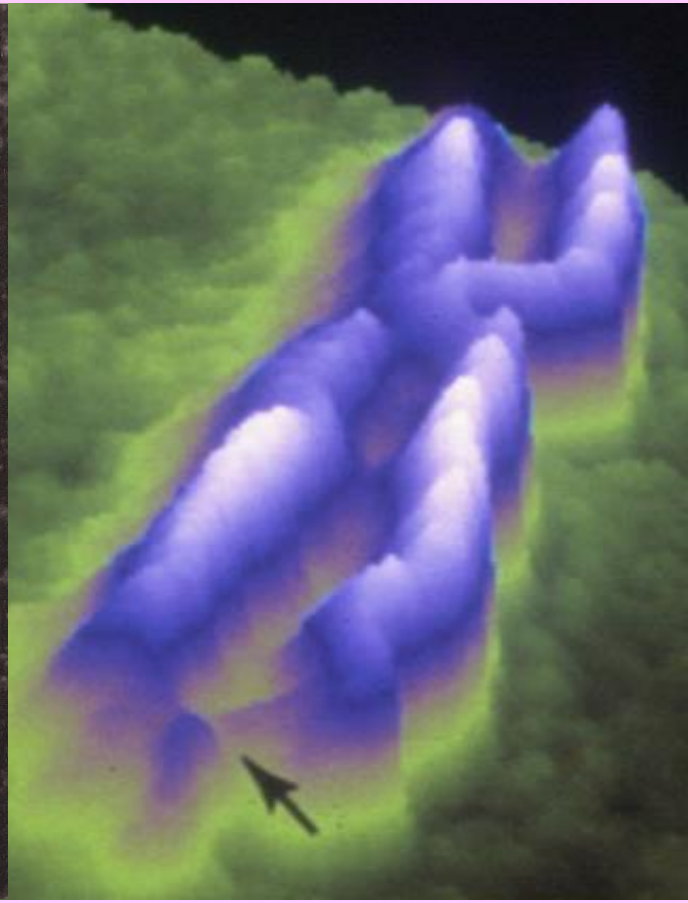
[4] X-VÁZANÉ EPIGENETICKÉ PORUCHY
- Martin-Bellův syndrom
- Mentální retardace vázaná na α-thalasemii
- Cofflin-Lowryho syndrom

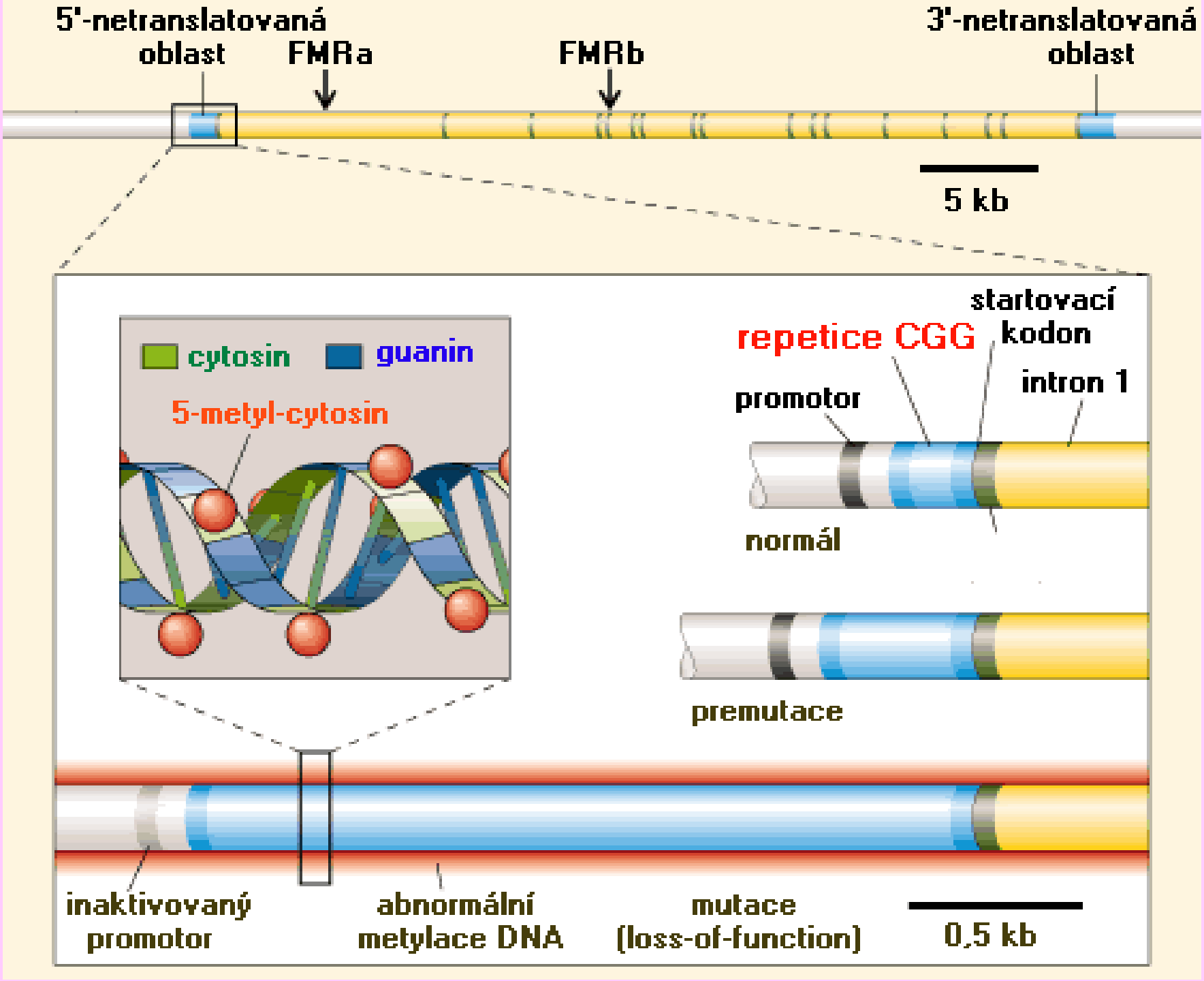
[5] NÁDOROVÉ BUJENÍ
- Wilmsův renální tumor

FRAGILNÍ HROMOSOM X
(Martin-Bellův syndrom)







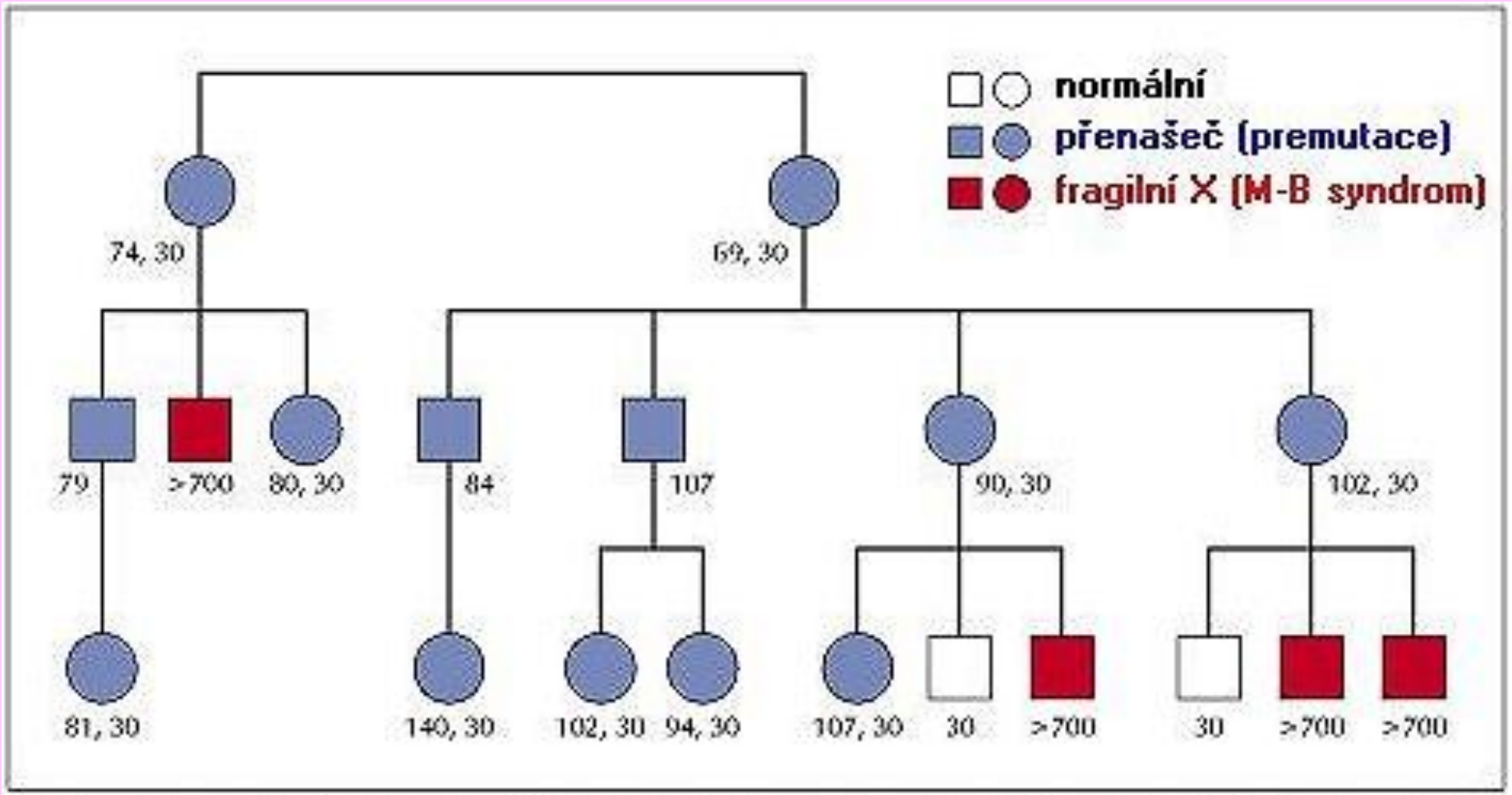

5'-netranslatovaná oblast
FMRa
FMRb
3'-netranslatovaná oblast
5 kb
cytosin
guanin
5-metyl-cytosin
repetice CGG
startovací kodon
promotor
intron 1
normál
premutace
inaktivovaný promotor
abnormální metylace DNA
mutace (loss-of-function)
0,5 kb

