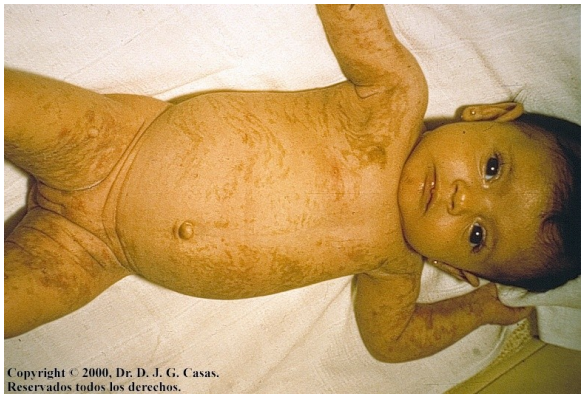
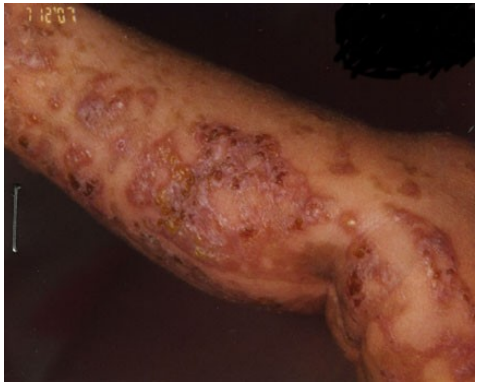
Incontinentia pigmenti

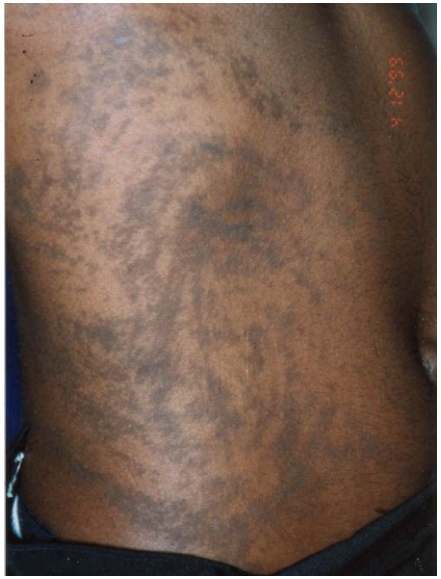
• severe X-linked genodermatosis, associated with mutations in **the *NEMO* gene** (NFkB essential modulator),

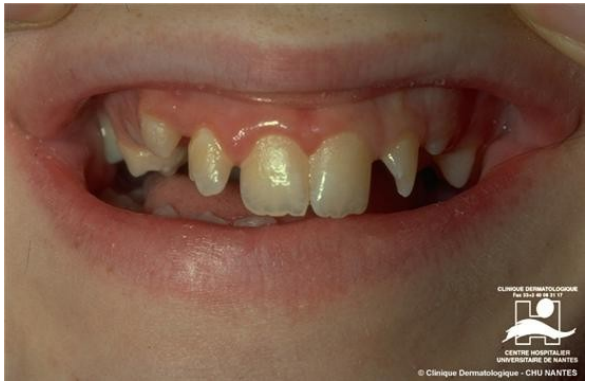
• affects almost exclusively females (males die *in utero* before the second trimester),

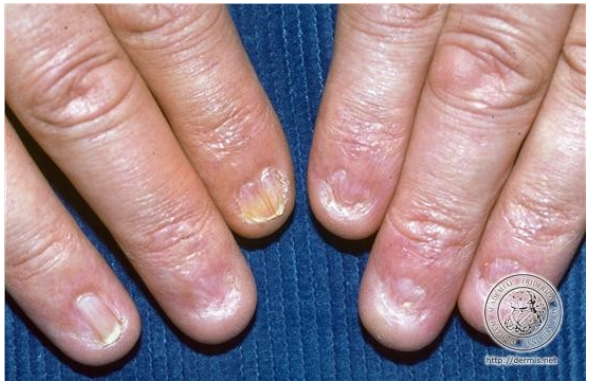
• highly variable in clinical manifestations but always associated with skin defects.











IP is characterized by **four distinct dermatological stages** that begin within 2 weeks after birth with blisters and an inflammatory response (Stage I/Vesicular Stage, Fig. 1). Subsequently, verrucous hyperkeratotic lesions develop (Stage II/Verrucous Stage, Fig. 2) and disappear over time, leaving areas of hyperpigmentation due to melanin accumulation (Stage III/Hyperpigmented Stage, Fig. 3). These areas generally disappear by the second decade (Stage IV/Atrophic Stage), but adults may still show areas of dermal scarring with lack of hair follicle (Fig. 4,5) ……

Fig. 1

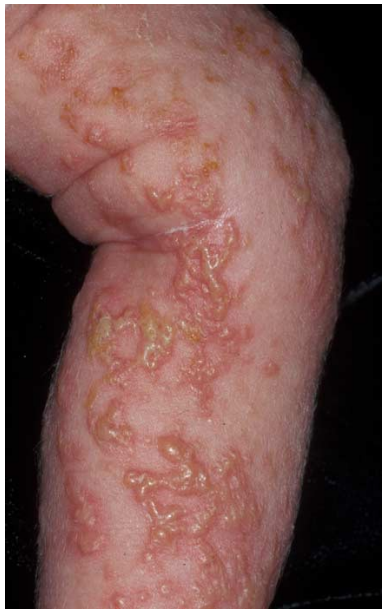


Fig. 2

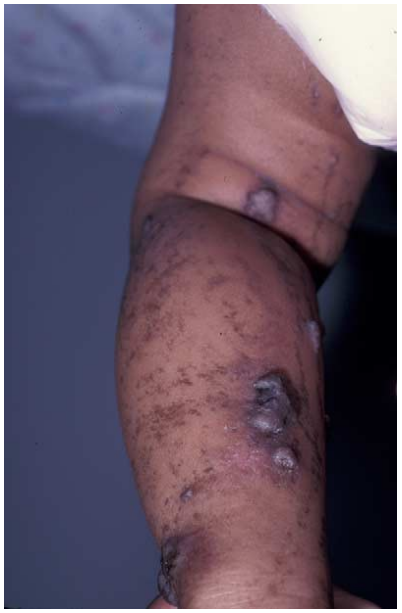


Fig. 3

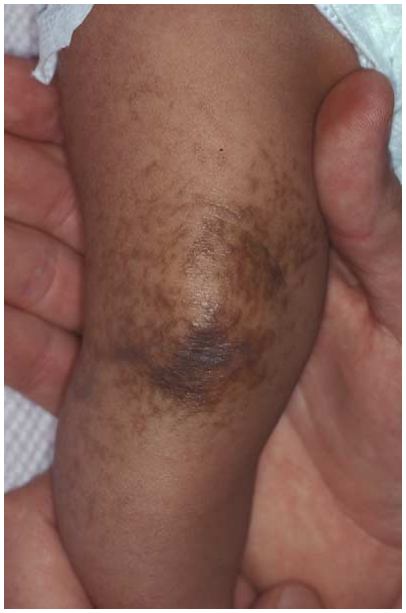


Fig. 4

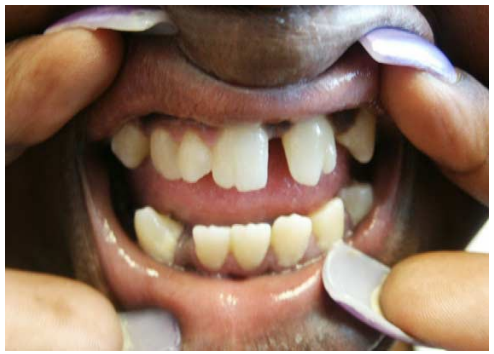
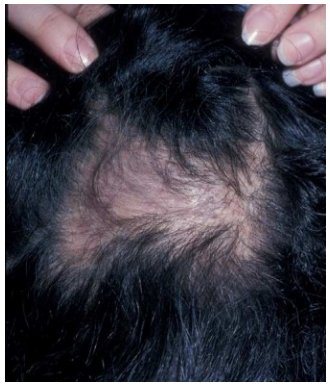
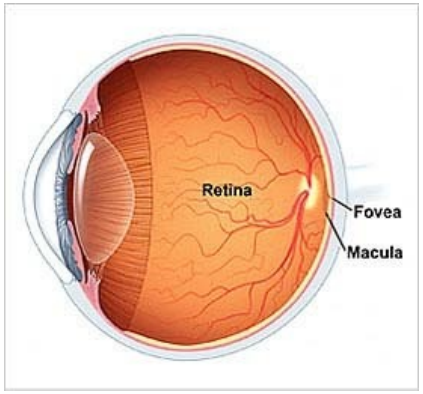
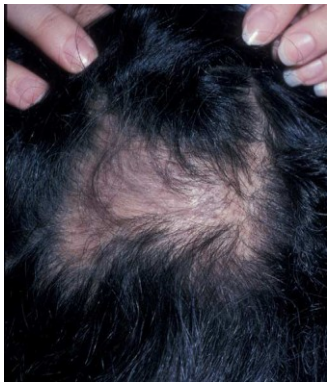


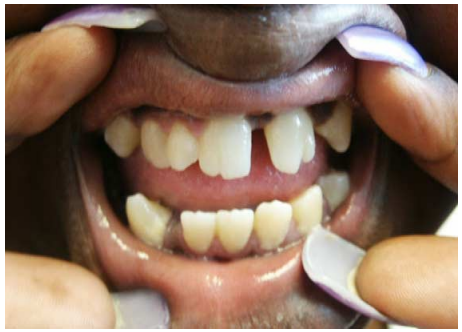
Fig. 5

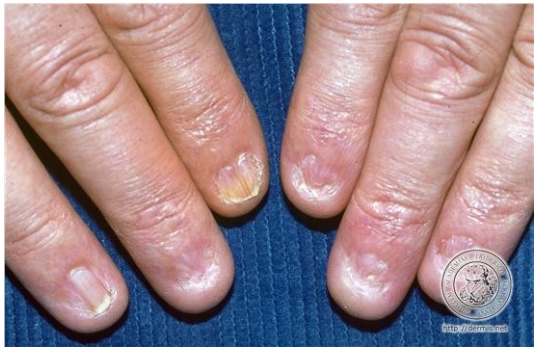


• While every IP patient exhibits **skin abnormalities** to some degree, **blindness** and **central nervous system anomalies** are occurring in about 40% and 30% of patients, respectively.
• Eye manifestations in IP patients (retinal detachment and consequent blindness) ← deficient vascularization of retina.
• CNS manifestations in IP patients (ischemia, generalized atrophy, seizures, paralysis, mental retardation, ...) ← deficient vascularization of brain.
• In addition to the dermal, visual and brain defects, IP patients exhibit some less medically significant problems, including hair loss (alopecia), conical, peg-shaped or absent teeth (anodontia), and nail dystrophy.





