Molecular mechanisms of disease

Relating genotype and pathology

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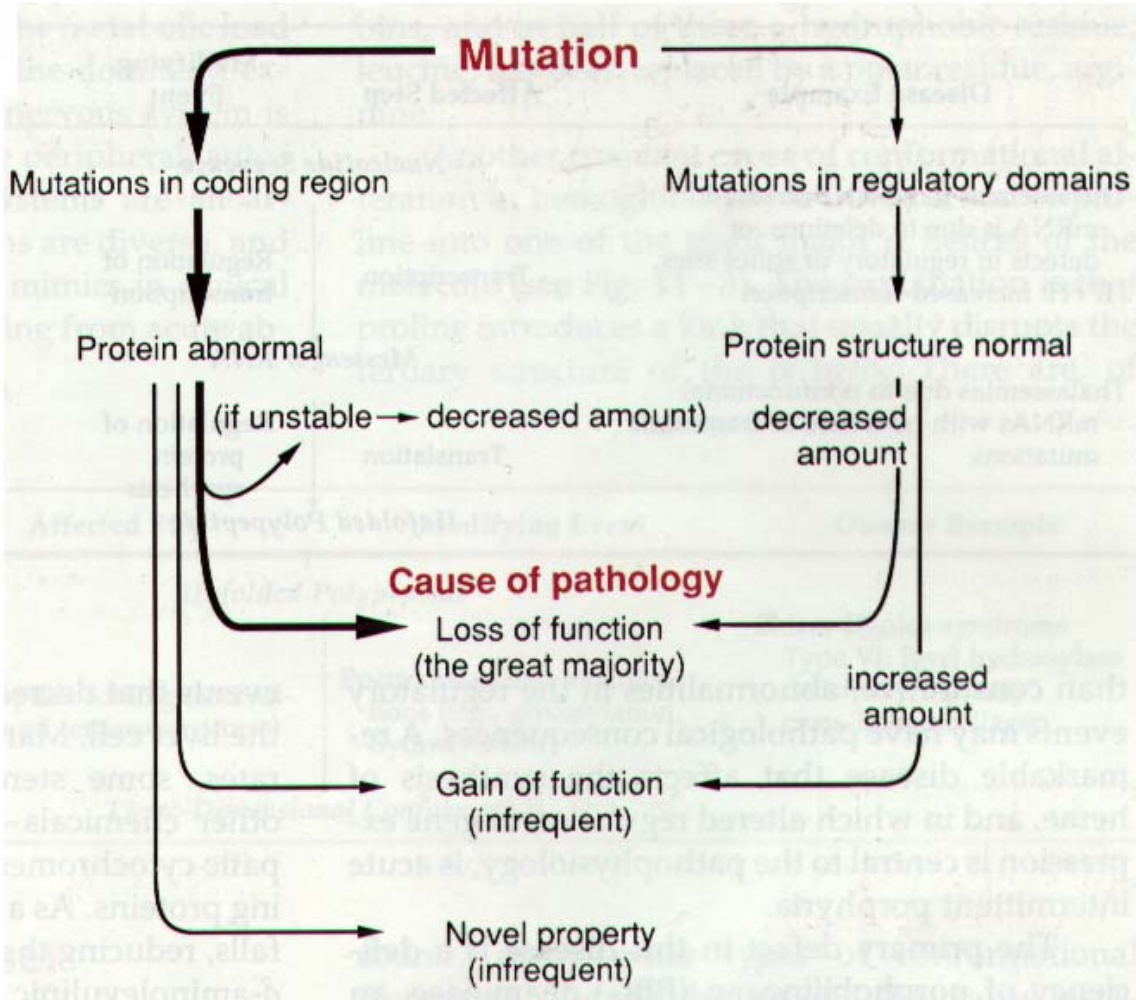
Functional classes of proteins and example disorders

- Enzymes
  - amino acids (PKU), carbohydrates (galactosemia), organic acids (MM-CoA mutase), lipids, purines (ADA, Lesh Nyhan), porphyrins (AIP)
- Transport
  - interorgan (Hb), organelle membrane, intracellular transport (Menkes), epithelial membrane (CF)
- Structural
  - extracellular (OI), cell membrane struct (spherocytosis, DMD), organelle (Zellweger: peroxisome biogenesis)
- Extracellular homeostatis
  - immune, hemostasis (hemophilia), protease inhibition (AAT deficiency)

Functional classes of proteins
(continued)

- Control of growth and differentiation
  - tumor suppressors (retinoblastoma/osteosarcoma), proto-oncogenes (leukemia, other tumors)
- Intercellular metabolism and communication
  - Light receptors (RP, color blindness), hormones (dwarfism), hormone receptors (rickets, AR: testicular feminization), signal transducers (pseudohypoparathyroidism: hypocalcemia and hyperphosphatemia), metabolite receptors (hypercholesterolemia)

Outline of pathogenetic mechanisms

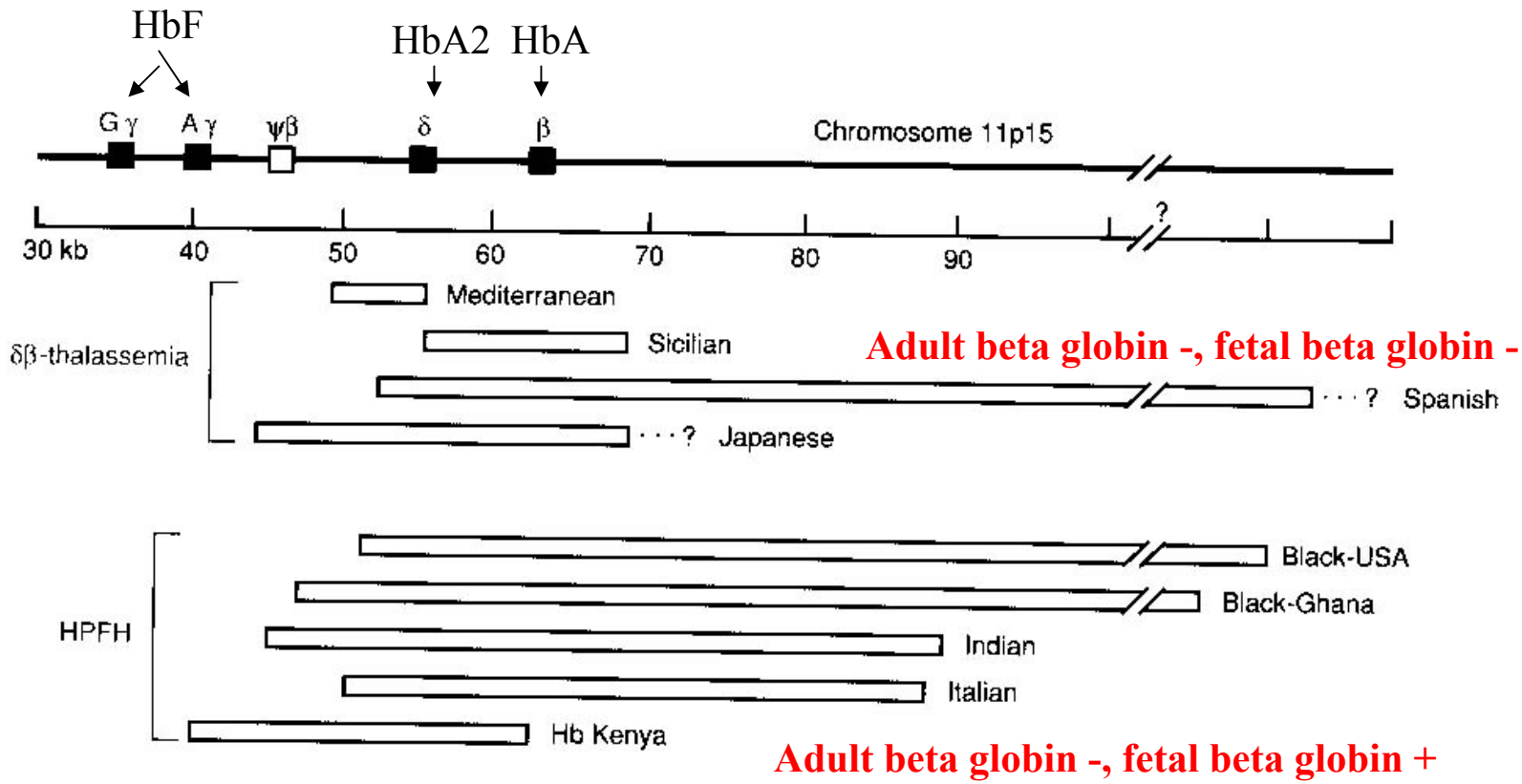


Enzyme deficiencies & disease

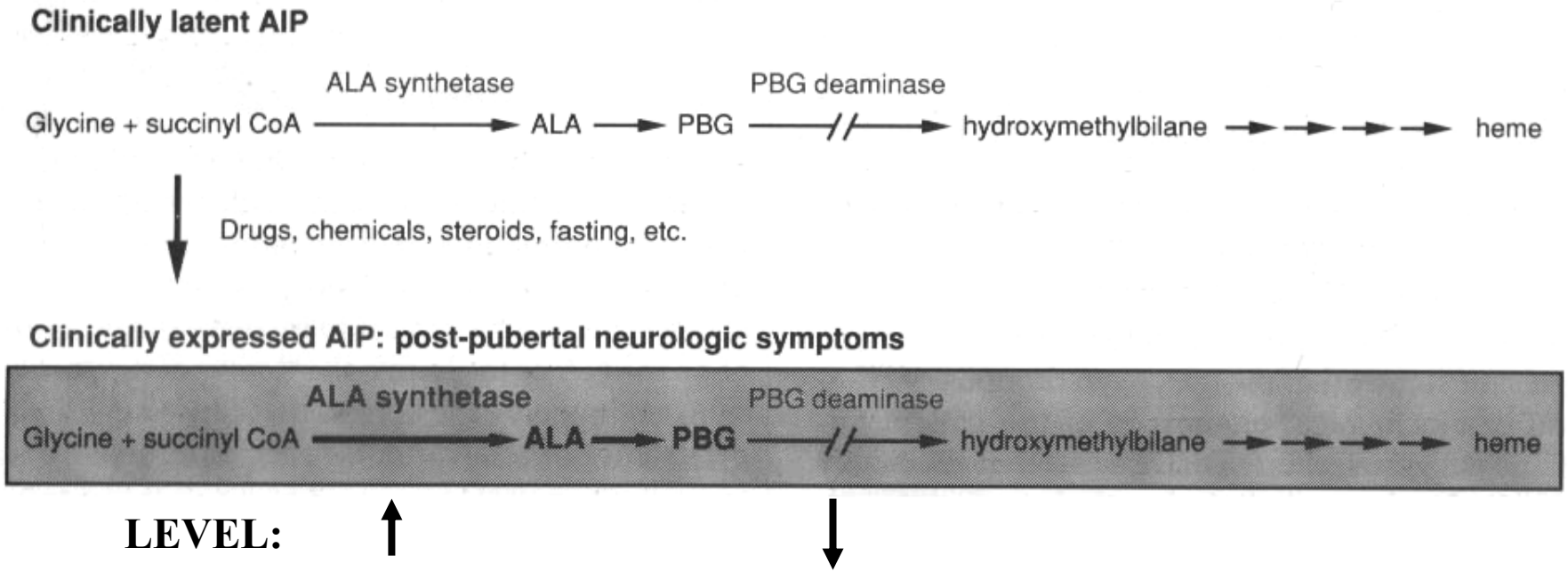
- Almost all recessive. Many enzymes can maintain normal substrate and product levels with Vmax<10% normal
- Pathophysiology due either to accumulation of substrate, deficiency of product, or both
- If substrate is macromolecule, pathology confined to tissue where it accumulates. If diffusable substrate, multisystem involvement more likely.
- Multienzyme deficiency results from cofactor defect, they share common subunit, or if the cellular compartment defective.
- Phenotypic homology: diseases of other enzymes in same area of metabolism, or partial vs. complete deficiencies at same locus.

Mutations altering gene expression:
thalassemia vs. hereditary persistence of fetal hemoglobin

Deletion mapping of mutations in beta globin gene cluster



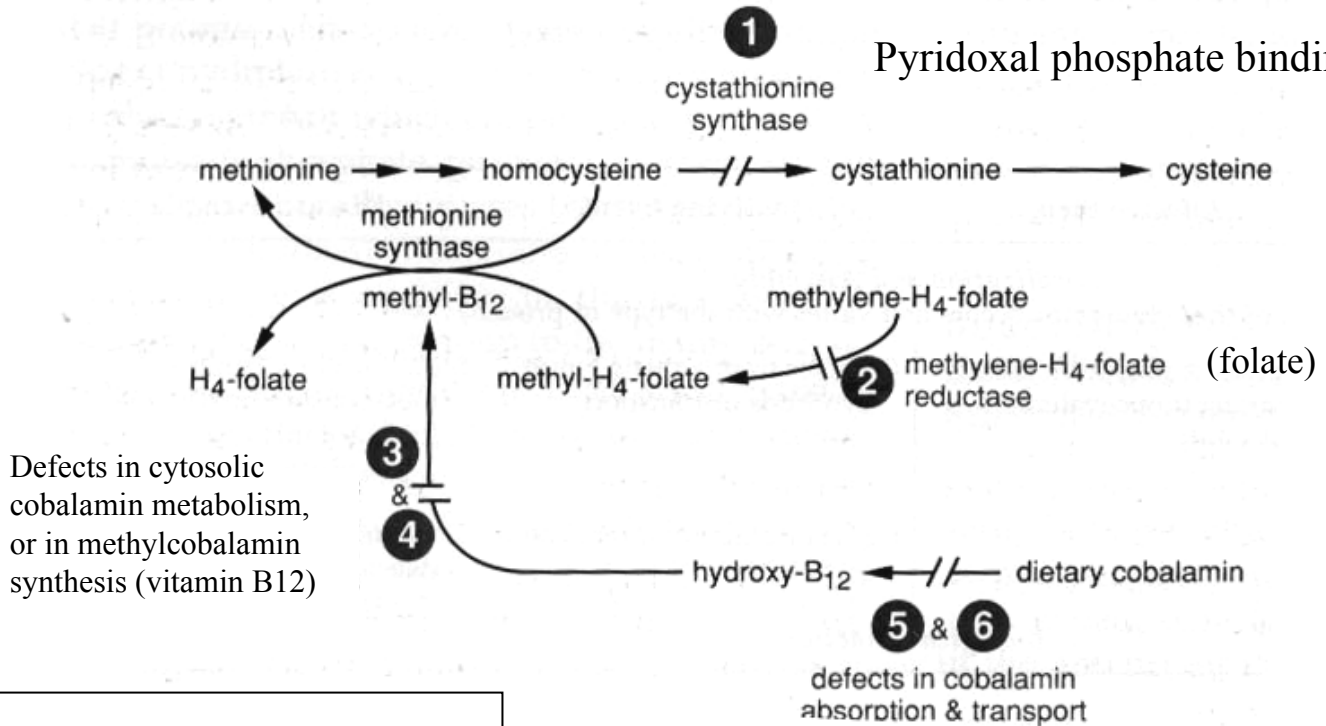
Mutations altering protein synthesis: acute intermittent porphyria



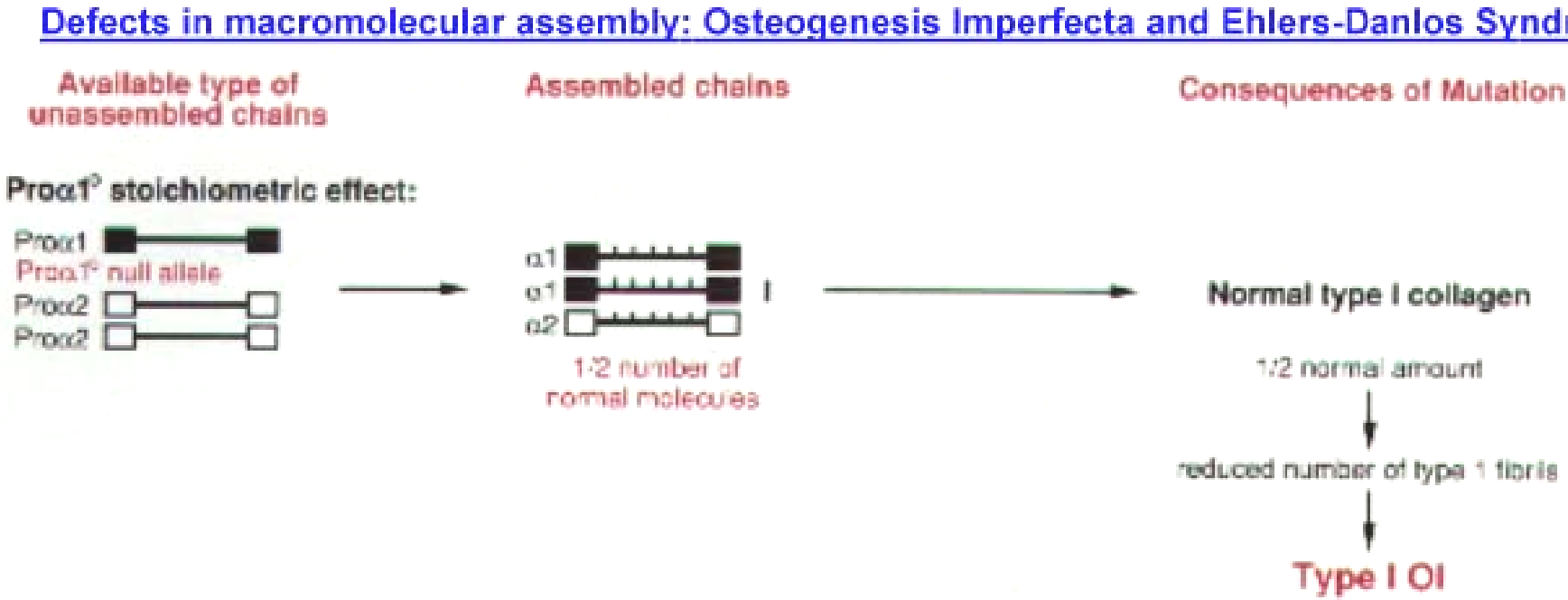
Increase synthesis of cytochromes 450. Lowers heme levels, alleviates feedback inhibition on ALA synthesis. Excess ALA&PBG produces peripheral, autonomic, and CNS phenotype.

Mutations impairing cofactor binding

Homocystinuria

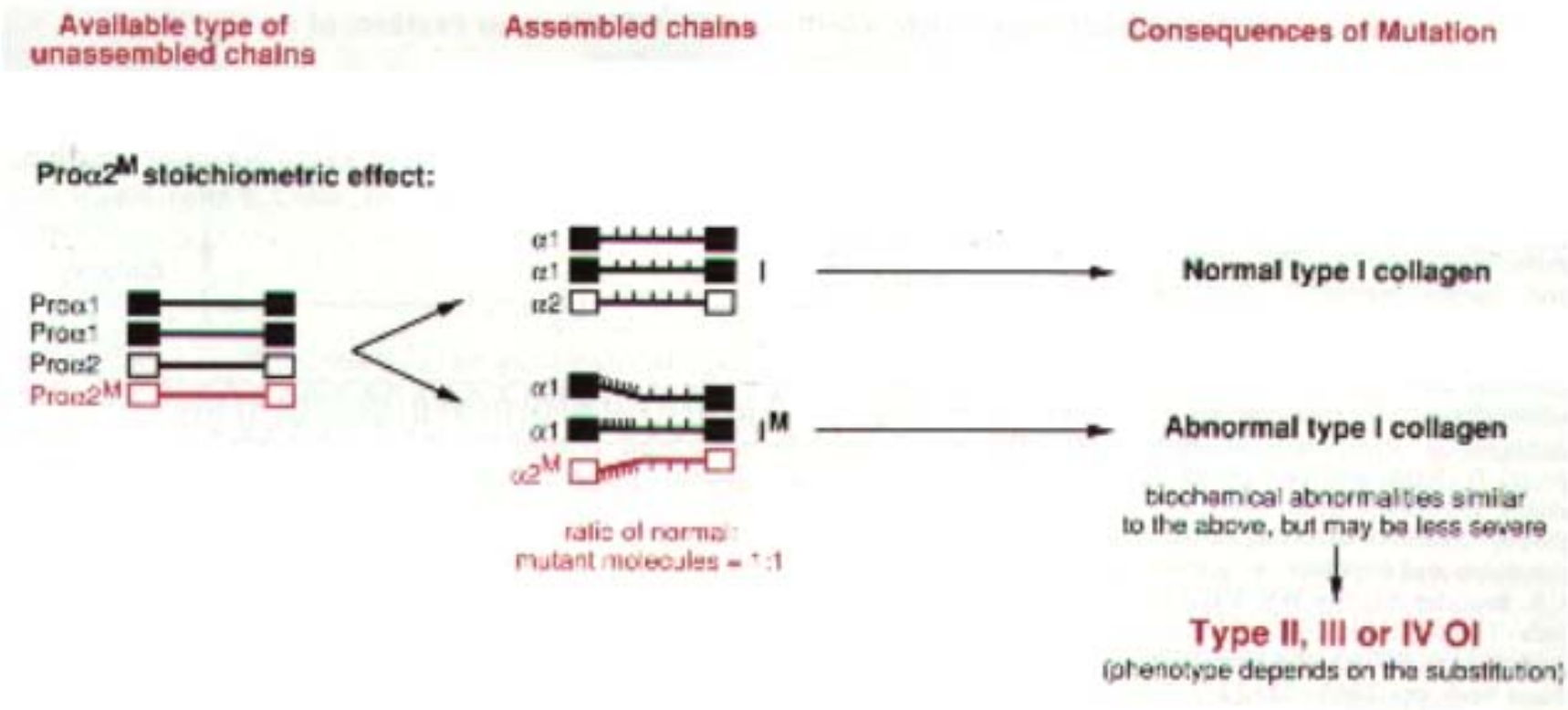


Recessive: ectopia lensis, MR, osteoporesis, lengthening/thinning bones, thromboembolism of veins and arteries

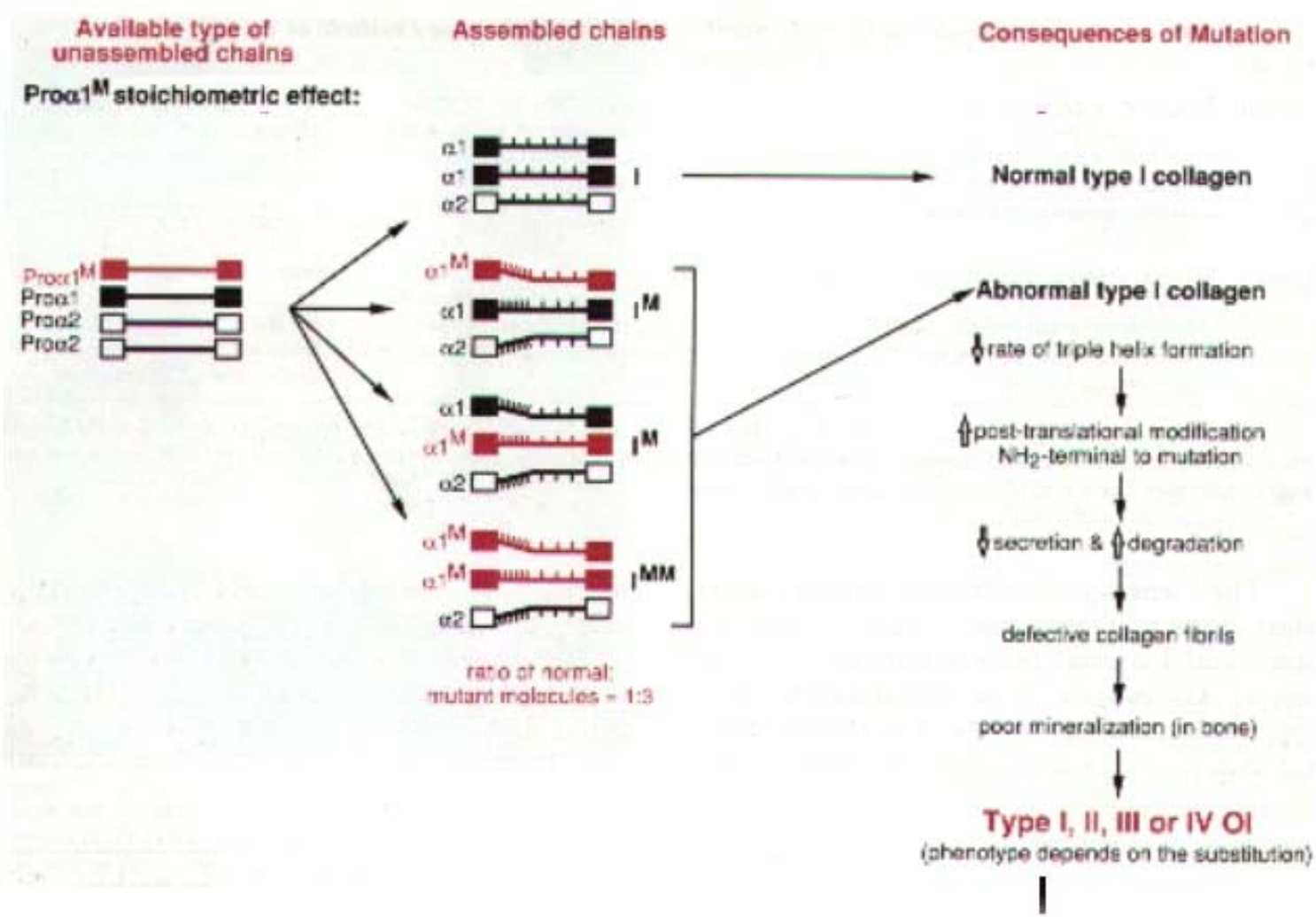


Abnormal stochiometry - mild

Macromolecular assembly (dominant negative mutation)



Macromolecular assembly (dominant negative α1 mutation)



