Subject: HLS- Biochemistry

Topic: Hemoglobinopathies

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Hemoglobinopathies

Diseases	Mutation	Changes in Hb	Changes in RBCs	Notes
Qualitative				
Sickle Cell Hemoglobin	Point mutation in the 6th residue in the β chain. (α2βs2) Glu→Val	Clumping of Hb molecules together, forming chains of Hb molecules (deoxygenated state).	❦The clumping of these Hb molecules causes deformation in the RBC, leading to its sickle appearance. ❦Decreasing in the flexibility of the RBCs, impairing their ability to squeeze through capillaries and block blood flow causing **local hypoxia** which over time leads to damage in the kidney, lungs, and heart. ❦Decreasing in the lifespan of RBCs from 120 days to <20 days **(hemolytic anemia)**.	❦Repeated cycles of oxygenation and deoxygenation lead to irreversible sickling. ❦The mutated valine of β2 chain forms a hydrophobic protrusion on the surface. ❦People with at least one HbS gene (Heterozygotes, contain both HbS and HbA) are protected aginst malaria **(plasmodium falciparum)**, this is because of the decreased lifespan of RBCs which doesn't allow the parasite to go through its lifecycle in the RBCs.

Hemoglobin C (HbC)	Point mutation in the 6th residue of the β chain. Glu→ Lys	This (HbC) is less soluble than HbA.	❦HbC molecules crystalize inside RBCs, altering their shape and decreasing their flexibility (reducing their deformability). ❦HbC leads to **water loss** from cells leading to **higher** hemoglobin concentration	❦The main clinical manifestation is **mild hemolysis**.
Hemoglobin SC (HbSC)	❦Mutation in both alleles of β chain. ❦Having an allele for HbS as well as HbC.			❦Patient could be **asymptomatic** or have **mild hemolysis.**
Hemoglobin E (qualitative & quantitative)	❦Point mutation in codon 26 of the β chain. Glu → Lys ❦Inherited.	❦Alternative **splicing site** in the mRNA of the β-globin gene producing unstable hemoglobin and tends to be degraded.		❦Individuals with this disease have decreased Hb production to around 60% of the normal amount having deficient O2 carrying capacity.

Hemoglobin Hammersmith	Point mutation in the 42 a.a of the β chain. Phe→ Ser	❦Making an <u>unstable hemoglobin</u> that gets <u>denatured</u> easily and has a decreased affinity for oxygen.		The mutation changes (nonpolar to polar) which compromises the nonpolar inward facing portion of the globin causing changes **heme positioning** resulting in **cyanosis**.
Hb Cowtown	**Substitution** of His146 to leucine.	Stabilization of **R state** (high affinity).		❦We talked about Hist146 earlier and how it causes something called the **Bohr effect** which causes changes in heme's affinity to oxygen.
Hb Kansas	Elimination of **hydrogen bonds** between the chains altering the quaternary structure . Asn → Thr	Stabilization of **T state.** (low affinity)		
Hb Yakima	Elimination of **hydrogen bonds** between the chains altering the quaternary structure . Asp → His	Stabilization of **R state.** (high affinity)		

Methemoglobin -emias	❦ **Causes of elevated methemoglobin (methemoglobinemia):** **1-**<u>Mutations in the globin chains that resist reductase:</u> - **Hb Boston: Distal His→ Tyr** resulting in oxidation of the ferrous iron by **tyrosine's oxygen**. It also attracts H2O into the pocket. - **HbM Iwate:** Proximal His → Tyr 2<u>- Deficiency in methemoglobin reductase.</u> 3<u>- Drugs or water contaminated with nitrates increase the probability that iron is oxidized.</u>	❦**Normally Reduced** Hb carries O2 to tissues (ferrous iron Fe^{+2}), during oxygen release from heme iron is **oxidized** to ferric form Fe^{+3} (can't carry oxygen) **forming methemoglobin (HbM**) which is **normally** reduced again by **NADH-methemoglobin reductase (**HbM to HbA) so it can bind O2 again. ❦In this disorder NADH-**methemoglobin reductase** is <u>disrupted</u> resulting in elevated HbM		❦ **chocolate cyanosis** (a brownish blue coloration of the skin and mucous membranes and brown-colored blood) <u>caused by</u> the dark-colored HbM ❦**cytochrome b5 reductase (NADH-methemoglobin reductase)** is the major enzyme for <u>methemoglobin reduction using **cytochrome b5**</u> as an electron acceptor and reduces it using NADH. ❦**Treatment**: <u>methylene blue.</u> Why? there's an **alternative** enzyme called **NADPH-methemoglobin reductase**, which requires an exogenous electron acceptor (like **methylene blue**) and reduces it using NADPH producing compound called **leukomethylene blue**, which is then oxidized to reduce methemoglobin to hemoglobin.

Quantitative				
Alpha thalassemias	❦Deletion in 1 or more of the 4 α globin genes. ❦There is underproduction of the alpha globin chains; HbA, HbF, HbA2 all are affected. ❦ there are four Levels of α-globin chain deficiencies.			Depending on the number of genes deleted, clinical manifestations can vary. **e.g.** One deletion results in a silent carrier state, asymptomatic.
Silent Carriers α – thalassemias	1 gene deletion.			**Completely** asymptomatic but carry the gene and can have kids with a thalassemia.
Minor α-Thalassemia (α -thalassemia trait)	2 α-globin genes are defective.			**Generally** asymptomatic patients.
Hemoglobin H (HbH) α - thalassemias intermedia	3 α-globin genes are defective.	These HbH molecules have a much <u>lower oxygen carrying capacity.</u>		❦Symptomatic but not fatal. ❦Mild to moderate anemia. ❦The decrease in α chains causes an increased chance of β chain tetramers to be formed. (β4 instead of α2β2).

Major α-Thalassemia **Hydrops Fetalis**	4 α-globin genes are defective	**Hb Bart** has no oxygen carrying capacity and causes oxygen starvation in the fetal tissues, which is fatal.		Increased chance of the formation of γ4 tetramers, which are called **Hb Bart.** The baby will be either stillborn or die shortly after birth.
β Thalassemias	Mainly caused by **point mutations** within the promoter, translation initiation codon, splicing positions, or polyadenylation termination signal.			β-globins are deficient and the α-globins are in excess and will form α-globin homotetramers , which are <u>insoluble</u> and causes **premature hemolysis** in the bone marrow and spleen.
β Thalassemia Major	Both genes are defective and there's a complete lack of HbA (**βo-thalassemia**)			Because the β-globin gene is not expressed until late in fetal gestation (healthy at birth); it presents after birth and during the first year of life. Patients have severe anemia and need regular transfusions. Long term transfusions cause iron accumulation in several organs, which eventually causes death in their teens or early 20s.

β Thalassemia Minor	These individuals are heterozygotes for the β genes with one normal gene and one mutated.			Patients are usually asymptomatic.
Hereditary Persistence of Fetal Hemoglobin (HPFH)				
	Large deletions in the δ and β coding regions on chromosome11, they don't have deletions of the fetal globin genes.	This causes a decrease in the HbA and HbA2 so the production of HbF is increased to make up for the decrease in oxygen carrying capacity.		❦Patients with HPFH continue making fetal hemoglobin (HbF) in their adult life. ❦Usually asymptomatic most individuals do not even know they carry a hemoglobin abnormality, so we use this advantage in treating patients with β thalassemia.

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