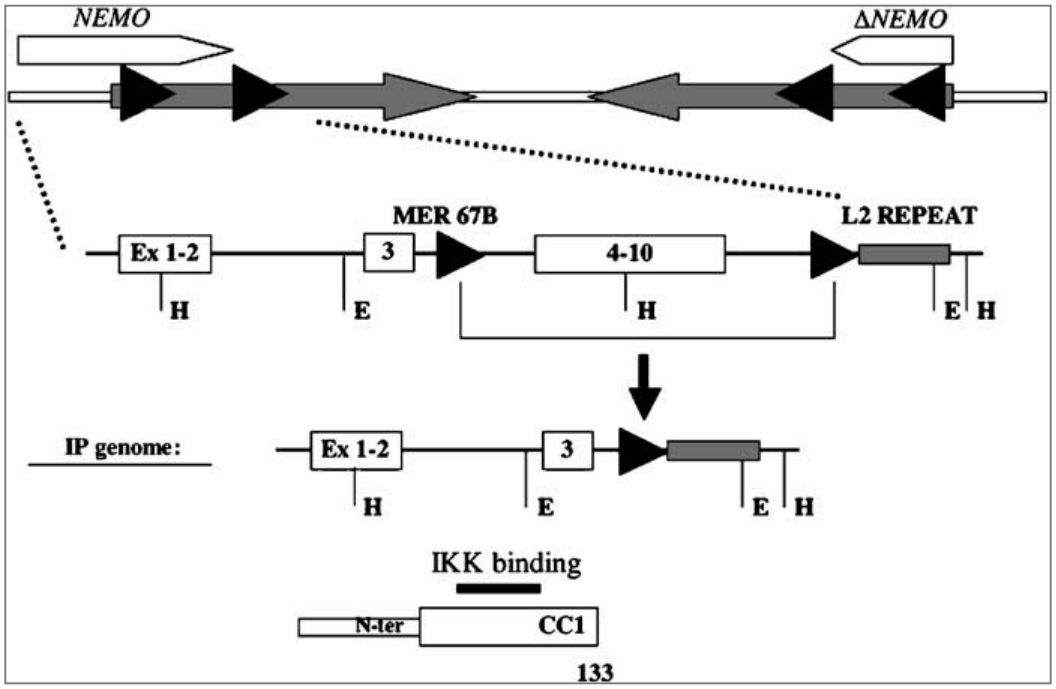




Genomic rearrangement of *NEMO* in IP

• The 35.5 kB genomic duplication that contains *NEMO* and *NEMO* pseudogene (gray arrow).

• IP rearrangement - excision of the region between two MER67B repeats located upstream of exon 4 and downstream of exon 10, respectively.



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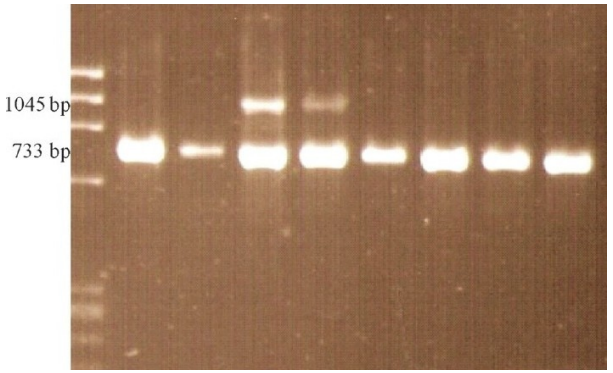
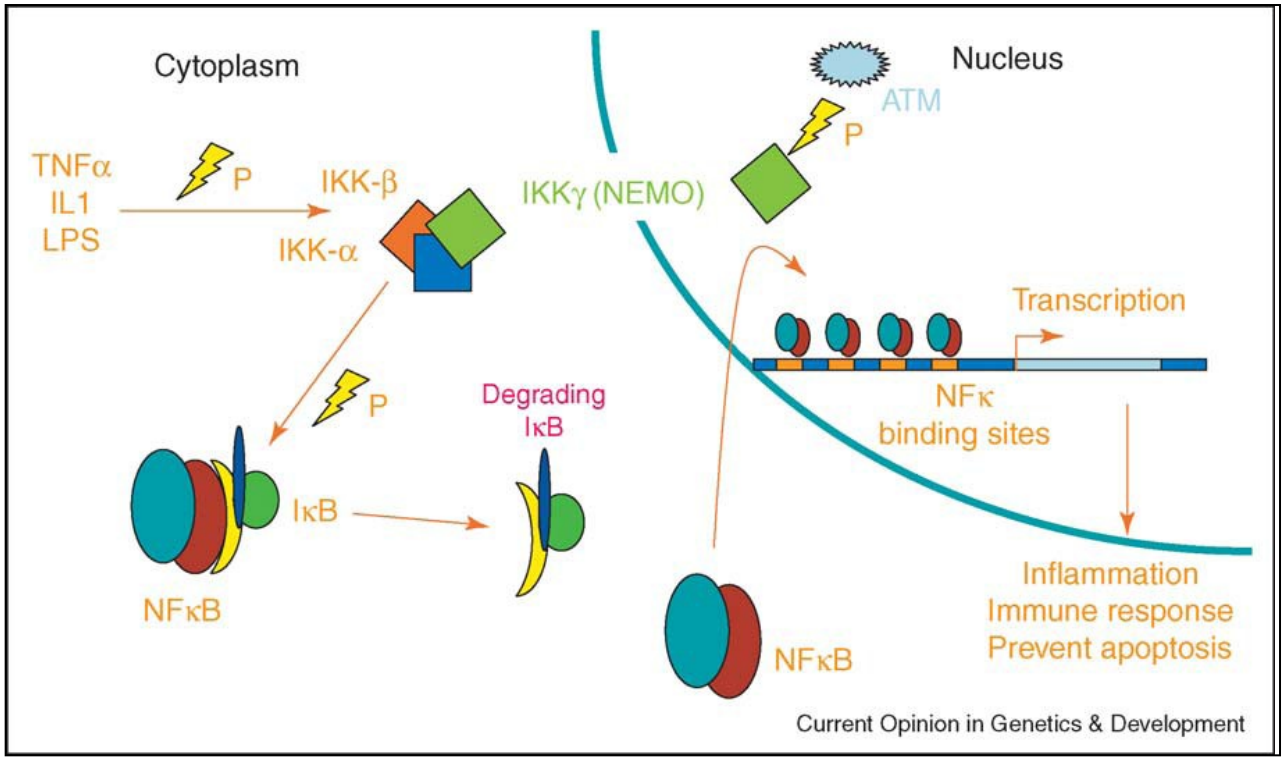


Multiplex PCR products in IP patients and controls. Presence of 1045 bp band indicates the presence of the common rearrangement in IP patients only. 733 bp product serves as internal amplification control.

• Resting cells: **NF-kB** (dimeric transcription factor) is kept **inactive** in **cytoplasm** through interaction with **inhibitory molecules of the IkB family**. In response to multiple stimuli (inflammatory cytokines, viral infection, stress) IkBs are phosphorylated → ubiquitination and destruction via the proteasome. As a consequence, free NF-kB enters the nucleus and activates transcription of genes participating in immune and inflammatory response, or protection against apoptosis.