⇨ **normální X má 6-60 tripletů CGG v 5'UTR genu FMR1 :**

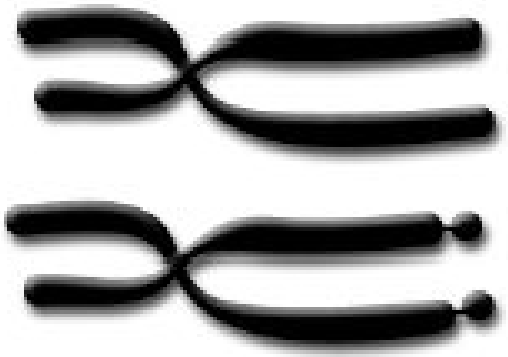
$(CGG)_{10}AGG(CGG)_9AGG(CGG)_9$

⇨ **muži-přenašeči nesou premutaci mezi 60 and 200 kopiemi**

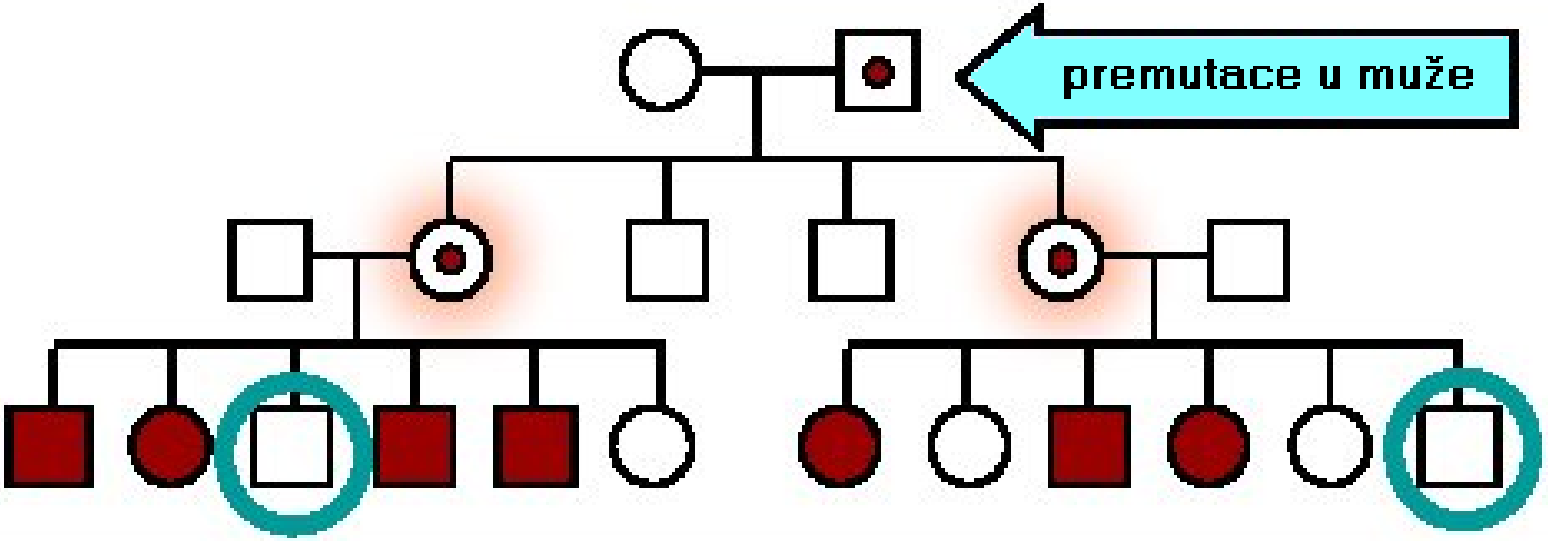
⇨ **M-B pacienti mají přes 200 kopií repetice**



SYNDROM FRAGILNÍHO X



dominantní, X-vázaný
vážná mentální retardace
neúplná penetrance
variabilní expresivita
vážnější a častější u mužů



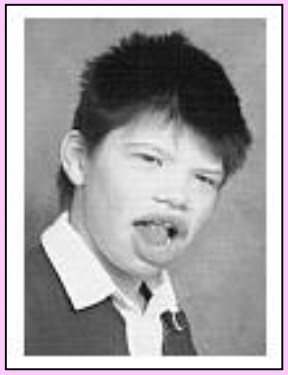
α-thalassemia X-vázaná mentální retardace (ATRX)

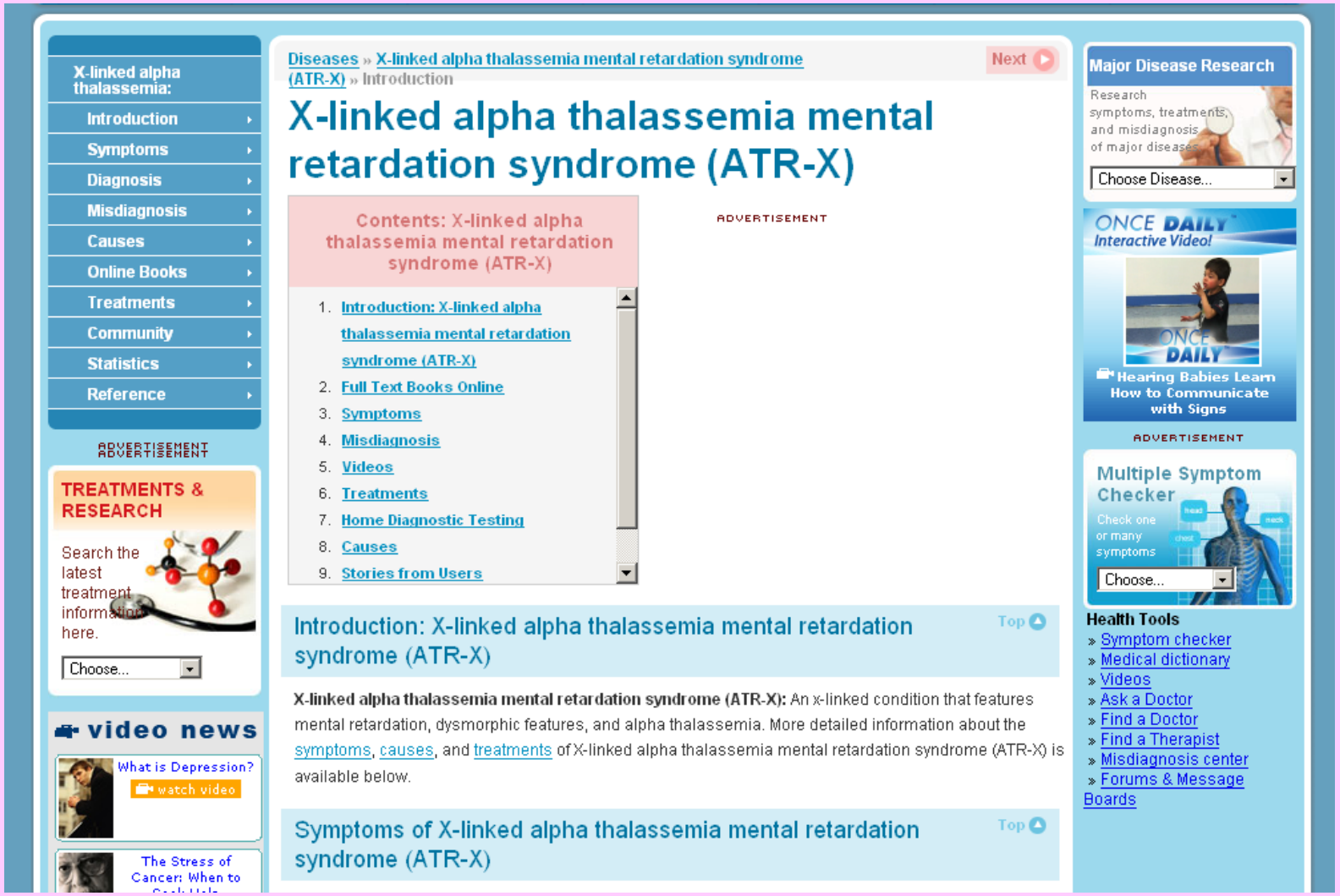
- muži mají thalasemii (porucha syntézy hemoglobinu), mentální retardaci, mikrocefalii, neschopnost chůze aj., ženy zpravidla asymptomatické

- gen *ATRX* (Xq13) kóduje chromatin-remodelující protein, jehož mutace způsobují blok expresi globinu a abnormální metylaci řady sekvencí DNA

- nestandardní (vysoká či nízká) hladina genového produktu ATRX způsobuje stejné neurodevelopmentální defekty

