# Fetal Hemoglobin's High Oxygen Affinity

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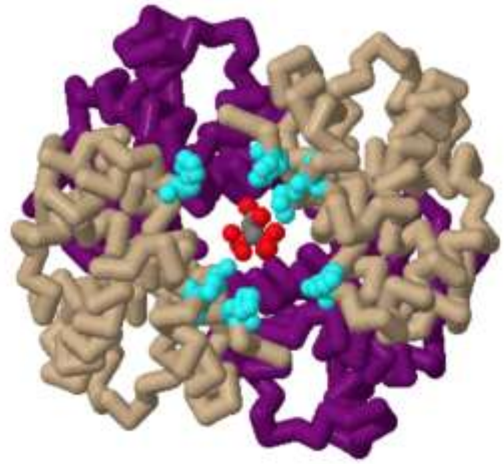


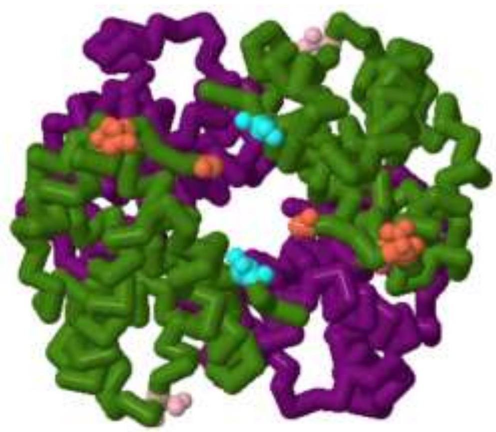
HbA (4L7Y)
α Subunits Purple
β Subunits Tan
Residues Binding with BPG – Cyan
Negative Regions of BPG Molecule - Red

**Primary Citations:** Yagami, T., Ballard, B. T., Padovan, J. C., Chait, B. T., Popowicz, A. M., & Manning, J. M. (2002). N-terminal contributions of the beta-subunit of fetal hemoglobin to its tetramer strength: Remote effects at subunit contacts. **Protein Science: A Publication of the Protein Society**, 11(1), 27-35.

Chen W, Dumoulin A, Li X, Padovan JC, Chait BT, Buonopane R, Platt OS, Manning LR, Manning JM. Transposing sequences between fetal and adult hemoglobins indicates which subunits and regulatory molecule interfaces are functionally related. **Biochemistry**. 2000 Apr 4;39(13):3774-81. PubMed PMID: 10736177.

**PDB Files:** 4L7Y (HbA), 1FDH (HbF)

There are multiple types of hemoglobin that humans produce throughout their lifetime. Each type of hemoglobin has a special role in human development and oxygen transportation. Fetal hemoglobin (HbF) has a higher affinity for oxygen than adult hemoglobin (HbA). This is important in oxygen transfer from maternal hemoglobin to fetal hemoglobin across the placenta. Fetal hemoglobin differs from adult hemoglobin in that HbF consists of two subunits α and two subunits γ whereas HbA consists of two α subunits and two β subunits. The difference between the β and γ subunits is crucial to the different behaviors of HbF and HbA.



HbF (1FDH)
α Subunits Purple
γ Subunits Green
Residues Effecting R-State Stability - Orange
Residues Preventing Full Opening of Cavity- Pink
Residues Repelling BPG Molecule - Cyan

2,3-bisphosphoglycerate, more commonly known as 2,3-BPG, is an allosteric effector of hemoglobin. 2,3-BPG is created in an alternative pathway in glycolysis. 2,3-BPG binds to HbA in its T-state when the central cavity of the protein is open. The negatively charged regions of the BPG molecule (red) bind with the positively charged residues His 2, Lys 82, and His 143 on the β subunits (cyan) of HbA. The binding of BPG to the hemoglobin helps to stabilize the T-state, thereby reducing hemoglobin's oxygen affinity. 2,3-BPG binds to HbA at higher rates than it does to HbF causing HbF to have a higher oxygen affinity than HbA.

BPG binds to HbF less than HbA due to the residues Asp 43 (pink) and Ser 143 (cyan) on the γ subunits. Asp 43 prevents the central cavity of the protein from completely opening in its T-state conformation. This gives BPG less room to bind to the hemoglobin. In HbA, Histidine 143 on the β subunits, a positively charged residue, binds with the negatively charged BPG molecule. In HbF, however, serine obtains the 143$^{rd}$ residue spot on the γ subunits (cyan). Serine is a negatively charged residue which will repel the negatively charged BPG molecule. Therefore, BPG is less likely to bind with HbF.

Finally, HbF has a higher oxygen affinity than HbA because HbF has a more stable R-state tetramer. The A helix of HbF is responsible for its more stable R-state. More specifically, Gly 1, Glu 5, and Asp 7 on the γ subunits (orange) are the main contributors to the increased tetramer strength of HbF.