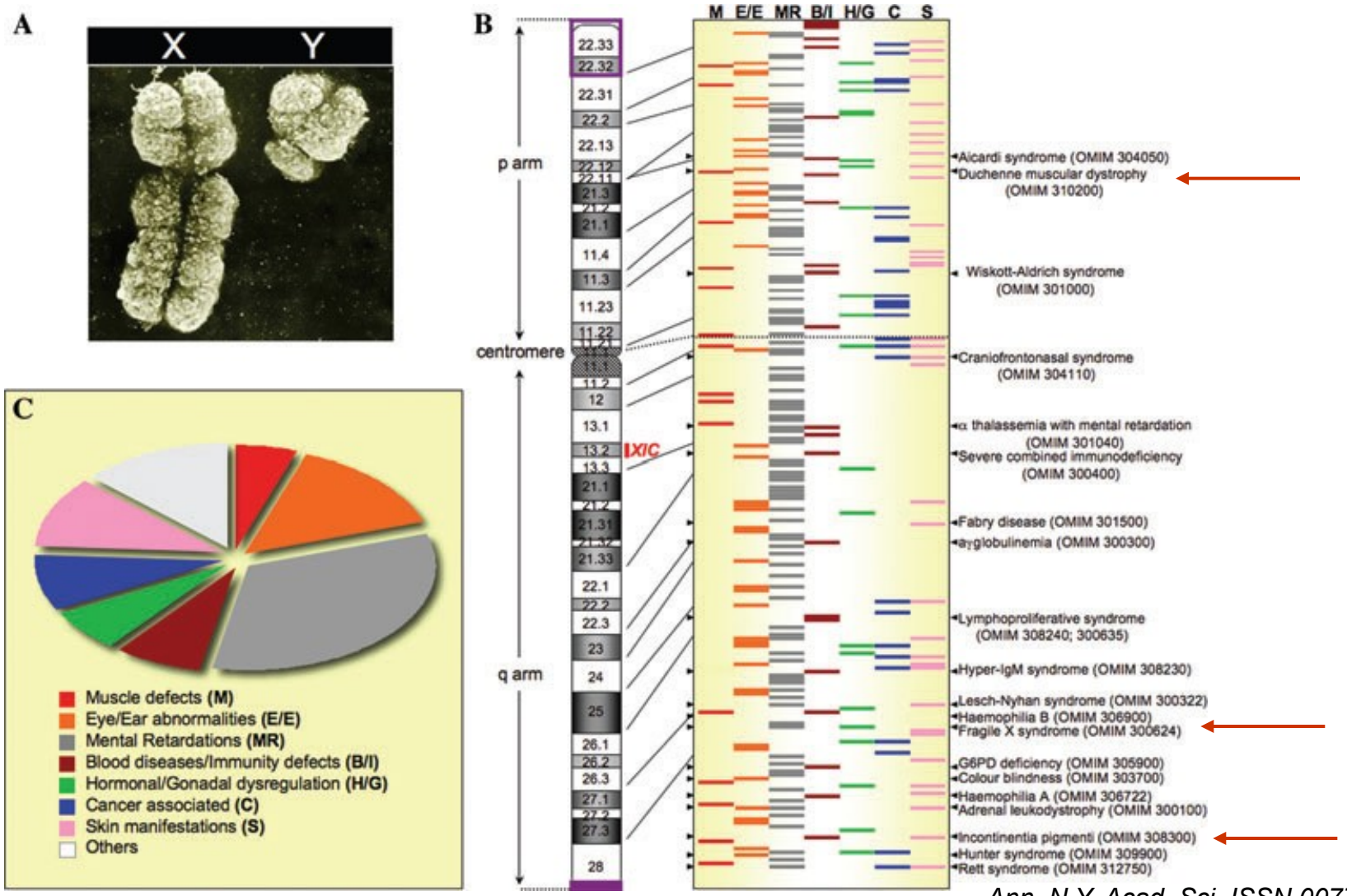
• The kinase that phosphorylates IkB, **IKK (IkB kinase)**, is a high-molecular-weight complex. It contains two catalytic subunits and one regulatory subunit (**NEMO**).



• DNA damage … ATM kinase phosphorylates NEMO … release of NFkB … stimulation transcription of anti-apoptotic genes.

Current Opinion in Genetics & Development 2006, 16:282–288

(A) Scanning electron micrograph of X and Y chromosome. (B) Ideogram of X chromosome showing the position of 275 known X-linked diseases and the associated clinical features (M, muscle defects; E/E, eye/ear abnormalities; MR, mental retardation; B/I, blood disease/immunity defects; H/G, hormonal/gonadal dysregulation; C, cancer; S, skin manifestations). (C) Graph showing the distribution of X-linked diseases within the seven categories of clinical features described in (B).