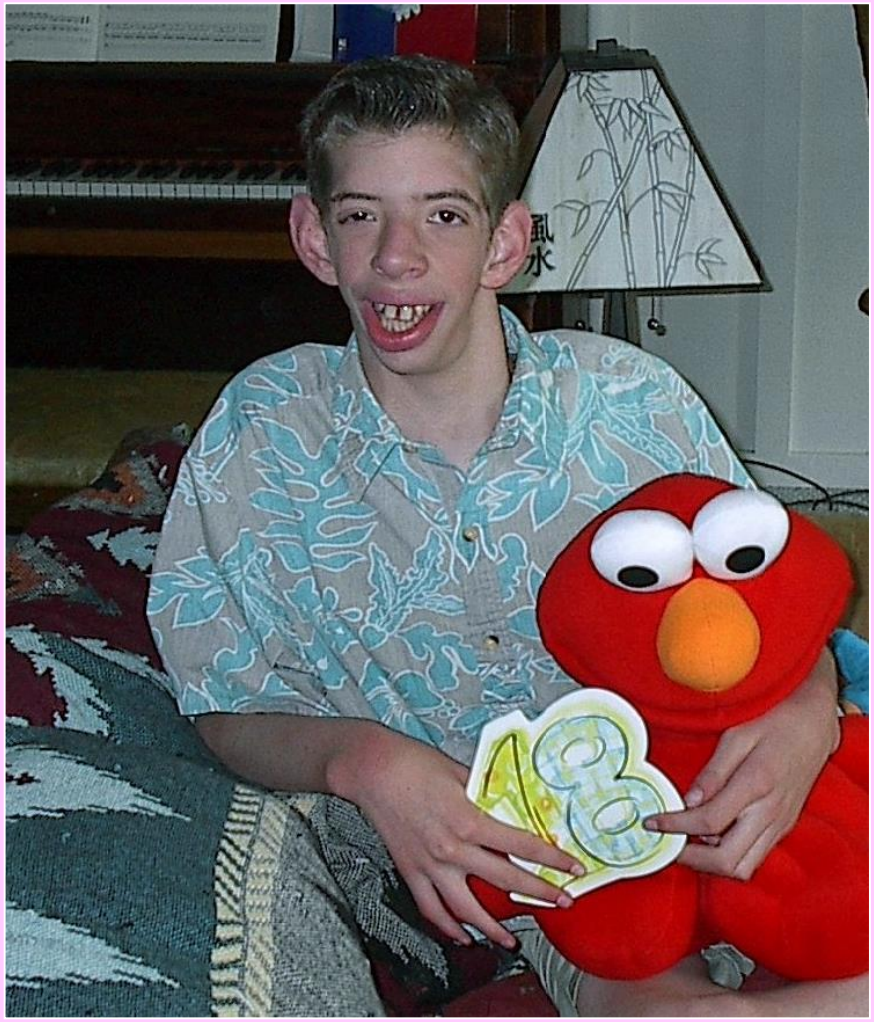
α-thalassemia X-vázaná mentální retardace (ATRX)





COFFLIN – LOWRY SYNDROM

psychomotorická retardace, skeletální abnormity,
X-vázaná choroba, souvisí s CREB, fosforyluje histon H3



Females may show mild mental retardation. The disorder is caused by a defective gene, RSK2, which was found in 1996 on the X chromosome (Xp22.2-p22.1). The gene codes for a member of a growth factor regulated protein kinase. It is unclear how changes (mutations) in the DNA structure of the gene lead to the clinical findings.

EPIGENETIKA A LIDSKÉ CHOROBY

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[5] NÁDOROVÉ BUJENÍ
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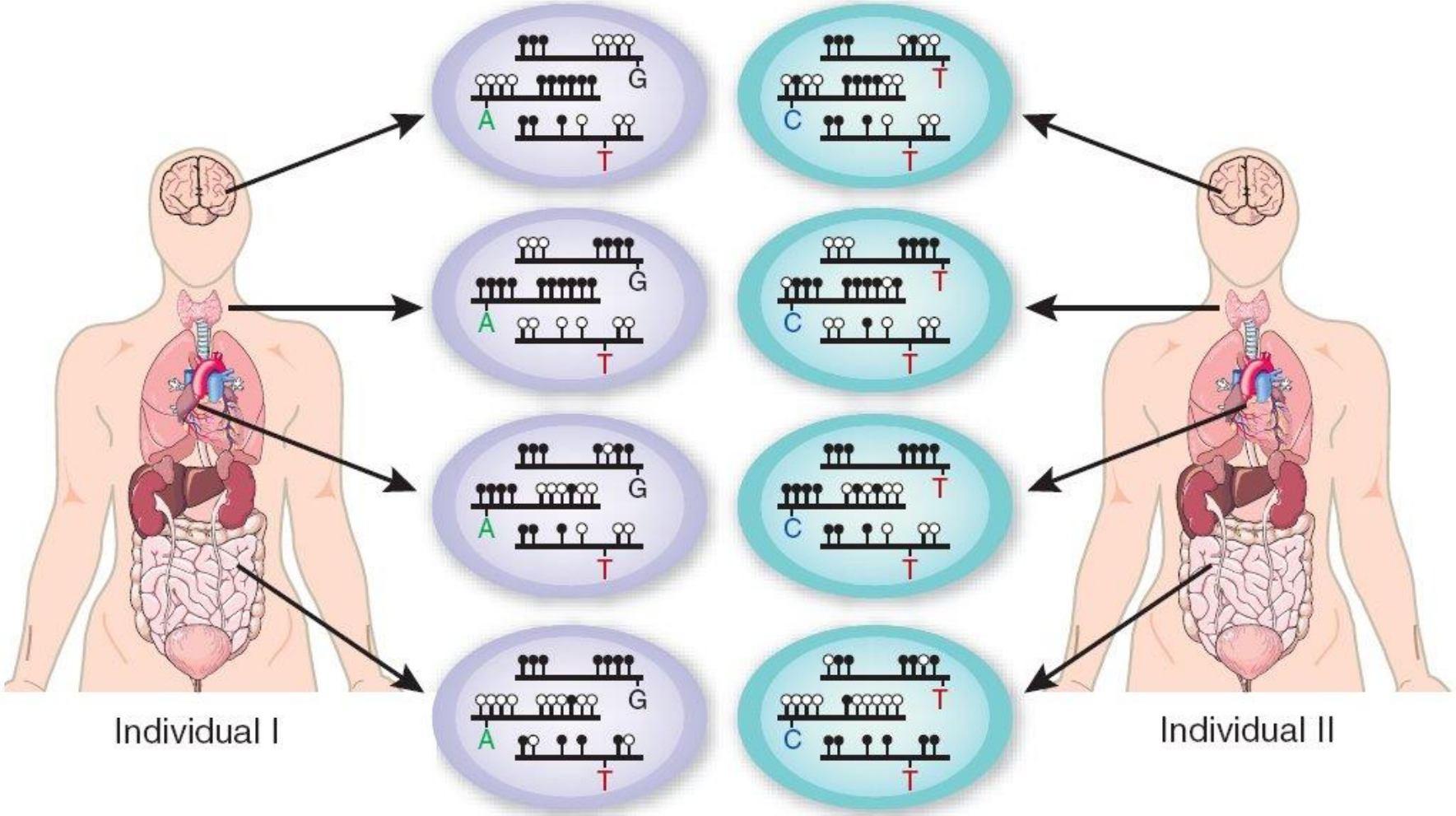
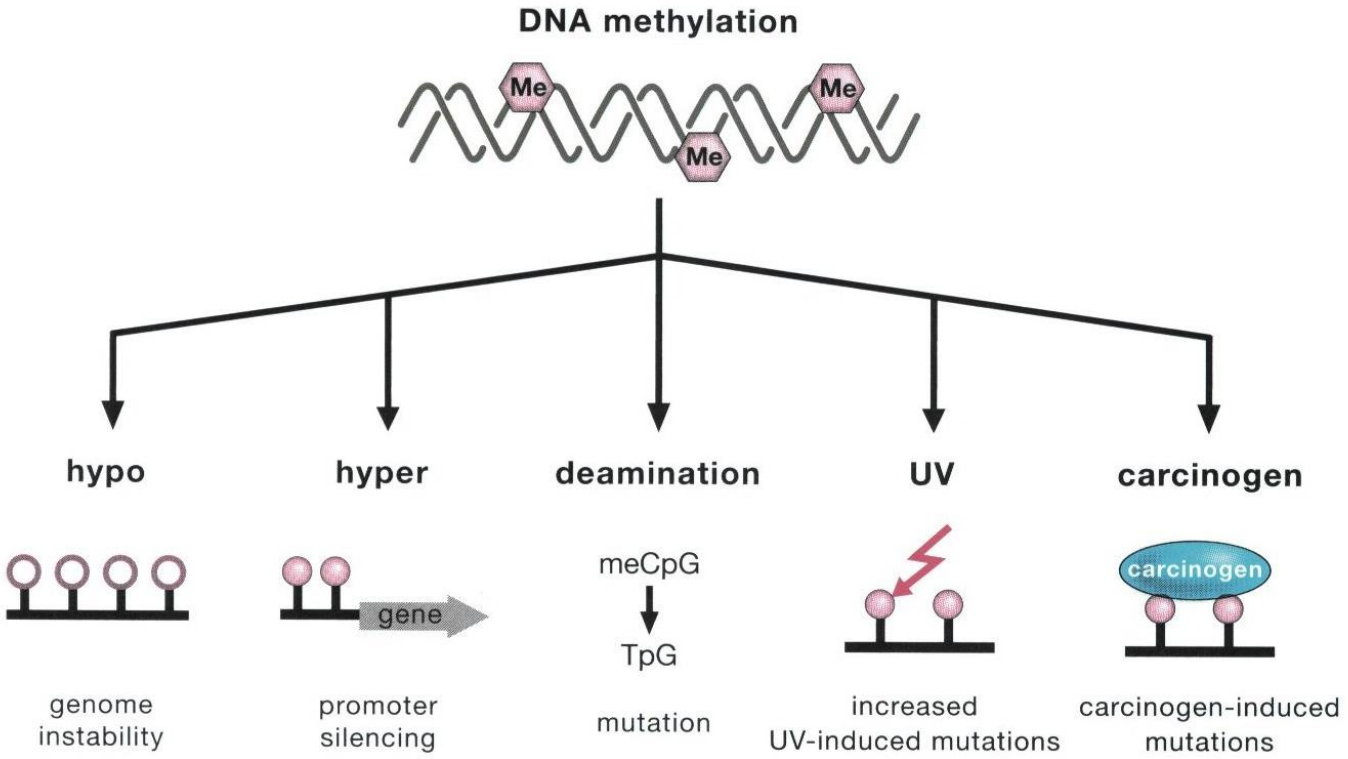