Summary of molecular features in different types of osteogenesis imperfecta

Type	Phenotype	Inheritance	Biochemical Defect	Gene Defect
Type I	**Mild:** blue sclerae, brittle bones, but no bony deformity. Often, presenile deafness.	AD	Common: All the Type I collagen made is *normal* (from the normal allele), but the quantity is reduced by half	Common: Null alleles that impair the production of proα1(I) chains, such as defects that interfere with mRNA synthesis
Type II	**Perinatal lethal:** severe skeletal abnormalities (fractures, deformities), dark sclerae, death within 1 month	AD* (new mutation)	Common: Production of *abnormal* type I collagen molecules due to substitution of the Gly in Gly-X-Y of the triple helical domain, toward the COOH-terminal part of the protein	Common: Missense mutations in the glycine codons of the genes for the α1 and α2 chains of type I collagen
Type III	**Progressive deforming:** fractures, often at birth, progressive bony deformity, limited growth, blue sclerae, dentinogenesis imperfecta, hearing loss	AD*	Gly substitutions in the triple helix, in general, towards the NH_2-terminal part of the protein	Missense mutations in the glycine codons of the genes for the α1 or α2 chains of type I collagen
Type IV	**Normal sclerae, deforming:** mild to moderate bony deformity, short stature, fractures, hearing loss, dentinogenesis imperfecta	AD	Gly substitutions in the triple helix, in general, towards the NH_2-terminal part of the protein	Missense mutations in the glycine codons of the genes for the α1 or α2 chains. Exon-skipping mutations in 5′ end of the α2 chain gene

Protein modification: Ehlers-Danlos syndrome Type VI

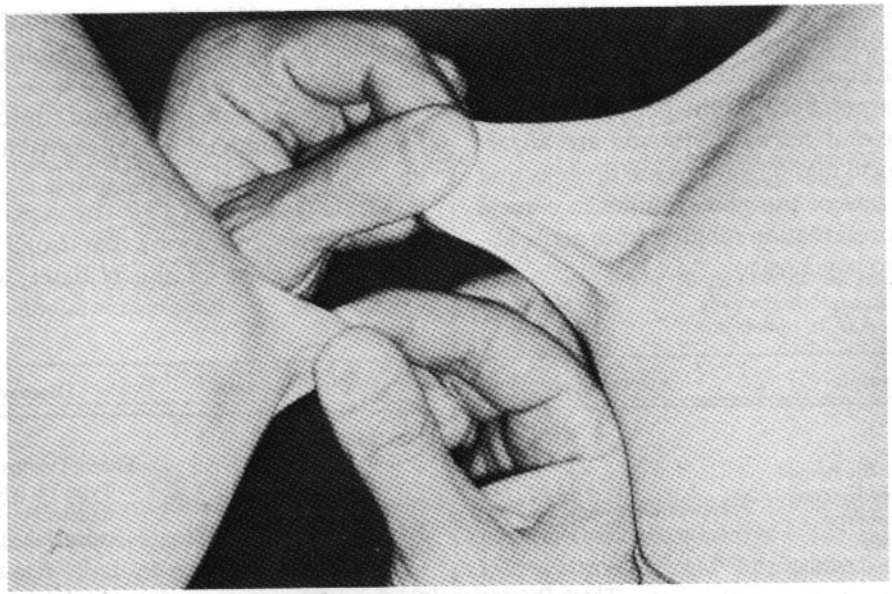
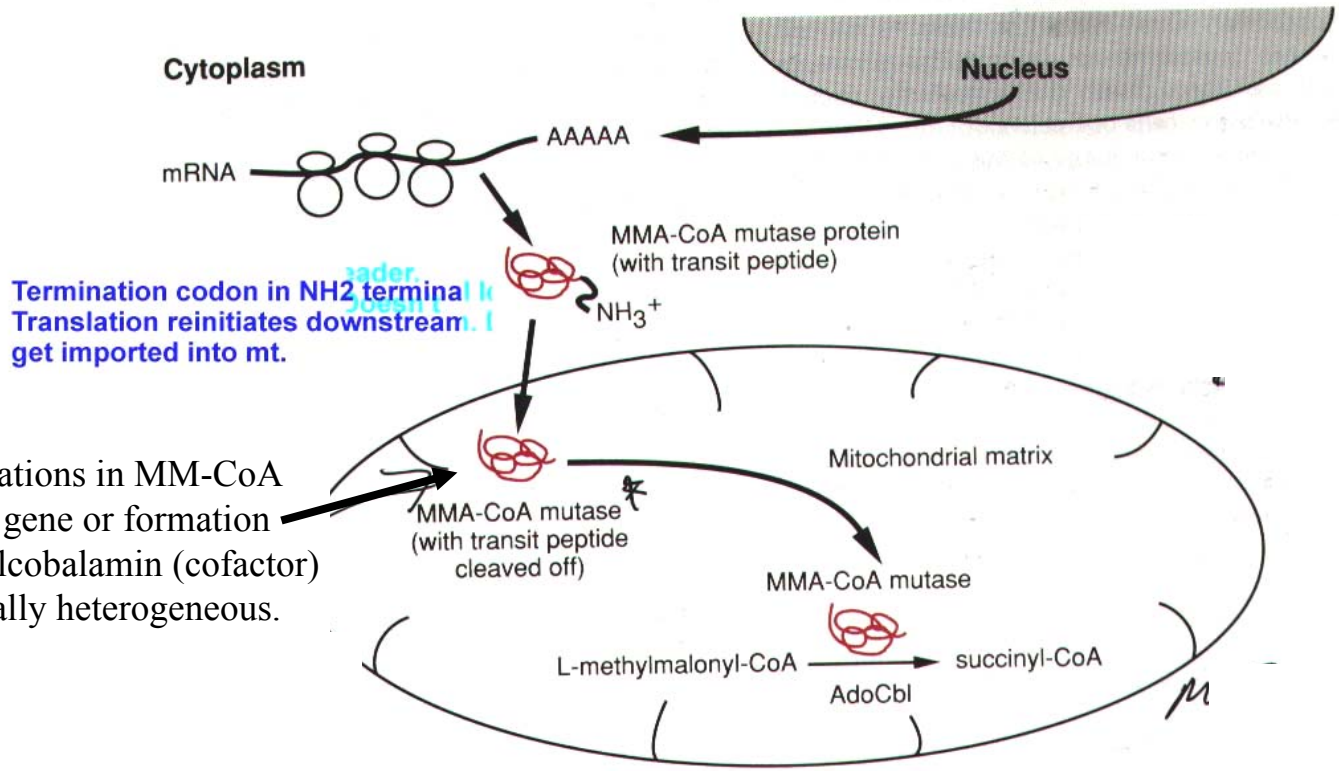


Figure 12–20. The hyperextensible skin of a patient with the Ehlers-Danlos syndrome. (Reproduced from Byers PH, Holbrook KA [1979] Heritable disorders of connective tissue. *In* Cohen AS [ed] The science and practice of clinical medicine, vol. 4: Rheumatology and immunology. Grune and Stratton, New York, p. 344.)

Caused by lysyl hydroxylase deficiency, which catalyzes posttranslational modification of collagen I and III chains. Modification req'd for intermolecular crosslinks to stabilize collagen fibrills.

Incorrect subcellular localization: methymalonic aciduria



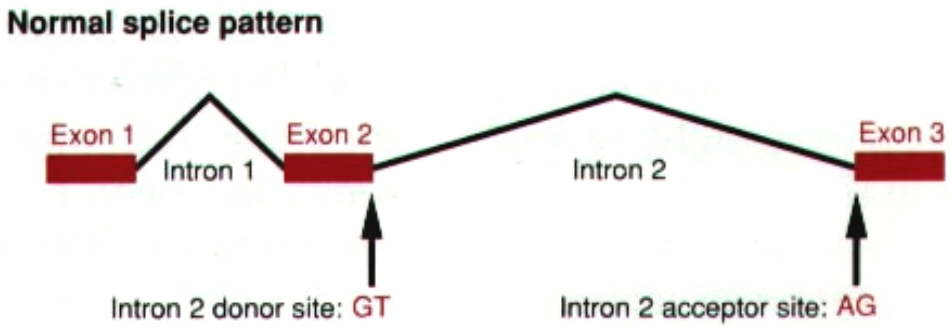
Most mutations in MM-CoA structural gene or formation of adensylcobalamin (cofactor) are clinically heterogeneous.

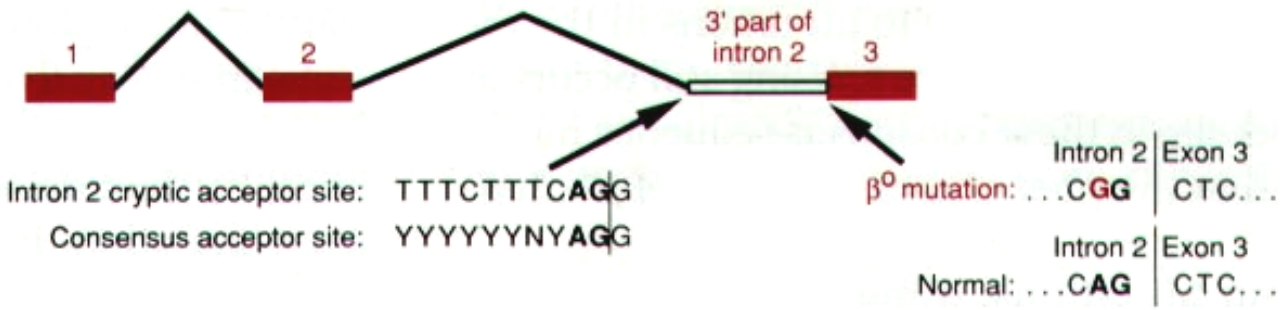
Phenotype: Metabolic acidosis. Severely affected patients are lethargic, fail to thrive and have recurrent emessis.

