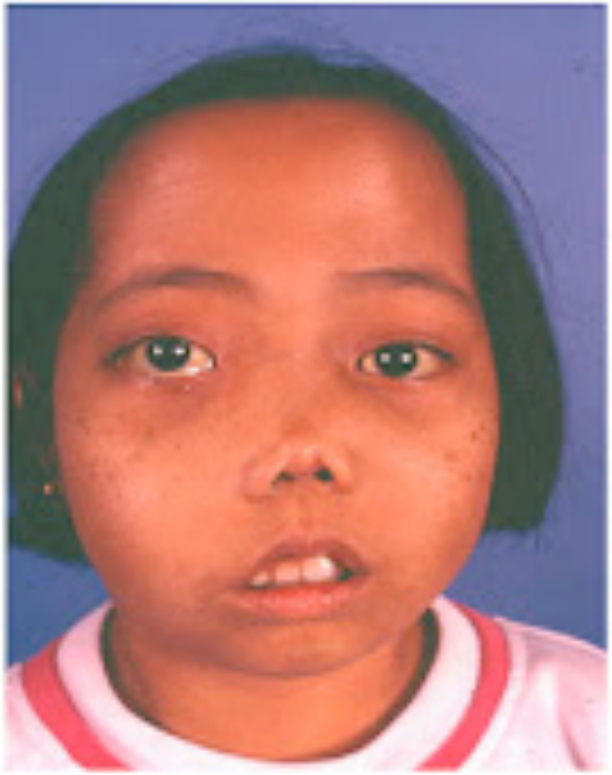
# Thalassemia

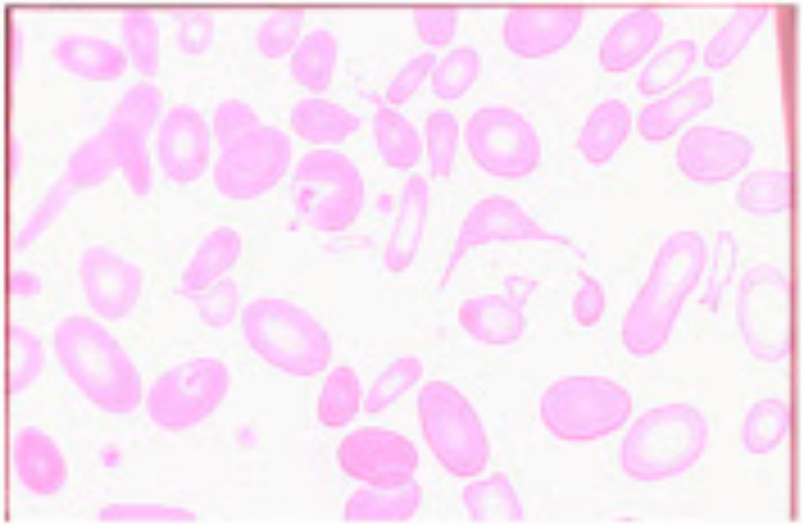
By: Rebecca Chang (Period 6)

# Physiology

- Two types of thalassemia: alpha and beta
- Autosomal recessive inheritance pattern
- Hemoglobin is damaged but symptoms greatly vary, especially for alpha thalassemia because there are four genes that control its production
- For both alpha and beta thalassemia, severity increases as the number of damaged genes also increases or deletion is larger
  - One or two alpha genes missing doesn't have drastic effects
  - Three or four can result in death if patients are not taken care of
- For beta thalassemia, patients can fall under three categories:
  - Thalassemia Minor: one gene damaged and minimal symptoms
  - Thalassemia Major: two genes damaged and drastic symptoms
  - Thalassemia Intermedia: one or two and the symptoms are in-between those shown in Minor and Major patients
- Symptoms include fatigue, jaundice, enlarged spleen and liver, anemia, paleness, coldness of skin, bone problems
- Red blood cells are deformed and not the proper shape

# Physiology Continued





# Molecular Cause

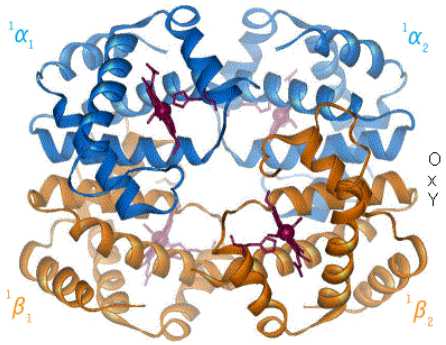



Figure A

- Hemoglobin has four chains: two alpha and two beta (Figure A)
- Each chain carries one oxygen molecule (Fig D)
- Alpha thalassemia is controlled by 2 genes on Chromosome 16 (Fig B)
- Beta thalassemia is controlled by 1 gene on Chromosome 11 (Fig C)
- Deletion of the whole gene or parts is what causes thalassemia
- Severity of the deletion correlates to severity of the symptoms
- Red blood cells of thalassemia patients carry less oxygen than average people

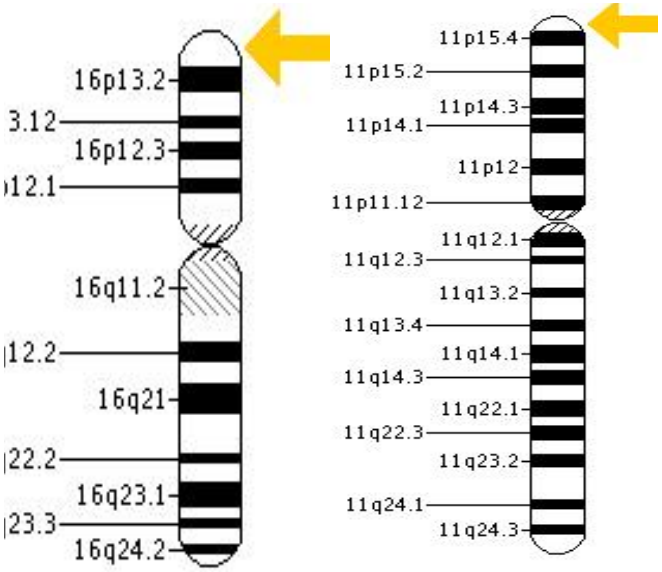



Figure B




Figure C

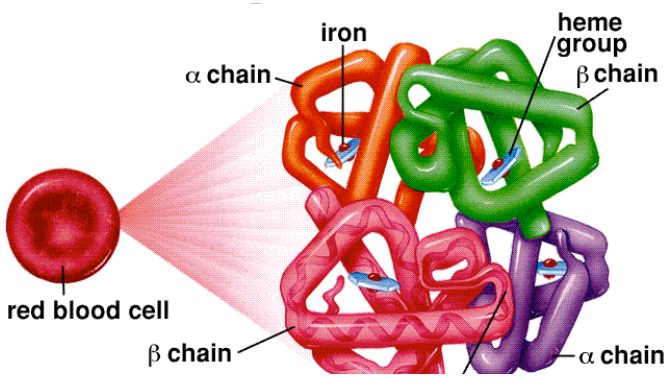
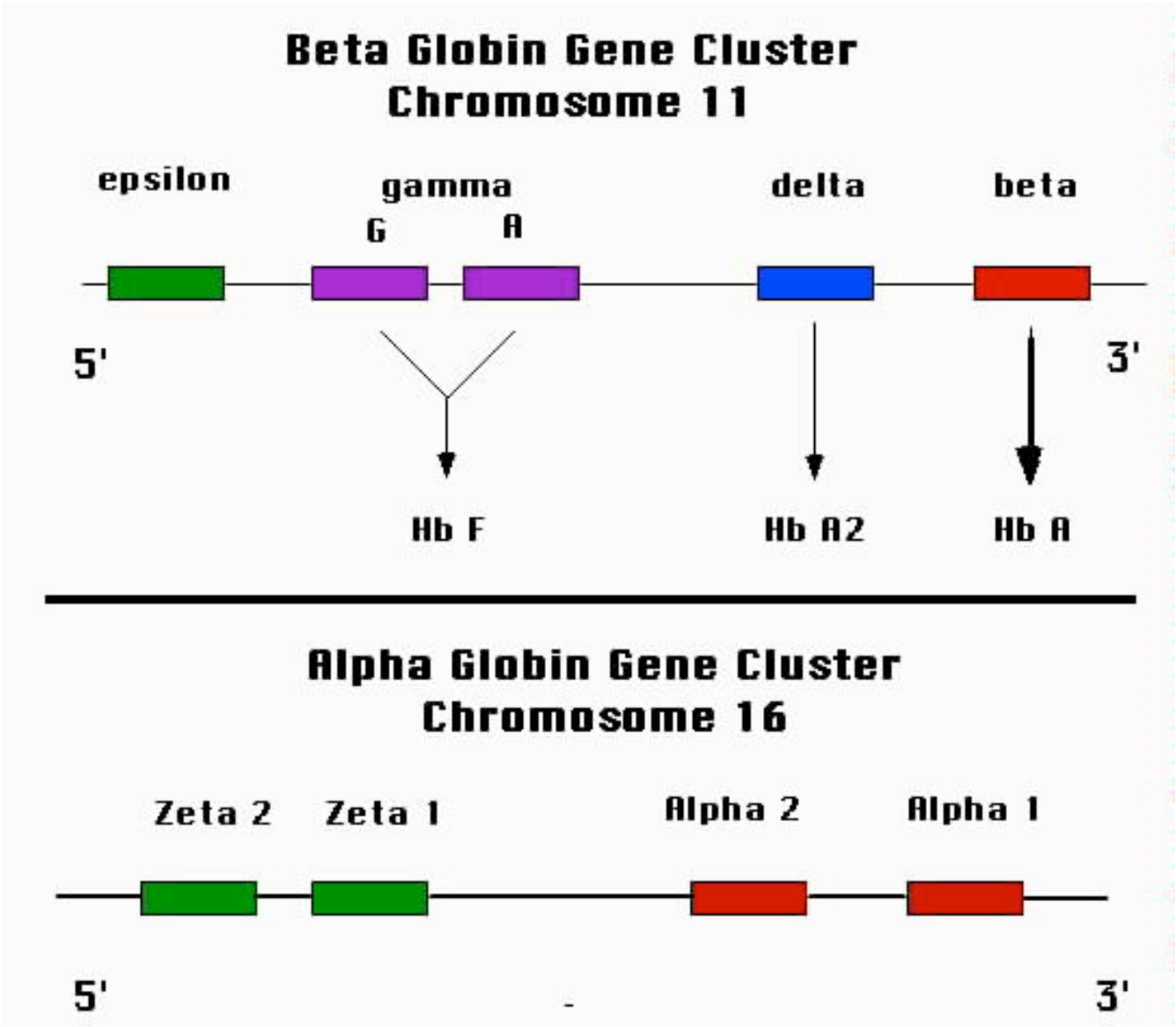