Tissue-specific DNA methylation and epigenetic heterogeneity among individuals. A subset of the DNA methylation patterns within a cell are characteristic to that cell type. Cell type–specific and tissue-specific DNA methylation are illustrated by organ-to-organ variations in the clusters of methylated CpGs within the same individual. Despite overall consistency in tissue-specific DNA methylation patterns, variations in these patterns exist among different individuals. Methylated CpGs are indicated by a filled circle and unmethylated CpGs by an open circle. SNPs are indicated by the corresponding base.

Epigenetické změny zahrnující metylace DNA vedou k nádorovému růstu prostřednictvím různých mechanizmů



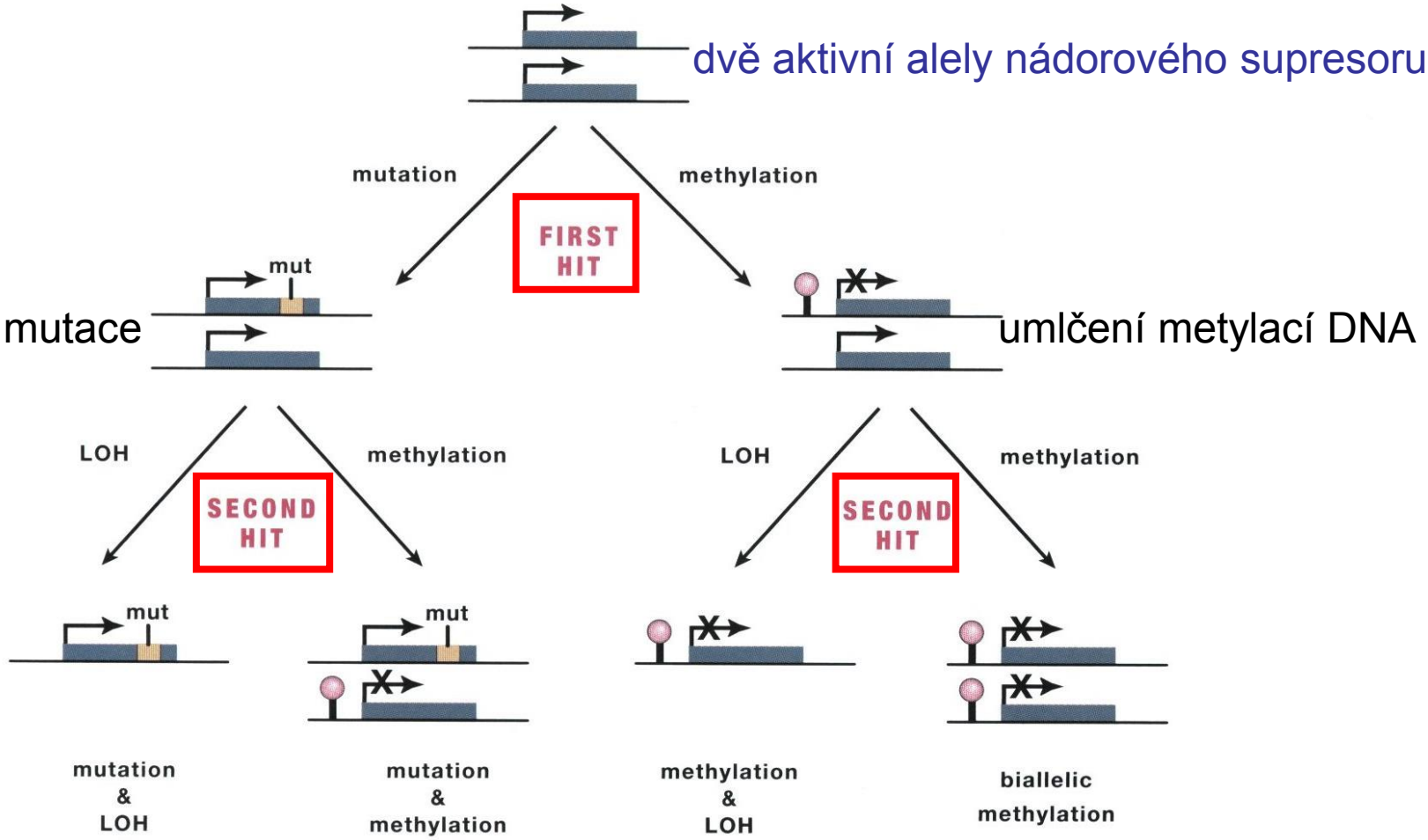
ztráta metylace vede k nestabilitě genomu

hydrolytická deaminace metylC vede k bodové mutaci

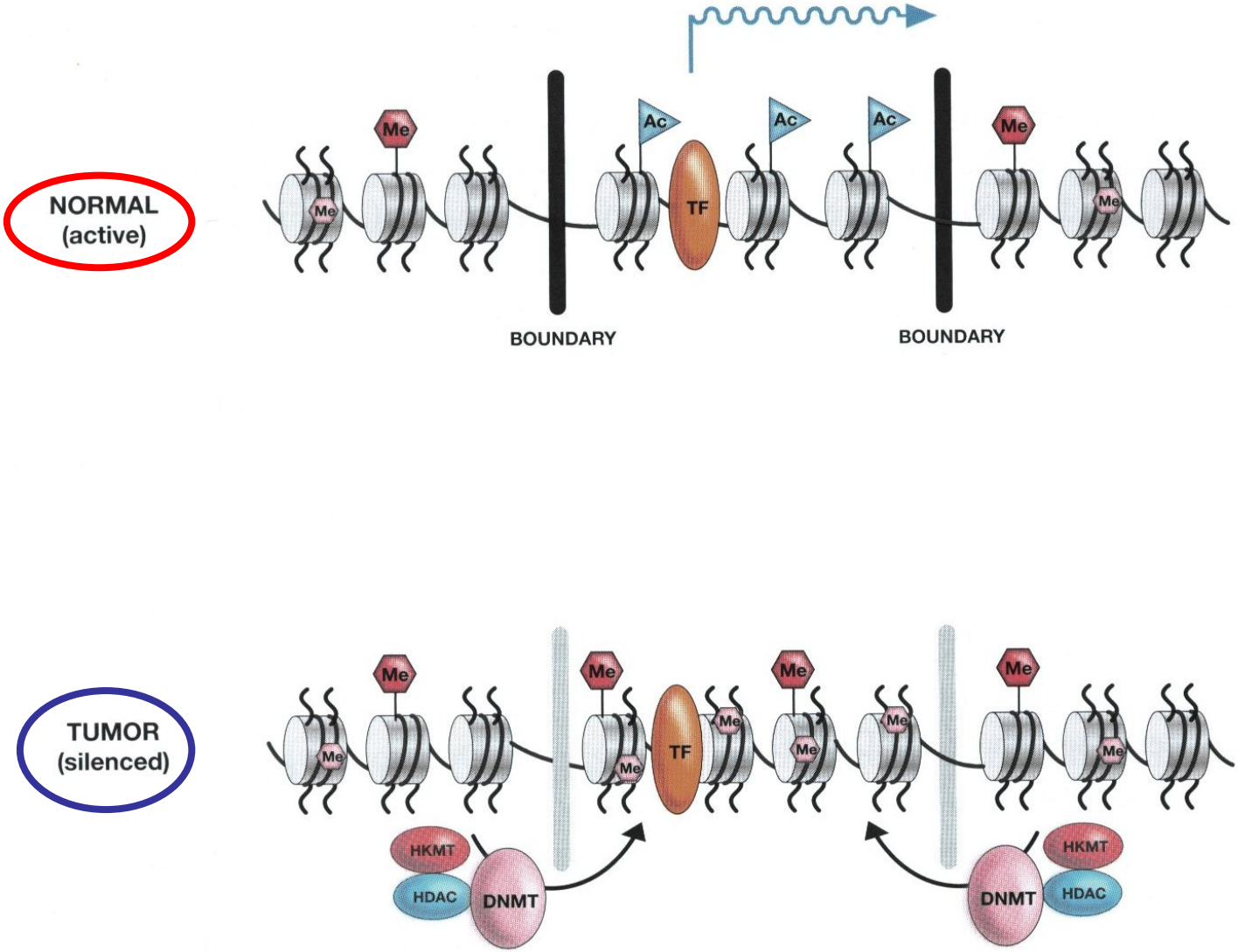
hypermetylace promotorů vede k dědičnému umlčování a k inaktivaci nádorových supresorů

metylace CpG zesiluje vazbu chemických karcinogenů k DNA a zvyšuje rychlost UV-indukovaných mutací

