THALASSEMIAS

• PATHOLOGY IN THALASSEMIA IS A CONSEQUENCE OF AN IMBALANCE IN ALPHA AND BETA GLOBIN CHAIN SYNTHESIS
• EXCESS ALPHA OR BETA CHAINS ARE INSOLUBLE IN THE RBC
• PRECIPITATED GLOBIN GENES DAMAGE THE RED CELL MEMBRANE SHORTENING RED CELL HALF LIFE
• ANEMIA CAN BE CORRECTED BY TRANSFUSION
• CONTINUOUS TRANSFUSION CAN LEAD TO IRON OVERLOAD
Hemoglobinopathies and Thalassemias

• Mutations which alter the function of either the alpha or beta globin genes
• Hemoglobinopathies--mutations which cause a change in primary structure of one of the globin chains--over 700 known
• Thalassemias--mutations which alter the level of expression of one of the globin chains--over 280 known
Mutations in $\beta$ thalassemia

Image removed due to copyright restrictions.
Genetic map of mutations that cause beta-thalassemia.

$\beta$ thalassemia alleles have been described for almost every process affecting gene expression.
\(\alpha\) and \(\beta\) chromosomal loci

Developmental expression pattern proceeds along
Each locus: \(\varepsilon \to \gamma \to \beta\) and \(\zeta \to \alpha\)
Strong expression requires upstream regulatory elements
Images removed due to copyright restrictions.
Illustrations of alpha-globin gene cluster on chromosome 16, and beta-globin gene cluster on chromosome 11.
# Thalassemia Genotypes and Syndromes

<table>
<thead>
<tr>
<th>Alpha Thalassemia</th>
<th>α genes</th>
<th>Globin Chains</th>
<th>Hemoglobin</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>αα/αα</td>
<td>α₂β₂</td>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>Silent Carrier</td>
<td>αα/α⁻</td>
<td>α₂β₂</td>
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<tr>
<td>Trait</td>
<td>α⁻/α⁻</td>
<td>α₂β₂</td>
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<td>Mild</td>
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<tr>
<td>Hb H disease</td>
<td>--/α</td>
<td>α₂β₂, β₄</td>
<td>A, H</td>
<td>Intermediate</td>
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<tr>
<td>Hydrops fetalis</td>
<td>--/--</td>
<td>γ₄, ζ₂γ₂</td>
<td>Barts Portland</td>
<td>Lethal</td>
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</table>

<table>
<thead>
<tr>
<th>Beta Thalassemia</th>
<th>β genes</th>
<th>Globin Chains</th>
<th>Hemoglobin</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>β/β</td>
<td>α₂β₂</td>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>Thalassemia minor</td>
<td>β⁺/β</td>
<td>α₂β₂, α₂δ₂, α₂γ₂</td>
<td>A, A₂, F</td>
<td>Mild</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>β⁺/β⁺</td>
<td>α₂β₂, α₂δ₂, α₂γ₂, α₂γ₂</td>
<td>A, A₂, F, F, A₂</td>
<td>Severe</td>
</tr>
<tr>
<td>HPFH*</td>
<td>γ/γ</td>
<td>α₂γ₂</td>
<td>F</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Figure by MIT OpenCourseWare.
Splice variants are one of the most frequent causes of β thalassemia alleles: A Mutation Can Create A New Splice Site in an Intron
LOSS OF A NORMAL SPLICE SITE DUE TO A SINGLE BASE CHANGE

Common Mediterranean Mutation for β Thalassemia IVS-1, position 1 (G → A)

Mutation of G to A destroys the normal splice signal adjacent to codon 30; an abnormal mRNA is produced which includes sequences from intron 1; incorrect amino acids are added after position 30 and a short polypeptide is produced following a termination codon which occurs in the intron 1 sequence.
Hemoglobin E: A Mutation in an Exon Creates a New Splice Site Causing 40% of mRNA made to be Non-functional; the remaining RNA encodes a β Globin with a single amino acid change—glutamic acid (GAG) to lysine (AAG) at position 26

HbE has a very high allele frequency and widespread distribution in southeast Asia
Mutations in the Promoter, the 3’ UTR or the poly A Site Can Reduce mRNA Expression Levels
The TATA box is an important sequence for most eukaryotic promoters because it binds the key transcription factor TBP.

β Thalassemia mutations in the TATA box include:
-31 A to G
-30 T to A and -30 T to C
-29 A to G
-28 A to G
An important CCCCC element is located upstream of the start of transcription between positions -86 and -90 of the β globin gene

β Thalassemia mutations in this element include:
-90 C to T
-88 C to A or T
-87 C to A or G or T
-86 C to G
Mutations affecting mRNA polyadenylation at the polyA site can cause $\beta$ thalassemia

- AATAAAA is the $\beta$ globin poly A site
- