Hemoglobinopathies

① Sickle cell disease.

position 6 valine substituted for glutamic acid

② Hemoglobin C disease

position 6 lysine substituted for glutamic acid

③ Hemoglobin D disease.

position 121 glutamine replace glutamic acid

④ Hemoglobin E disease

position 26 glutamic acid replace lysine

→ Hb S > Hb C > Hb C/S > Hb D/S > Hb E

↳ According to their danger.

Thalassemia

mutations

1. Mutation in the promoter
2. mutation in the noncoding interon
3. partial or total deletion
4. mutation at termination site.
5. nonsense mutation.

Heme synthesis

① Succinyl co A + glycine —(ALA synthase ⊕ pyridoxal phosphate "as co-enzyme")→ ALA (in mitochondria)

② 2 ALA molecule condensation —(ALA dehydrase or PBG synthase)→ porphobiliogen (PBG) in cytoblas

** These reaction lead to produce the first pyrrole ring

its active site has Zn which can bind lead (Pb) and cysteine.

③ 4 PBG condensation —(PBG deaminase or hydroxymethybilane)→ Hydroxymethylbilane ("tetrapyrrole" → linear ⊕ has symmetrical subsitution.)

in cytoplasm

④ cyclization of Hydroxymethylbilane. (in cytoblasm)

link ring 4 with ring 1

"uroPBG synthase" ⊕ uroPBG III cosynthase → uroporphobiliogen III

↳ asymmetrical subsitution (acetate, propionate) 3 times propionate, acetate.

↳ lead to Rotation in ring 4

⑤ Conversion of uroPBG III —(uroPBG decarboxylase, in cytoplasm)→ coproporphrigen III

↳ decarboxylation of 4 acebate.

↳ its substution (methyl, propionate) 3 (propionate (methyl)

⑥ oxidative decarboxylation - Coproporphrigen —(coproporphyrinogen oxidase)→ protoporphorinogen XI

↳ decarboxylation of 2 propionl to vinyl

enter mitochondria

(methyl, vinyl, methyl, vinyl methyl, propionyl propionyl, methyl)

⑦ oxidation by protoporphorigen oxidase.

⑧ Insection of Ferrous Iron by Ferro cheletase.

* Regulations of Porphyrin synthesis

- ALA synthase ⟶ inhibited by protohemin
- Hydroxy methylbilane synthase ⟶ enhanced by erythropoietin.
- Lead (Pb) inhibit ⟶ ① ALA dehydrase or Hydroxymethylbilane synthase
  ② Ferrocheletase.

* Iron metabolism and proteins

① Iron regulation proteins :- ① ferritin ② Transferrin
③ Iron regulatory protein (hepcidin ④ matriptase)

② Cellulary membrane transportation of Iron :- ① metal transporter-1
② Ferroportin
③ transferrin receptor
④ ferroxidase " duodenal cytochrome B"
⑤ ceruloplamin
⑥ heme carrier protein.

* Regulation of Iron absorption

↑↑ Iron level ⟶ Hepcidin is secreted to induce Ferroportin degradation.

In the absence of Hepcidin ⟶ Ferroportin maintained on cell membrane ⟶ Iron is facilitated. (Iron Transportation)

* Hepcidin is considerd an antimicrobal peptide because by ↓ Iron ⟶ limit bacterial growth.

* mutations of hemochromatosis
① Transferrin receptor ② A protein HFE
③ Hemojuvelin (Iron-sensing protein)
④ Impaired synthesis of hepcidin.

porphyrias

① ↓ALA synthase → sideroblastic anemia → (X-linked)
- accumulation: (Fe), glycine, succinyl CoA

② ↓ALA dehydrase → ALAD-deficient porphyria → (Autosomal ressive)
- neurovisceral
- no cutaneous.
- Acute form.
- hepatic

③ ↓ PBG deaminase → Acute intermittent porphyria → Autosomal dominant
- Acute form
- neurovisceral
- hepatic
- No cutaneous.

more in women
- more in psychiatric population.

④ ↓ uroPBG co synthase → Congenital Erythropoietic porphyria (Gunther's disease) → Autosomal ressive
- chronic form
- Erythropoitic.
- photocutaneus.
- porphyrin. in E

Diagnosis by: ↑ uroporphyrin I, coproporphyrin I (U and E)
- elevation of both water soluble and lipid soluble porphyria.
- (Burning and blistering) phototoxic
- porphyria in bone marrow.

⑤ ↓ uroPBG decarboxylase → porphyria cutanea Tarda → Aquired and Autosomal dominant
- chronic form
- Hepatic
- Diagnosis by: ↑ 7-carboxylate porphyria, ↑ isocoproporphyrin
- photocutaneous
- No neurologic manifestation.

⑥ ↓ Coproporphyrinogen oxidase → Hereditary Coproporphyria → Autosomal dominant
- Acute form
- Both photocutaneous and neurovisceral

⑦ ↓ protoporphyrinogen oxidase → variegate porphyria → Autosomal dominant
- Acute form
- Both photocutaneous and neurovisceral
- ~~Porphyria in BM~~
- ~~most common in childhood~~

⑧ ↓ Ferrochelatase → Erythropoietic protoporphyria → Autosomal dominant.
- chronic
- Porphyria in BM
- most common in childhood
- photocutaneus
- Diagnosis by ↑ protoporphyrin E and E and plasma

* plasma protein

- electrophoresis

There are 5 bands of protein :

① Albumin
② α_1 globulins: as ① α_1 antitrypsin, ② TBG, ③ transcortin, ④ α-fetoprotein.
③ α_2 globulins: as ① haptoglobin, ② ceruloplasmin, ③ α_2 macroglobulin
④ β globulins: as ① CRP, ② transferrin, ③ β_2 microglobulin, ④ lipoprotein
⑤ γ globulins:- Antibodies

The main plasma protein that maintain osmotic pressure → Albumin.

α-Fetoprotein:- • If it ↑↑ in maternal → associated with Neural tube defect and anencephaly.
• If it ↓↓ in maternal → associated with ↑ risk of Down's syndrome.

α_2-macroglobulin :- Inactivate All protease and thus is important in vivo anticoagulant

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Hypergammaglobulinemia

① polyclonal hypergammaglobulinemia
- γ globulin band appears large in electrophoresis.
- Clinical Condition → Acute/chronic infection, Autoimmune disease chronic liver disease.

② Monoclonal Hypergammaglobulinemia.
- Appear as separated dense band (paraprotein or M band) in electrophoresis.
- Clinical condition: Multiple myeloma.

Molecular basis of some blood coagulation disorders

- Regulation of clotting factor and cascade.

① protein "C" → is switched on by thrombin
→ Function: digest Va, VIIIa factor

thrombin → "switch off" for blood coagulation
→ "switch on" by formation fibrin.

② Terminating blood clotting by specific inhibitor:-
① Tissue factor pathway inhibitor
→ which inhibit TF - VIIa - Xa
② Anti-thrombin-III → inactivate thrombin.

① vWD → (Gentic or acquired)
↑aPTT / ↑BT / Normal plt. count.

→ its types
① Type 1 → Autosomal dominant
→ level of vWF (20%-50%)
→ quintity. defect

② Type 3 → Autosomal regsive.
→ level of vWF (5-10%)
→ quaintity. defect

③ Type 2 → quality defect.
→ missense mutation.
→ has 4 subtypes.

④ Acquired vWD → result after a diagnosis of Autoimmune disease.

② Hemophilia

A. Hemophilia "A" → ↑ aPTT | Normal BT | Normal Plt. Count.

→ X-linked recessive disorder

→ mutations : ① missense mutations
② Nonsense / Stop mutations
③ Inversion mutation in intron 1 or 22

→ deficiency in factor VIII

B. Hemophilia "B"

→ X-linked recessive disorder

→ mutations : ① deletions
② premotor mutations.

→ deficiency in factor IX

C. Hemophilia "C"

→ deficiency of factor XI

→ autosomal recessive disorder.

D. parahemophilia :

→ Autosomal recessive disorder

→ deficiency of factor V

DIC :- Commonly in obstertic complications.

- Sudden widespread of fibin thrombi in microcirculation.

TTP → Widespread of Hyline thrombi. in microcirculation

→ protein are deficient (ADAMTS13)