Jak mohou metylace DNA přispívat k inaktivaci genů kódujících nádorové supresory

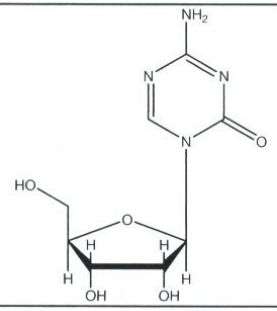
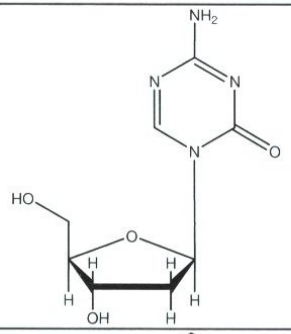
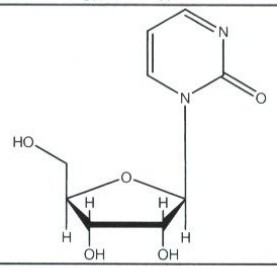


ztráta heterozygotnosti (LOH) a přídatné epigenetické umlčování



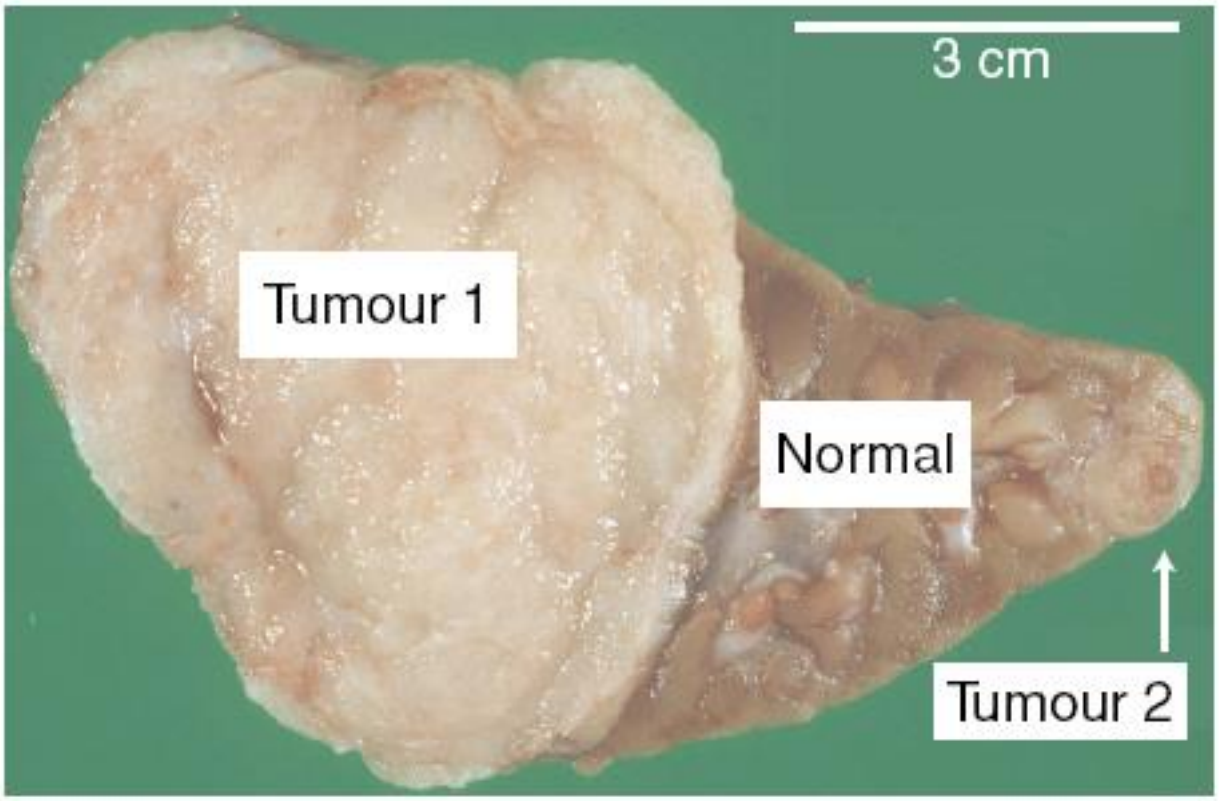
Vztah mezi metylací DNA a modifikací histonů v promotoru genu

V normální buňce (gen je aktivní, rozhraní brání metylaci cytosinu v CpG oblasti),
a nádorové buňce (rozhraní nefungují: dochází k aktivitě DNMT = DNA metyltransferázy, HDAC = histon deacetylázy, HKMT = histon metyltransferázy)

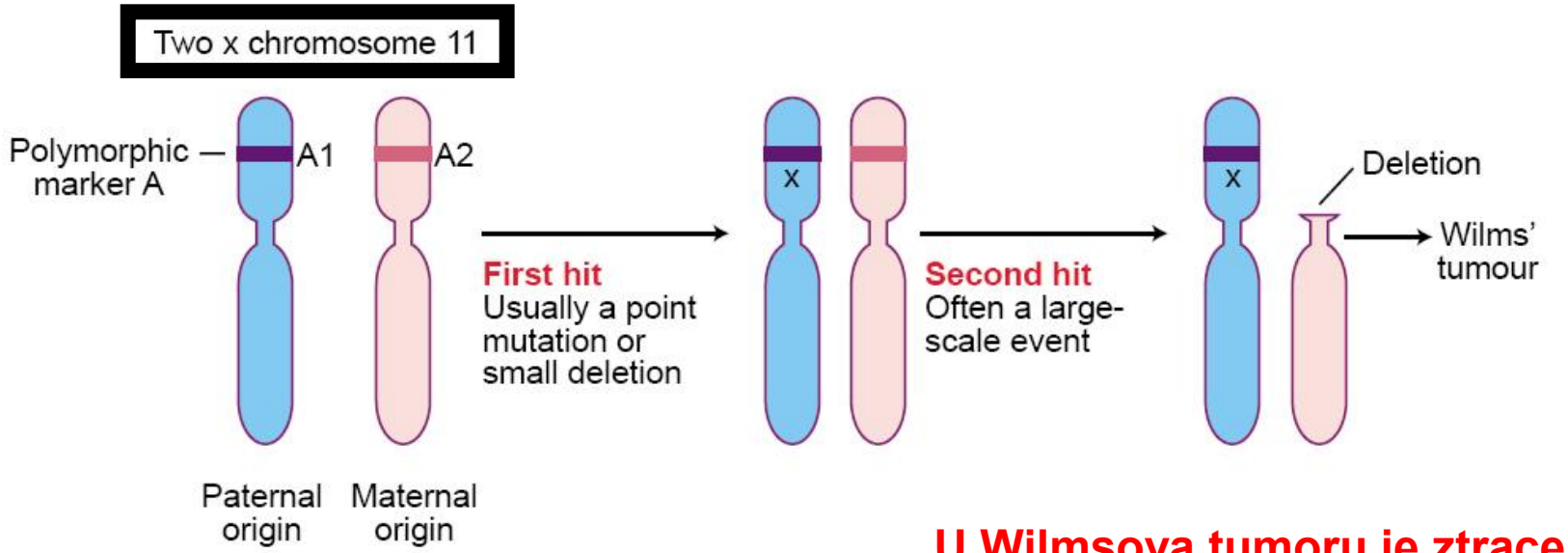
Compound	Structure	Cancer Type	Clinical Trials
DNA METHYLATION INHIBITORS			
5-Azacytidine 5-Aza-CR Vidaza		MDS; Hematologic malignancies	I, II, and III; FDA-approved for MDS
5-Aza-2'-deoxycytidine 5-Aza-CdR Dacogen		MDS; Hematologic malignancies	I, II, and III
Zebularine 1-β-D-ribofuranosyl-2(1H)-pyrimidinone		N/A	Preclinical

Struktura nukleosidových analogů – terapeutických inhibitorů metylace DNA

Inhibují metylaci cytosinu po inkorporaci do DNA: Vidaza (čs. objev) a Dacogen se používají k léčbě leukemie; Zebularine je v testování