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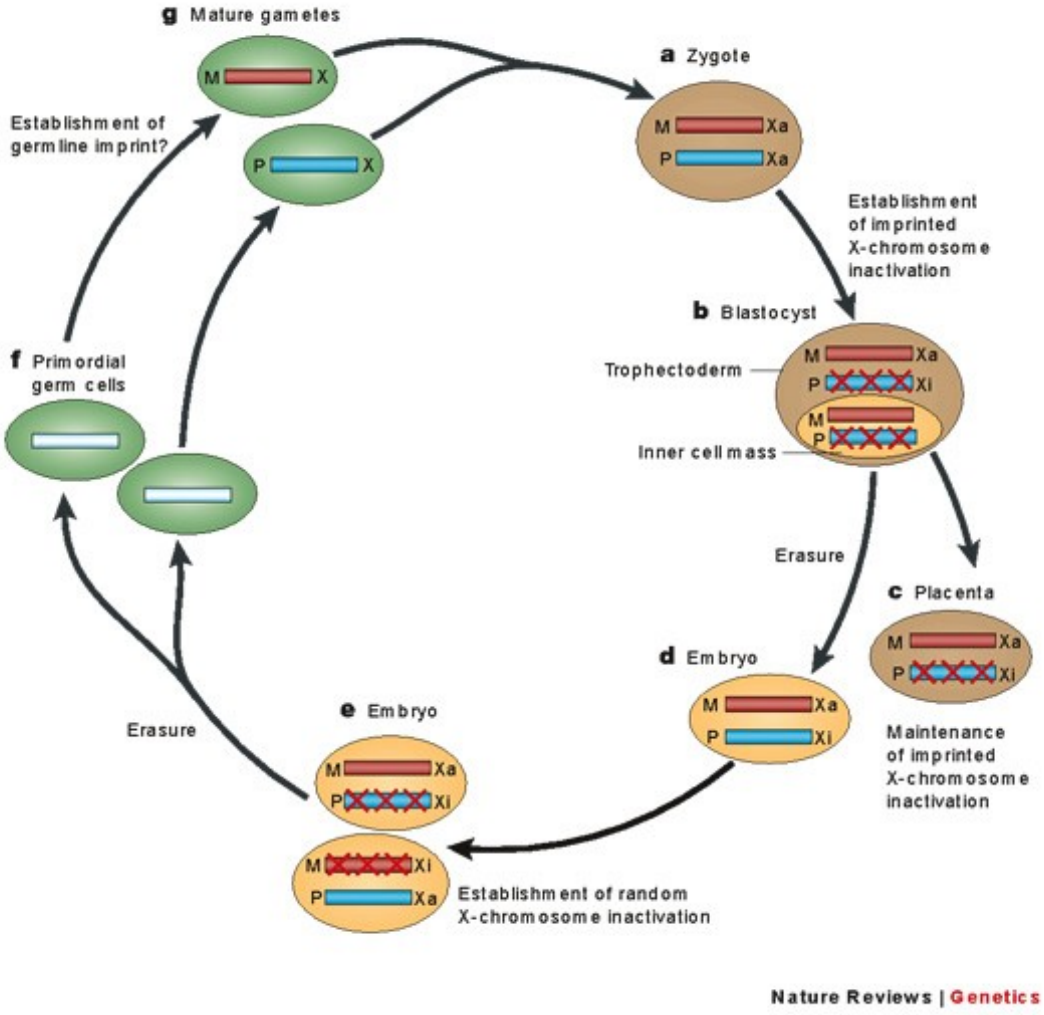
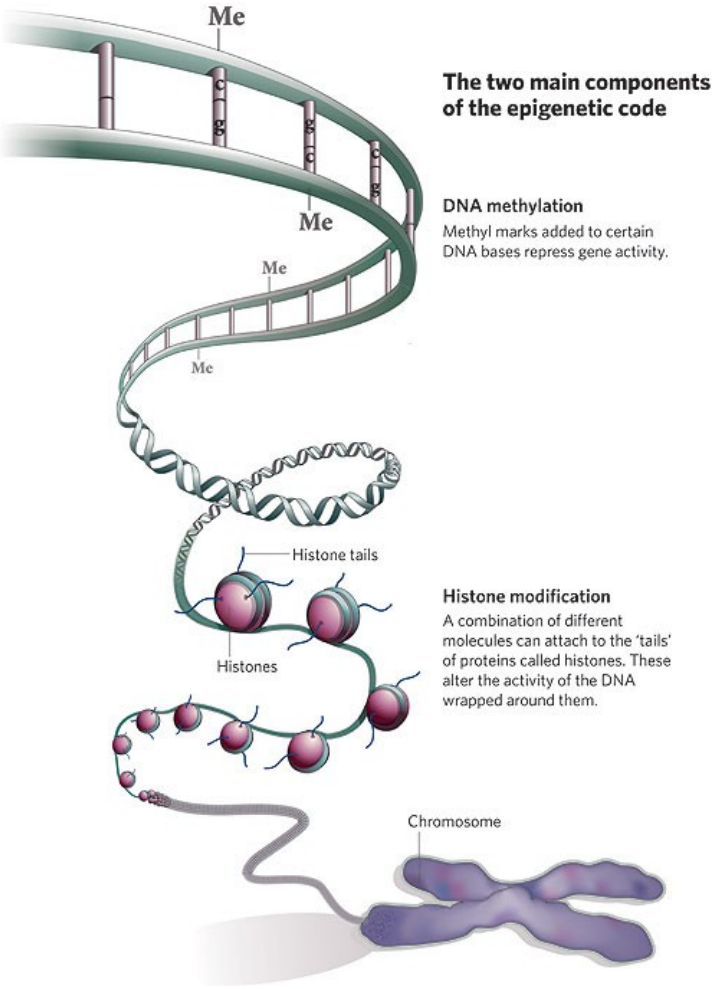


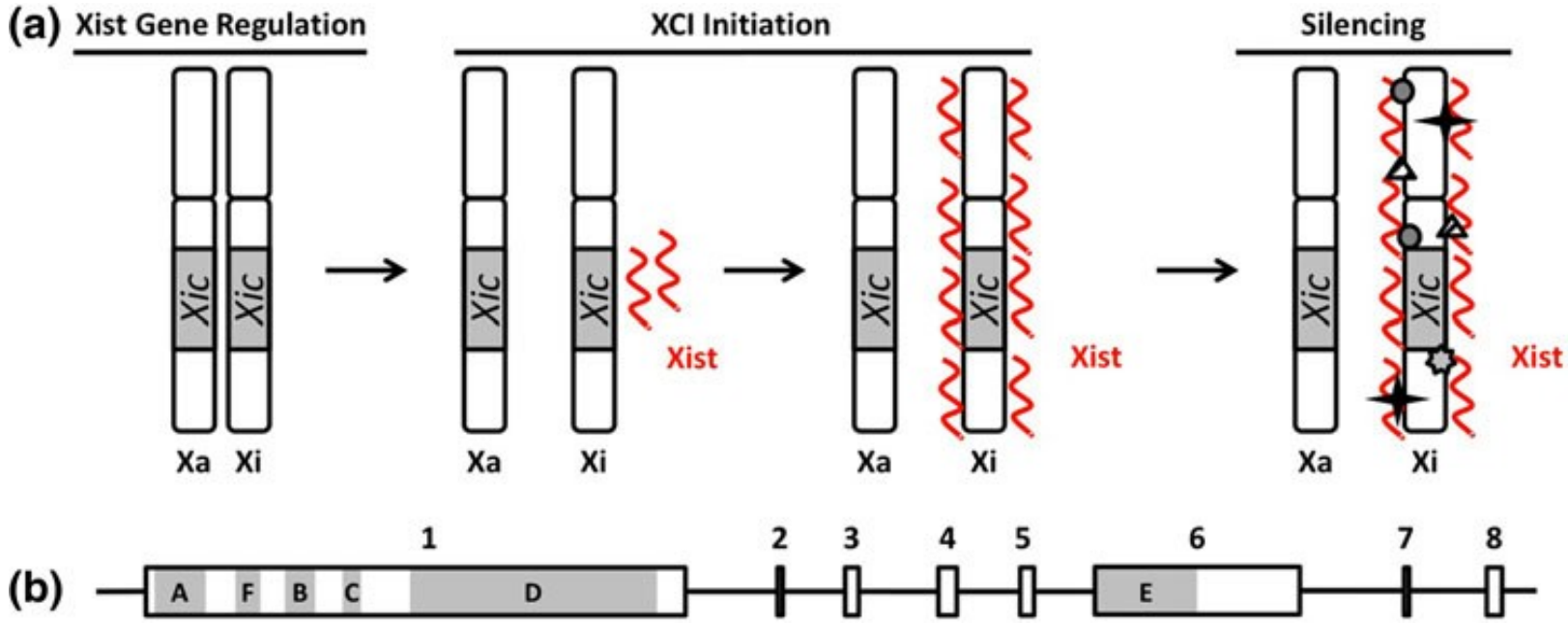
Red rectangles - X chromosome of maternal origin (M), blue rectangles - X of paternal origin (P). The active and inactive X chromosomes are indicated by Xa and Xi, respectively. The zygote (**a**) – both X chromosomes are potentially active. The blastocyt (**b**) – inactivation of imprinted paternal X chromosome is established (red crosses). The placenta and other extra-embryonic tissues (**c**) – inactivation of imprinted paternal X chromosome is maintained. The embryonic tissues (**d**) – inactivation of imprinted paternal X chromosome is erased and random X-chromosome inactivation is then established (**e**) and maintained throughout adult life.