Figure D

# Molecular Cause Continued



# Treatments/Risk and Limits

- Typical way to diagnose thalassemia is through a CBC from blood test.
- Patients are suspected of thalassemia if they have a low blood cell count and also fall within the target ethnicities. Iron deficiency test can be administered for confirmation.
- Can also be diagnosed through familial patterns (pedigree) or amniocentesis
- For those with minor symptoms, regular blood tests are needed.
- For those with major symptoms, regular blood transfusions (frequency depends on the severity)
- Because blood transfusions add unwanted iron, it must be removed through iron chelation therapy
  - Deferoxamine (under the skin) or Deferasirox (oral)
- Limitation: Problems with blood, hassle in transfusions and therapy
- For those with serious thalassemia, a bone marrow transplant may be used. However, it can be hard to find a suitable donor and is expensive.
- Idea to reactivate fetal hemoglobin in the blood because it utilizes alpha and gamma chains (does not help alpha thalassemia patients)
- Would utilize a lentiviral vector that contains zinc finger transcription factors to reactivate the promoter of the gamma globin gene to start production

# Proposed Cure and Limits

- I wanted to build on the fetal hemoglobin idea, except make it applicable to patients with alpha thalassemia since that cure only works for beta thalassemia patients.
- Hemoglobin Portland I is one of the three types of embryonic hemoglobin produced, and contains two zeta and two gamma chains.
- Follows the approach formulated by researchers that have successfully increased fetal hemoglobin production
- Zinc finger transcription factors that are complementary to zeta and gamma globin promoters will be put into a lentivirus that will be surrounded by vesicular stomatitis virus G that will allow the transcription factors to "infect" the blood cell
- The transcription factors will activate the promoters that have been silenced and start transcription
- Possibly combine this with an approach of RNAi to stop the production of normal hemoglobin, but that has to be personalized to the sequence of the patient
  - May be more useful in the future when personalized medicine becomes more prominent

# Sources

*Physiology slides:*
- http://www.nhlbi.nih.gov/health//dci/Diseases/Thalassemia/Thalassemia_Signs.html
- http://www.marchofdimes.com/baby/birthdefects_thalassemia.html
- Picture: http://3.bp.blogspot.com/-HLEqRvqERV0/Tk2wg8BsthI/AAAAAAAAATU/sCvE-sdb2L4/s320/thalassemia.jpg

*Treatments/Risks and limits slide:*
- http://www.nhlbi.nih.gov/health/health-topics/topics/thalassemia/diagnosis.html
- http://www.aamds.org/node/82
- http://www.cincinnatichildrens.org/health/b/blood-transfuse/
- http://www.marchofdimes.com/baby/birthdefects_thalassemia.html

*Molecular Cause slides:*
- http://ghr.nlm.nih.gov/gene/HBA1
- http://ghr.nlm.nih.gov/gene/HBA2
- http://ghr.nlm.nih.gov/gene/HBB
- http://sickle.bwh.harvard.edu/thal_inheritance.html
- Pictures: http://upload.wikimedia.org/wikipedia/commons/b/ba/Hemoglobin_t-r_state_ani.gif
- http://ghr.nlm.nih.gov/dynamicImages/chromomap/HBA1.jpeg
- http://ghr.nlm.nih.gov/dynamicImages/chromomap/HBB.jpeg
- http://gassama.myweb.uga.edu/hemoglobinmolecule.gif

*Proposal Cure and Limits slide:*
- http://www.jbc.org/content/259/11/7325.full.pdf
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858469/