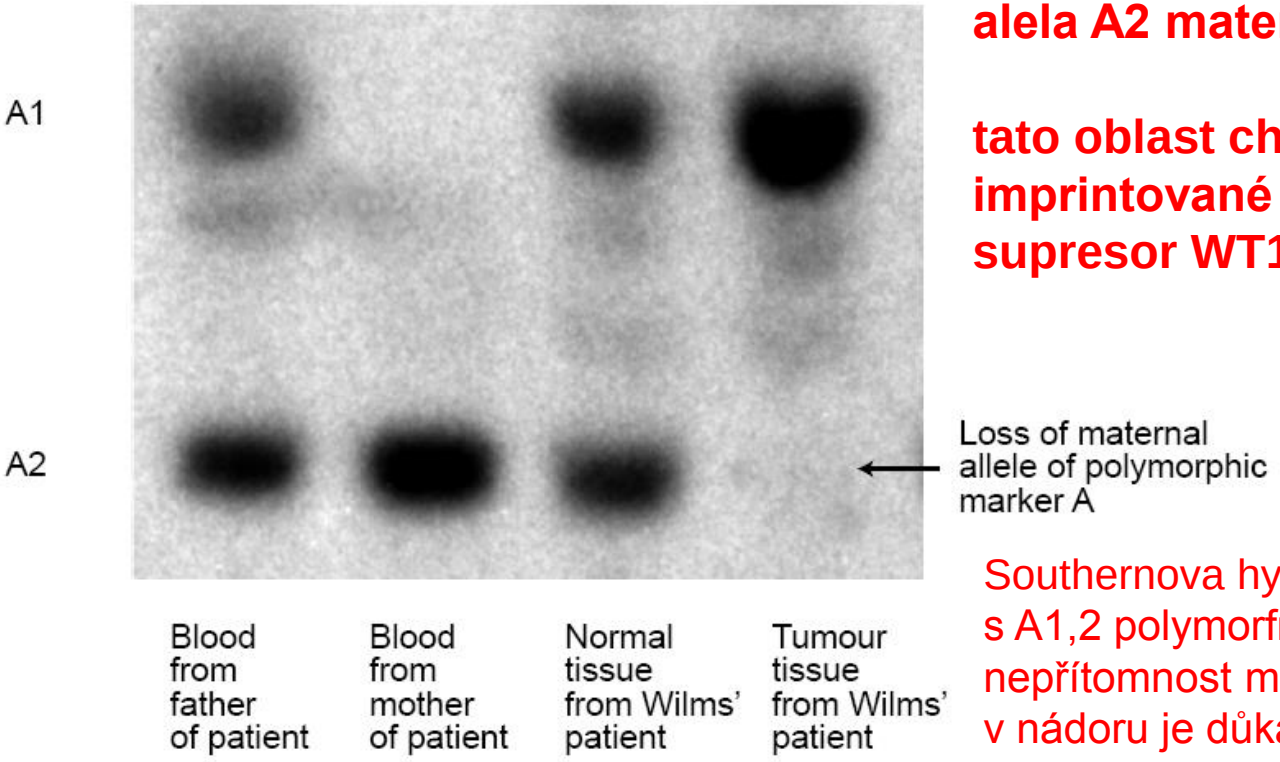


Gross pathology of Wilms' tumour. A cut section of a Wilms' tumour showing remaining normal kidney, a large tumour (Tumour 1) and a smaller additional tumour (Tumour 2).



U Wilmsova tumoru je ztracena vždy alela A2 maternálního původu:

tato oblast chromosomu 11 obsahuje imprintované geny (mj. i tumorový supresor WT1)



Southernova hybridizace
s A1,2 polymorfními markery,
nepřítomnost maternálního A2
v nádoru je důkazem větší delece

Germline epimutation of *MLH1* in individuals with multiple cancers

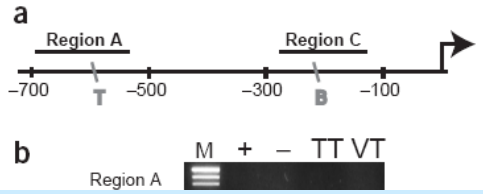
Catherine M Suter[1], David I K Martin[2,3] & Robyn L Ward[1,4]

nature genetics

Epigenetic silencing can mimic genetic mutation by abolishing expression of a gene. We hypothesized that an epimutation could occur in any gene as a germline event that predisposes to disease and looked for examples in tumor suppressor genes in individuals with cancer. Here we report two individuals with soma-wide, allele-specific and mosaic hypermethylation of the DNA mismatch repair gene *MLH1*. Both individuals lack evidence of genetic mutation in any mismatch repair gene but have had multiple primary tumors that show mismatch repair deficiency, and both meet clinical criteria for hereditary nonpolyposis colorectal cancer. The epimutation was also present in spermatozoa of one of the individuals, indicating a germline defect and the potential for transmission to offspring. Germline epimutation provides a mechanism for phenocopying of genetic disease. The mosaicism and nonmendelian inheritance that are characteristic of epigenetic states could produce patterns of disease risk that resemble those of polygenic or complex traits.

Epigenetic silencing is a stable but reversible alteration of gene function mediated by histone modification, cytosine methylation, the binding of nuclear proteins to chromatin and interactions among these[1,2]. It does not require, or generally involve, changes in DNA sequence. Errors in the elaborate apparatus of epigenetic silencing possessed by higher can predispose to cancer[9]. Tumor suppressors are also commonly methylated (and inactivated) in the course of neoplastic progression[10], but the causal relationship between hypermethylation and tumorigenesis has not been established.

We hypothesized that some individuals are predisposed to develop cancer because they carry germline epimutations of tumor suppressor genes. We selected 94 individuals for this study: 18 with hyperplastic polyposis[11], 11 with personal histories of colorectal cancer and 65 with a family history of colorectal cancer but without deleterious germline changes in *MSH2*, *MLH1* or *APC*[12]. We screened a subset of 44 individuals for promoter methylation of *MLH1*, *CDKN2A*, *TMEFF2*, *HIC1*, *RASSF1*, *BRCA1*, *APC* (promoters 1A and 1B), *BLM* and *MGMT*. We subjected bisulfite-modified DNA from peripheral blood to either combined bisulfite-restriction analysis (COBRA)[13] or methylation-specific PCR (MSP)[14]. We identified one individual (TT) with methylation of the *MLH1* (mutL homolog 1) promoter (**Fig. 1**). We



- u dvou pacientů s dědičným kolorektálním nádorem zjištěna somatická i germinální hypermetylace reparačního genu *MLH1*

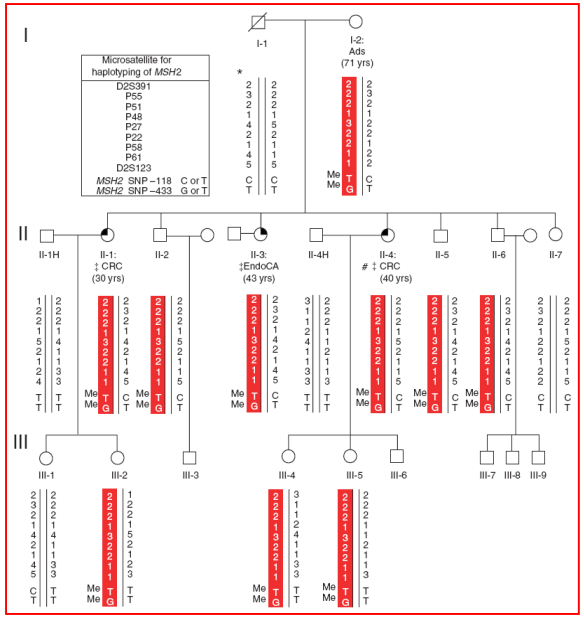
VOLUME 38 | NUMBER 10 | OCTOBER 2006 NATURE GENETICS

nature genetics

Heritable germline epimutation of *MSH2* in a family with hereditary nonpolyposis colorectal cancer

Tsun Leung Chan[1,2], Siu Tsan Yuen[1,2,3], Chi Kwan Kong[4], Yee Wai Chan[1,2], Annie SY Chan[1], Wai Fu Ng[5], Wai Yin Tsui[1], Michelle WS Lo[1], Wing Yip Tam[1], Vivian SW Li[1] & Suet Yi Leung[1]

Epimutations in the germline, such as methylation of the *MLH1* gene, may contribute to hereditary cancer syndrome in human, but their transmission to offspring has never been documented. Here we report a family with inheritance, in three successive generations, of germline allele-specific and mosaic hypermethylation of the *MSH2* gene, without evidence of DNA mismatch repair gene mutation. Three siblings carrying the germline methylation developed early-onset colorectal or endometrial cancers, all with microsatellite instability and MSH2 protein loss. Clonal bisulfite sequencing and pyrosequencing showed different methylation levels in different somatic tissues, with the highest level recorded in rectal mucosa and colon cancer tissue, and the lowest in blood leukocytes. This mosaic state of germline methylation with different tissue distribution could act as the first hit and provide a mechanism for genetic disease inheritance that may deviate from the mendelian pattern and be overlooked in conventional leukocyte-based genetic diagnosis strategy.



- somatická i germinální hypermetylace reparačního genu *MSH2* ve třech generacích pacientů s kolorektálními tumory

Neurobiologie

OPEN ACCESS Freely available online

PLoS one

Promoter-Wide Hypermethylation of the Ribosomal RNA Gene Promoter in the Suicide Brain

Patrick O. McGowan[1,2,3], Aya Sasaki[1,2,3], Tony C. T. Huang[3,4], Alexander Unterberger[3,4], Matthew Suderman[3,5], Carl Ernst[1,6], Michael J. Meaney[1,2,3], Gustavo Turecki[1,6]*, Moshe Szyf[3,4]*

1 Department of Psychiatry, Douglas Mental Health University Institute, Montreal, Quebec, Canada, **2** Department of Neurology and Neurosurgery, McGill Program for the Study of Behaviour, Genes and Environment, McGill University, Montreal, Quebec, Canada, **3** Sackler Program for Epigenetics & Psychobiology, McGill University, Montreal, Quebec, Canada, **4** Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada, **5** McGill Centre for Bioinformatics, McGill University, Montreal, Quebec, Canada, **6** McGill Group for Suicide Studies, Douglas Mental Health University Institute, Montreal, Quebec, Canada