• **X-chromosome inactivation (XCI, the transcriptional silencing of one X chromosome in females) is the means for attainment of gene dosage parity between XX female and XY male.**

• Two distinct steps of XCI: initiation and maintenance. The initiation phase - the inactive X chromosome undergoes epigenetic transcriptional inactivation. The maintenance phase - replicated copies of the inactive X-chromosome are maintained inactive through multiple rounds of cell division into descendant cells.
Both phases of XCI occur during discrete stages of early embryogenesis.

• XCI is a highly regulated process involving large noncoding RNA, chromatin remodeling, and nuclear reorganization of X chromosome.





Hum Genet (2011) 130:247–253

(a) A model illustrating the XCI process starting with the regulated expression of Xist (X-inactive specific transcript,*red*) from the X inactivation centre (*Xic*). Subsequently, Xist RNA coats the entire chromosome in cis thus facilitating gene silencing through the recruitment of repressive factors (polycomb repressor proteins, specific histone variants, CpG island methylation of promoter regions, …) that modify the chromatin structure. These multiple modifications ensure the stabilization and maintenance of the inactive state throughout subsequent mitotic divisions. (b) Gene structure of the human *XIST.*

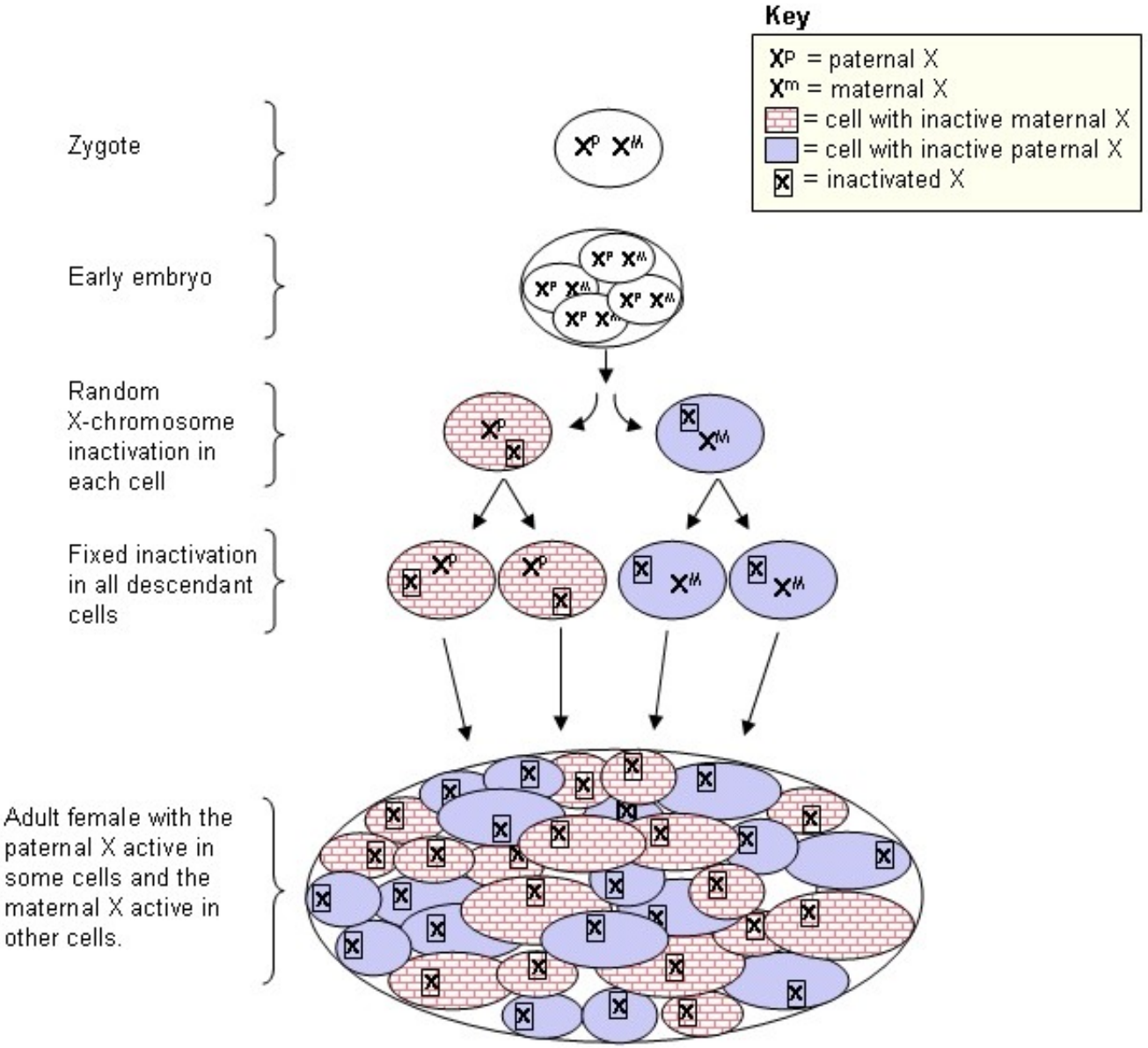


Illustration adapted from Thompson & Thompson Genetics in Medicine, 6th Edition; RL Nussbaum, RR McInnes, HF Willard, *Patterns of Single-Gene Inheritance*, Figure 5-16, pg 67, Copyright 2001, with permission from Elsevier.