Mutations affecting protein degradation: G6PD A- (VAL68MET, ASN126ASP, XR)

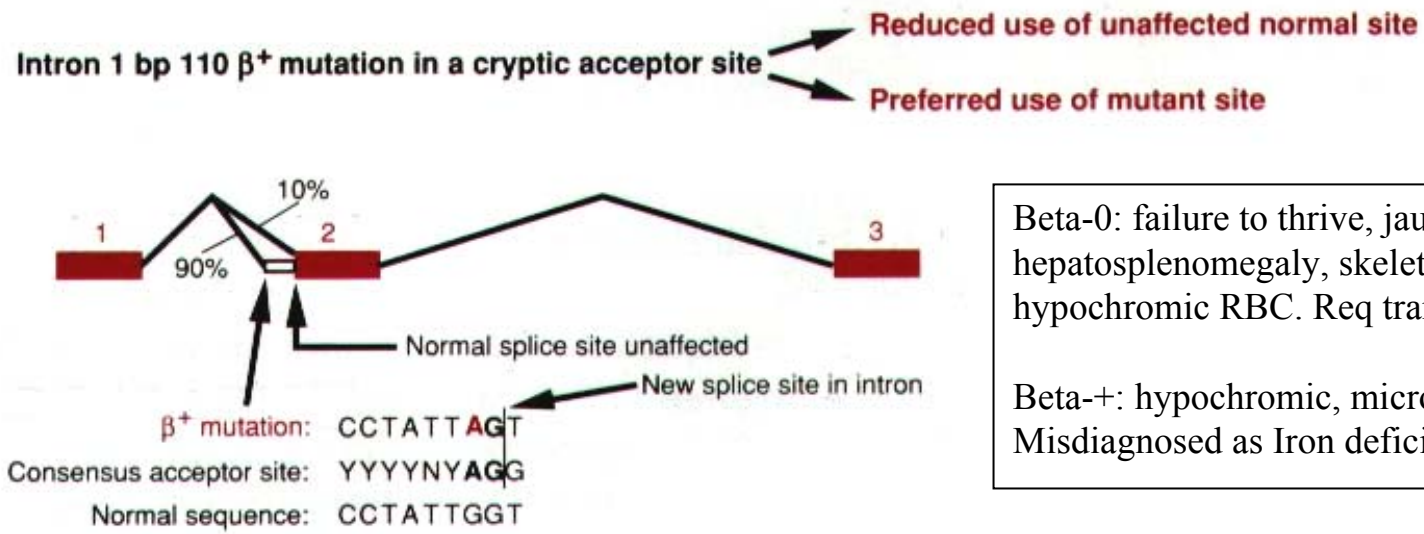
- G6PD deficiency phenotype: severe chronic granulomatous disease from neutrophil dysfunction, hemolytic anemia, splenomegaly
- High freq. in Africans, Mediterraneans and Asians, heterozygote advantage viz-a-viz malaria
- G6PD critical for NADPH regeneration, essential for protection against and repair of oxid. damage. G6PD- red cells are more sensitive to hydrogen peroxide generated by the malaria parasite, making them a poor host.
- **Instability of the mutant enzyme results from protein degradation (4% yield), not decreased activity.**

Allelic heterogeneity: splicing mutations causing Beta+ vs. Beta0 thalassemia



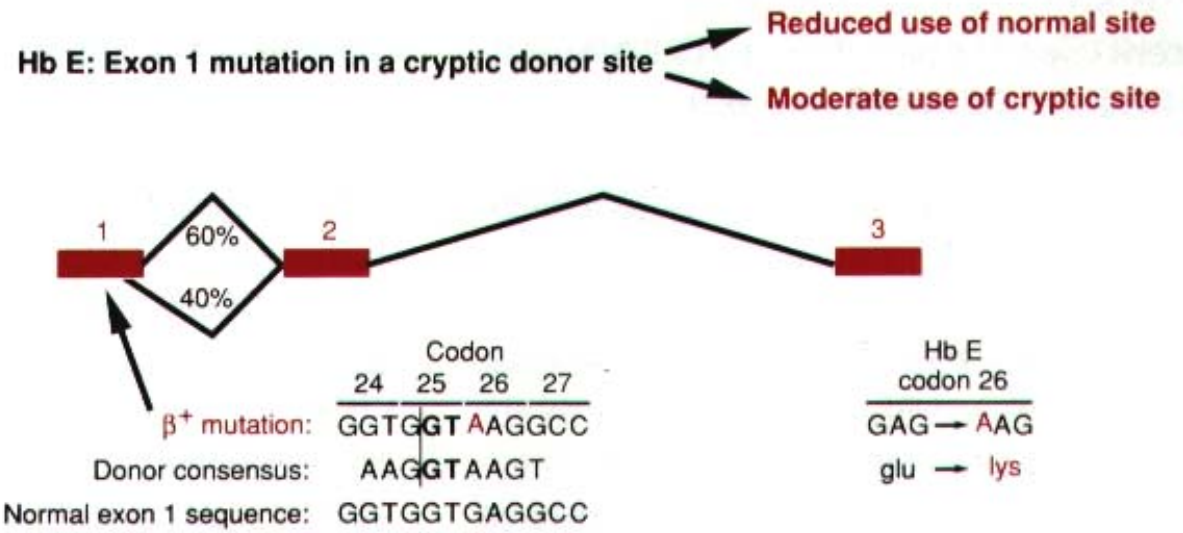


Milder phenotype- partial expression of beta globin



Beta-0: failure to thrive, jaundice, hepatosplenomegaly, skeletal changes, hypochromic RBC. Req transfusion

Beta-+: hypochromic, microcytic RBC Misdiagnosed as Iron deficiency.



Summary: Molecular pathology and phenotype

- Different mutations in a single gene may produce very different clinical phenotypes.

  Variation in clinical presentation reflects specific property of protein that has been perturbed. Example: thalassemia versus methemoglobinemia.

- The biochemical and clinical consequences of a mutation are often unpredictable.

  Examples: HbS and sickling, PKU and MR, Rhodopsin and degenerative RP