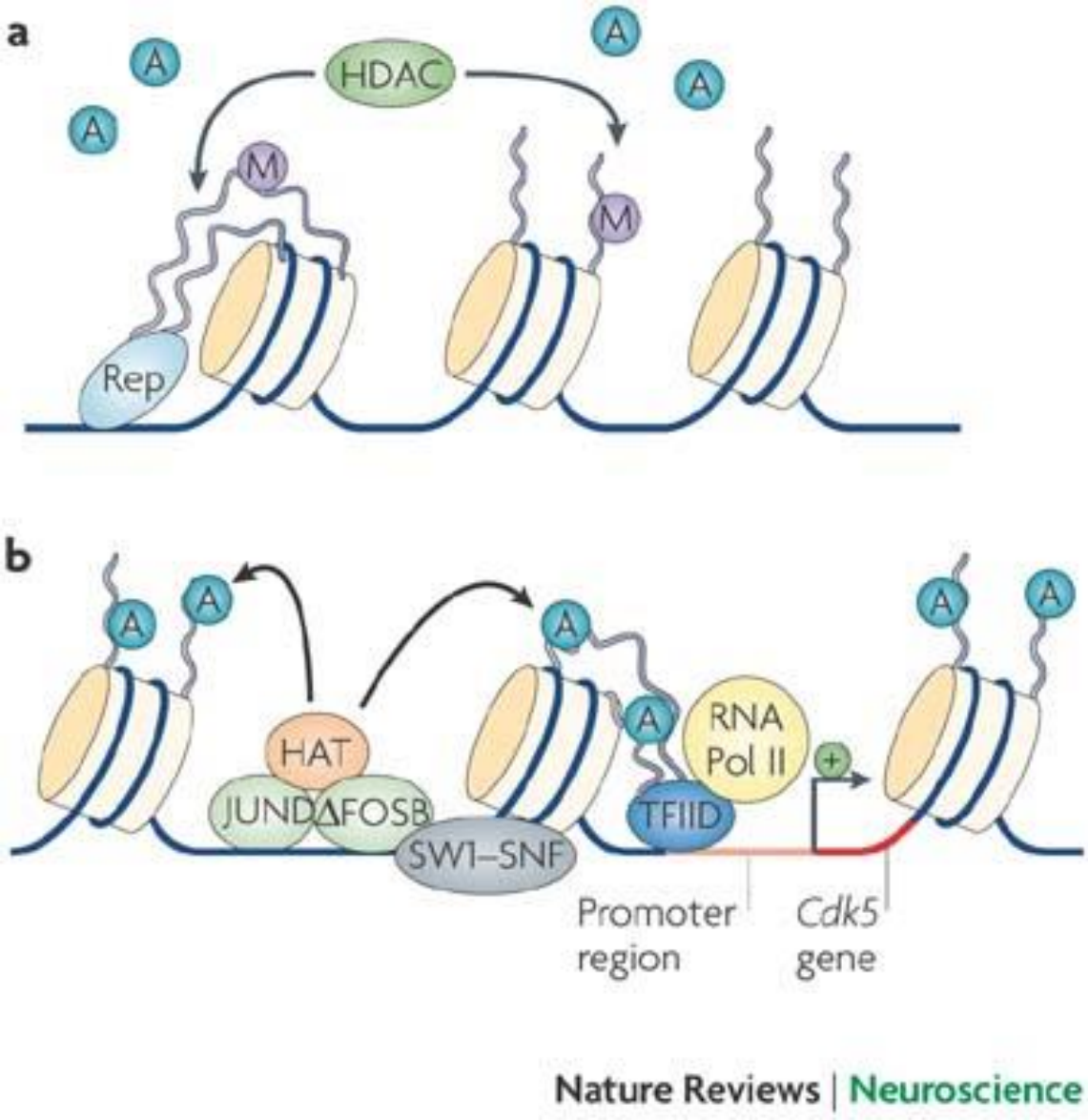
Abstract

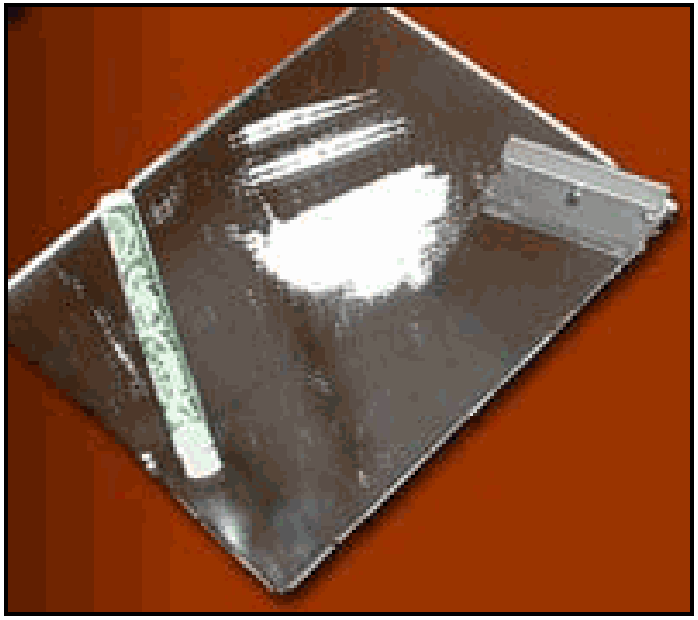
Background: Alterations in gene expression in the suicide brain have been reported and for several genes DNA methylation as an epigenetic regulator is thought to play a role. rRNA genes, that encode ribosomal RNA, are the backbone of the protein synthesis machinery and levels of rRNA gene promoter methylation determine rRNA transcription.

Methodology/Principal Findings: We test here by sodium bisulfite mapping of the rRNA promoter and quantitative real-time PCR of rRNA expression the hypothesis that epigenetic differences in critical loci in the brain are involved in the pathophysiology of suicide. Suicide subjects in this study were selected for a history of early childhood neglect/abuse, which is associated with decreased hippocampal volume and cognitive impairments. rRNA was significantly hypermethylated throughout the promoter and 5′ regulatory region in the brain of suicide subjects, consistent with reduced rRNA expression in the hippocampus. This difference in rRNA methylation was not evident in the cerebellum and occurred in the absence of genome-wide changes in methylation, as assessed by nearest neighbor.

Conclusions/Significance: This is the first study to show aberrant regulation of the protein synthesis machinery in the suicide brain. The data implicate the epigenetic modulation of rRNA in the pathophysiology of suicide.

Citation: McGowan PO, Sasaki A, Huang TCT, Unterberger A, Suderman M, et al. (2008) Promoter-Wide Hypermethylation of the Ribosomal RNA Gene Promoter in the Suicide Brain. PLoS ONE 3(5): e2085. doi:10.1371/journal.pone.0002085





Proposed chromatin remodelling events at a cocaine-activated gene. a | Repressed state of chromatin, where a site-specific repressor (Rep) recruits a histone deacetylase (HDAC) complex, which removes acetyl groups (A) from histone amino-terminal tails. Gene inactivation may also involve other modifications, such as methylation (M) of histone tails. **b** | Active state of chromatin around a cocaine-activated gene (for example, cyclin-dependent kinase 5 (*Cdk5*)), where a cocaine-induced transcriptional activator (for example, an activator protein 1 dimer composed of ΔFOSB–JUND) recruits a histone acetyltransferase (HAT) and a chromatin remodelling complex (mating switching and sucrose non-fermenting complex, SWI/SNF), which induce acetylation (and perhaps demethylation and other modifications) of histone tails and repositioning of nucleosomes. These actions facilitate the binding of general transcription factors and the basal transcriptional apparatus (for example, transcription factor IID (TFIID) and RNA polymerase II (PolII)) to the promoter.

Aktivace genové exprese kokainem

NeuroReport
For Rapid Communication of Neuroscience Research www.neuroreport.com

DNA hypermethylation of the alpha synuclein promoter in patients with alcoholism.

MOLECULAR NEUROSCIENCE

Neuroreport. 16(2):167-170, February 8, 2005.
Bonsch, Dominikus; Lenz, Bernd; Kornhuber, Johannes; Bleich, Stefan CA

Abstract:
The aim of this study was to investigate whether the DNA methylation pattern within the alpha synuclein promoter region is altered in intoxicated and early abstinence patients with alcoholism undergoing alcohol withdrawal. We observed a significant increase of the alpha synuclein promoter DNA methylation in patients with alcoholism which was significantly associated with their elevated homocysteine levels. No significant differences of the promoter DNA methylation within a control gene (presenilin-1) in alcoholics and controls were found. The present results hint to a gene specific DNA promoter hypermethylation within the alpha synuclein gene. Since hypermethylation of DNA is an important epigenetic factor in the down regulation of gene expression and since alpha synuclein has been linked to craving these findings may explain the reduced value of craving under alcohol drinking conditions.

ACUTE *IN VIVO* EFFECT OF ETHANOL (BINGE DRINKING) ON HISTONE H3 MODIFICATIONS IN RAT TISSUES

JEE-SOO KIM[1] and SHIVENDRA D. SHUKLA*

Department of Medical Pharmacology and Physiology, School of Medicine, University of Missouri–Columbia, Columbia, MO 65212, USA

(*Re* ALCOHOL AND ALCOHOLISM)05)

Abstract — Aims: To investigate the effect of acute *in vivo* administration of ethanol on acetylation or methylation of histone H3 at lysine9 in different tissues in rat. **Methods:** Ethanol was injected into the stomach of Sprague–Dawley rats (8-weeks-old) using blunt tipped needle. The rats were divided into three groups based on ethanol exposure times (1, 3, and 12 h). Each group was compared with water-injected control group. The tissues from 14 different organs were removed. We essentially used similar type of protocol, tissue homogenization method, and sucrose density gradient centrifugation for isolation of nuclei with only minor modifications for some organs. Histone was isolated from the nuclei using acid extraction method. Acetylation of histone H3 at lysine9 (Ac-H3-lys9) and methylation of histone H3 at lysine9 (Me-H3-lys9) were analysed by western blotting. **Results:** Effect of ethanol on Ac-H3-lys9 was investigated in 11 out of 14 rat tissues. In liver, we observed an increase in Ac-H3-lys9 with maximal increase of ~6-fold after 12 h exposure. Lung also showed ~3-fold increase. In spleen, ethanol-induced Ac-H3-lys9 in all three ethanol-treated groups with similar increase (1.5- to 1.6-fold). Testes showed significant increase (3-fold increase) of Ac-H3-lys9 only at 1 h ethanol exposure. Ethanol had no affect on Ac-H3-lys9 in other tissues: kidney, brain, heart, stomach, colorectum, pancreas, and vessels. Ethanol had little effect on Me-H3-lys9 in all rat tissues examined. **Conclusions:** After *in vivo* administration of ethanol, analogous to binge drinking condition, the acetylations of H3-lys9 in rat tissues are not universal but tissue-specific events with different patterns of responses. Ac-H3-Lys9 in liver, lung, and spleen were significantly affected and it was demonstrated that ethanol causes this epigenetic alteration in rat tissues selectively.