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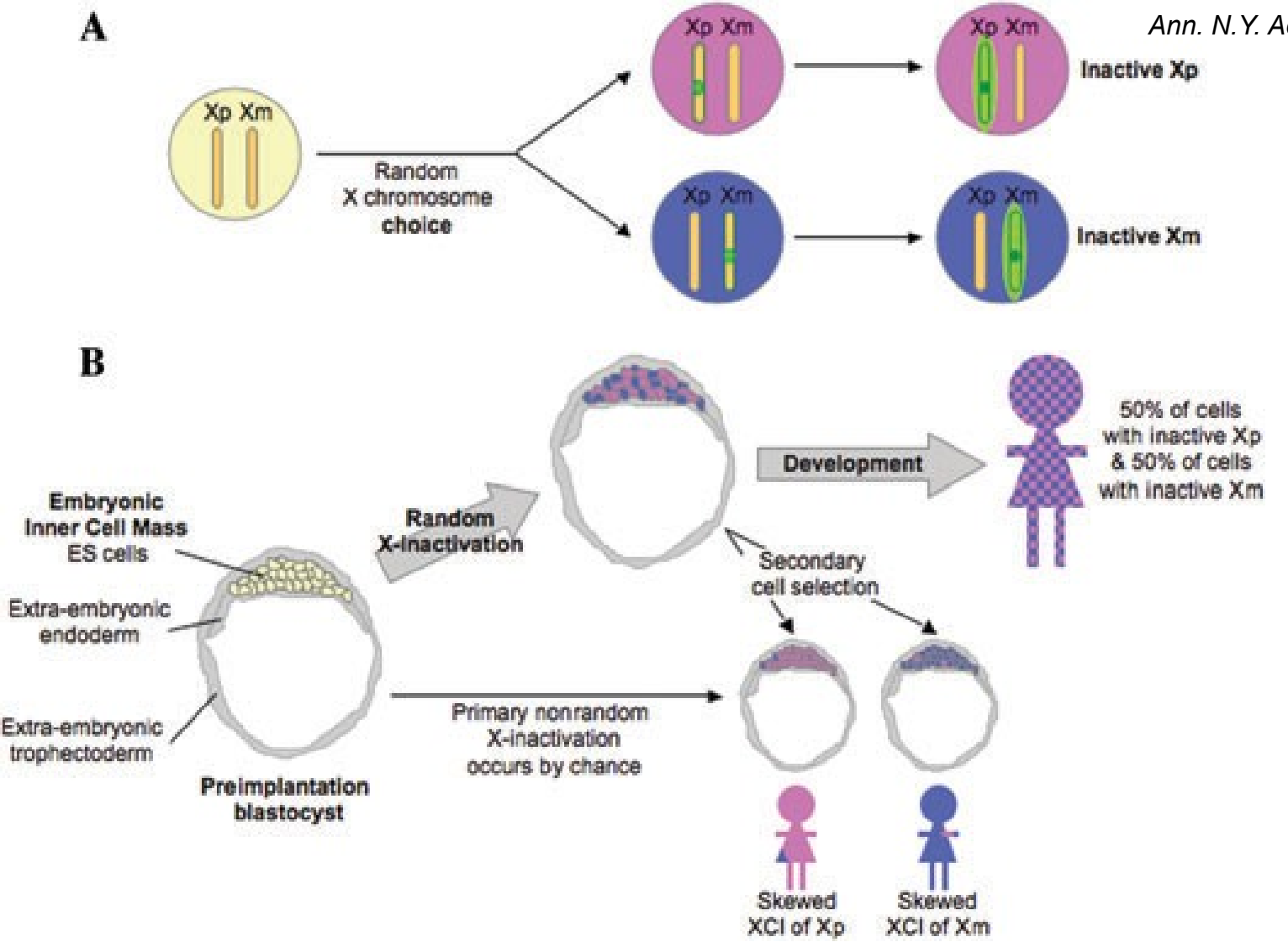


(A) Before XCI, both X (the maternal Xm and the paternal Xp) are active. *XIST* RNA is randomly selected to be expressed from either Xm or Xp. *XIST* coats the chromosome from which it is produced (green) and triggers its transcriptional silencing and condensation.