Transgenerational effects of fetal and neonatal exposure to nicotine

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Alison C. Holloway[1], Donald Q. Cuu[1], Katherine M. Morrison[2], Hertzel C. Gerstein[3] and Mark A. Tarnopolsky[2, 3]

(1) Reproductive Biology Division, Department of Obstetrics & Gynecology, McMaster University, RM HSC-3N52, 1200 Main Street West, Hamilton, ON, Canada, L8N 3Z5

(2) Department of Pediatrics, McMaster University, Hamilton, ON, Canada, L8N 3Z5

(3) Department of Medicine, McMaster University, Hamilton, ON, Canada, L8N 3Z5

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Abstract A wide variety of in utero insults are associated with an increased incidence of metabolic disorders in the offspring and in subsequent generations. We have shown that fetal and neonatal exposure to nicotine results in endocrine and metabolic changes in the offspring that are consistent with those observed in type 2 diabetes. This study examines whether fetal and neonatal exposure to nicotine has transgenerational effects in the F2 offspring. Female Wistar rats were given either saline or nicotine (1 mg/kg/d) during pregnancy and lactation to create saline- and nicotine-exposed female F1 progeny. These F1 females were then bred to produce F2 offspring. We examined glucose homeostasis, serum lipids and fat pad weights, mitochondrial enzyme activity in skeletal muscle and blood pressure in these F2 offspring between 13 and 15 weeks of age. Offspring of nicotine- versus saline-exposed mothers had elevated fasting serum insulin concentrations and an enhanced total insulin response to the glucose challenge. This apparent insulin resistance was unrelated to changes in skeletal muscle mitochondrial volume or activity. The offspring of nicotine-exposed mothers also had elevated blood pressure. These data demonstrate that adverse effects of fetal and neonatal exposure to nicotine can influence aspects of metabolic risk in subsequent generations.

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Covalent Modification of DNA Regulates Memory Formation

Courtney A. Miller[1] **and J. David Sweatt**[1],*

[1] Department of Neurobiology and the Evelyn F. McKnight Brain Institute,University of Alabama at Birmingham, Birmingham, AL 35294, USA

Summary

DNA methylation is a covalent chemical modification of DNA catalyzed by DNA methyltransferases (DNMTs). DNA methylation is associated with transcriptional silencing and has been studied extensively as a lifelong molecular information storage mechanism put in place during development. Here we report that DNMT gene expression is upregulated in the adult rat hippocampus following contextual fear conditioning and that DNMT inhibition blocks memory formation. In addition, fear conditioning is associated with rapid methylation and transcriptional silencing of the memory suppressor gene *PP1* and demethylation and transcriptional activation of the synaptic plasticity gene *reelin*, indicating both methyltransferase and demethylase activity during consolidation. DNMT inhibition prevents the *PP1* methylation increase, resulting in aberrant transcription of the gene during the memory-consolidation period. These results demonstrate that DNA methylation is dynamically regulated in the adult nervous system and that this cellular mechanism is a crucial step in memory formation.

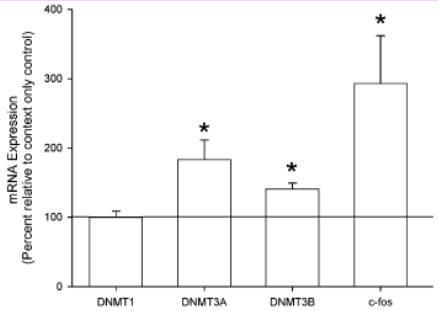


Figure 1. Fear Conditioning Is Associated with an Upregulation of DNMT mRNA

DNMT3A, DNMT3B, and c-*fos* mRNA in area CA1 are upregulated within 30 min of fear conditioning in context-plus-shock animals, relative to context-only controls. *$p < 0.05$. Error bars represent SEM.

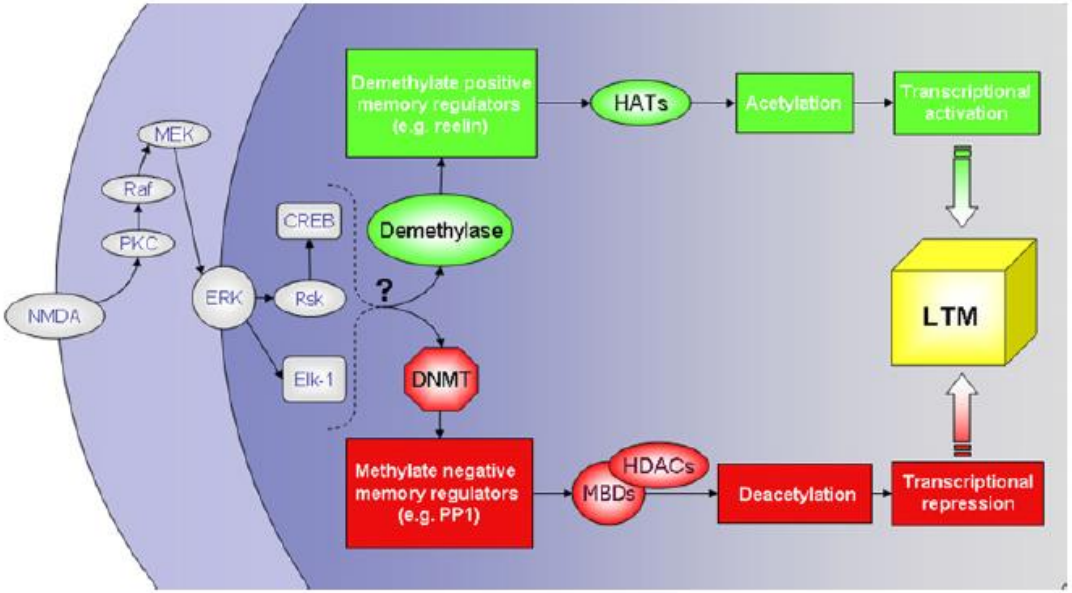


Figure 9. Schematic Representation of the Role DNA Methylation May Be Playing in the Transcriptional Regulation of Memory Formation in the Hippocampus

Note: The receptors, kinases, and transcription factors depicted in gray play established roles in hippocampal memory consolidation. However, the present study does not address the potential link between these proteins and the DNA methylation we report here to be important for memory formation.

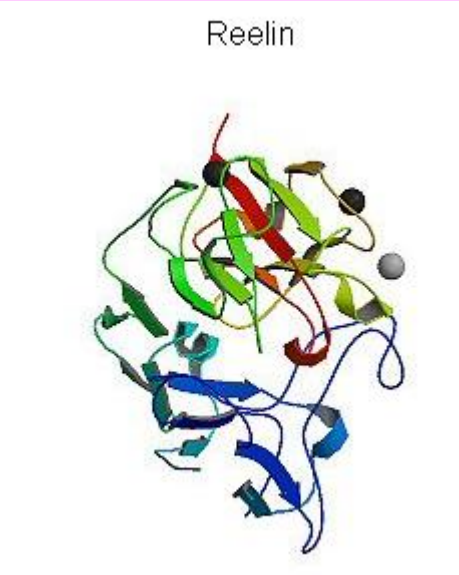
Reelin

From Wikipedia, the free encyclopedia

Reelin is a protein found mainly in the brain, but also in the spinal cord, blood and other body organs and tissues. Reelin is crucial for regulating the processes of neuronal migration and positioning in the developing brain. Besides this important role in the early period, reelin continues to work in the adult brain. It modulates the synaptic plasticity by enhancing LTP induction and maintenance.[1][2] It also stimulates dendrite development[3] and regulates the continuing migration of neuroblasts generated in adult neurogenesis sites like subventricular and subgranular zones.

Reelin is implicated in pathogenesis of several brain diseases: significantly lowered expression of the protein have been found in schizophrenia and psychotic bipolar disorder. Total lack of reelin causes a form of lissencephaly; reelin also may play a role in Alzheimer's disease, temporal lobe epilepsy, and autism.

Reelin's name comes from the abnormal reeling gait of *reeler* mice,[4] which were found to have a deficiency of this brain protein and were homozygous for the RELN gene, which encodes reelin synthesis. The primary phenotype associated with loss of reelin function is inverted cortex, a neuroanatomical defect in which the six cortical layers are inverted. Heterozygous mice for the reelin gene have very little obvious neuroanatomical defect but those that they have resemble the changes of the human schizophrenic brain.



Maternální programování epigenetických stavů

Maternální péče jako model „experience-dependent“ chromatinové plasticity

mateřská péče o novorozence (lízání a mazlení)

serotonin

mozkový transmitter

cAMP

cyklický adenosin monofosfát

PKA

protein kináza A

DNA demetylázy

histon-acetyltransferázy

NGFI-A

mozkový transkripční faktor

NGFI-A

Ac

Ac

CH_3 CH_3

DNMT

DNA-metyltransferáza

DOBRÁ MATEŘSKÁ PÉČE
vysoká exprese genu kódujícího glukokortikoidní receptor - STABILNÍ PSYCHIKA DOSPĚLÉHO POTOMSTVA (Ac = acetylace histonů)

ŠPATNÁ MATEŘSKÁ PÉČE
nízká exprese genu GR, STRESOVÁ PSYCHIKA DOSPĚLÉHO POTOMSTVA (CH_3 = metylace DNA)