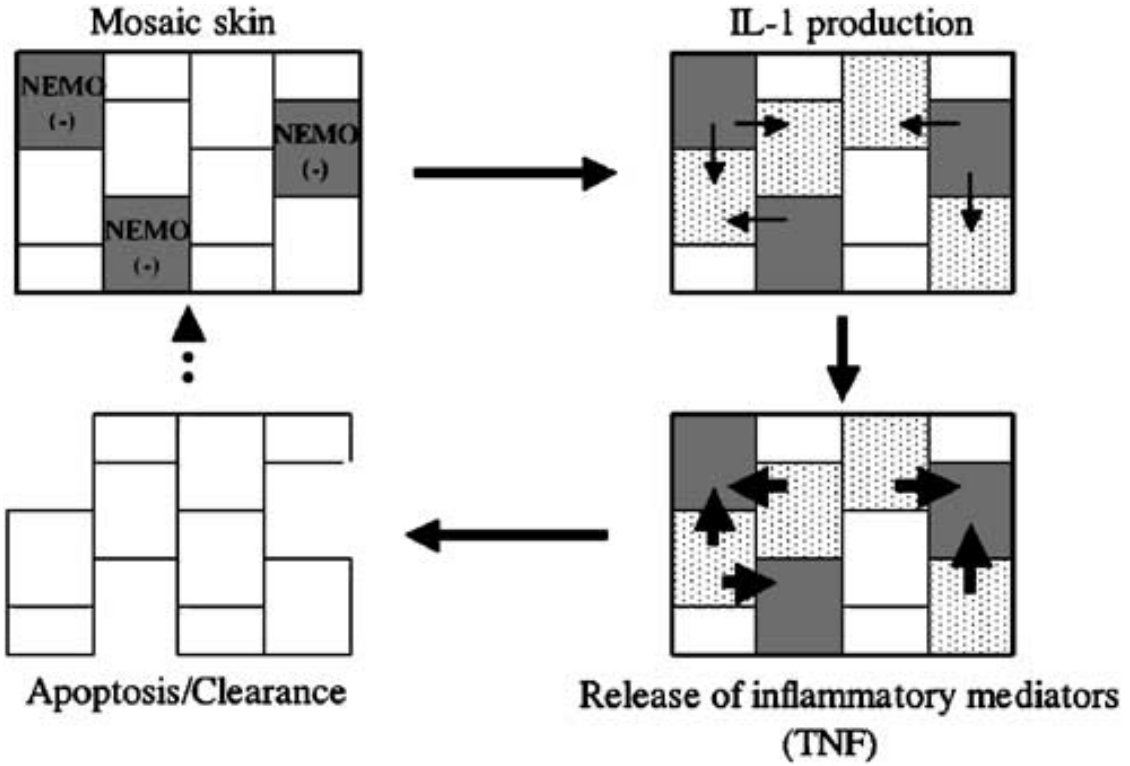
(B) During embryogenesis, XCI is initiated in the inner cell mass (cells carrying two active X). In most cases, **random XCI** results in a mosaic of cells with inactive Xm (blue) or inactive Xp (pink). Further development and cell divisions this random distribution is maintained. In **primary nonrandom XCI**, some factors alters this randomness, so that either Xp or Xm is preferentially inactivated. In **secondary cell selection**, random XCI occurs normally but some factors (conferring growth advantage or inducing cell lethality) favor the selection of cells carrying either inactive Xp or inactive Xm.

X-linked inherited diseases

• **Lesch-Nyhan syndrome** – **the mutation eliminates cells in which is expresed** - blood cells expressing the mutated allele show a growth disadvantage and progressively disappear from the population of blood cells.
• **Adrenal leukodystrophy** – **the mutation confers a proliferative advantage of the cells in which is expressed** - the mutant cell populations progressively exceed the normal cell populations and increase disease severity.
• **Fabry's disease** – **the mutation confers a metabolic cooperation**, which involves the exchange of molecules between cells. In the case, normal cells secrete a critical lysosomal enzyme that can be taken up by adjacent abnormal cells by endocytosis, reducing the eventual clinical severity of the mutation.
• **Incontinentia pigmenti**

• IP patients present at birth with a mosaic skin composed of cells expressing either wt or mutated NEMO.
• In response to some unknown signals mutated cells start to produce proinflammatory cytokines such as IL-1, a well-known stress-response molecule of epidermis.
• This, in turn, appears to induce the release of TNF by wild-type cells, which acts back by inducing hyperproliferation and inflammation of wild-type cells and apoptosis of mutated cells.

• **The whole process results in elimination of the mutated cells and, consequently, disappearance over time of the skin lesions.**
In this hypothetical model, the mutated cells initiating the process are therefore indirectly responsible for their own elimination.



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IP manifests typically as a male-lethal disorder, **whereas most female patients survive because of selective elimination of cells expressing the mutant X chromosome.**

• Some tissues undergo **this selection early in development** and are therefore spared any apparent phenotype at the time of birth (**leukocytes and hepatocytes**).

• Other tissues undergo **this selection after birth during proliferation** (hair roots and tooth bulbs). This leads to abnormalities such as anodontia and alopecia, in which cells harboring the NEMO mutation fail to proliferate. Cells with an active normal X chromosome contribute to these tissues, resulting in patchy alopecia, and mix of oddly shaped and normal teeth.

• Epidermis undergo **this selection within 2 weeks after birth** causing IP associated dermatosis.

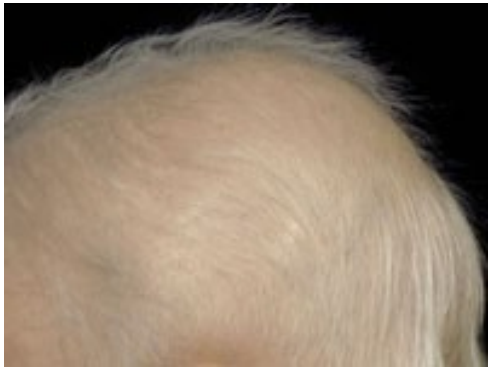
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)

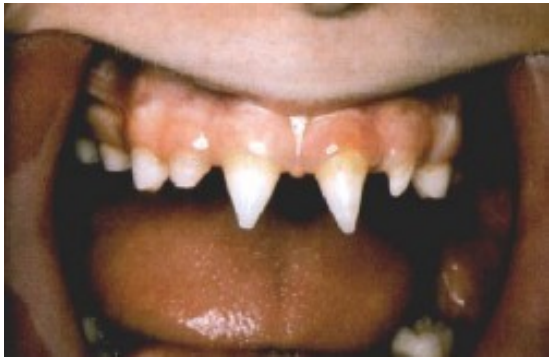
• a rare and complex X-linked pathology exclusively affecting males,

• combines a severe sensitivity to infection with abnormal development of skin adnexes (hair follicles, sweat glands and teeth),

• some similarities with IP led to the analysis of the NEMO gene in several EDA-ID patients. Most of them indeed carry mutations in NEMO but instead of leading to large truncations of the NEMO molecule as observed in IP, the mutations are mostly missense mutations or small deletions.

• all the EDA-ID mutations lead to reduced but not abolished NF-kB activation, explaining why affected male patients survive. In contrast, female patients carrying the same NEMO mutations remain healthy or exhibit very mild signs of IP, depending on the kind of mutation and X-inactivation pattern.





X-chromosome aneuploidies - **Turner (XO females) and Klinefelter's syndrome (XXY males)** – lead to syndromes having a relatively moderate clinical impact. This is due to the counting property of the XCI process, which triggers the transcriptional silencing of all but one X chromosome per diploid set of autosomes. The counting prevents XCI from occurring in XO female and inactivates one of the extra X in XXY males.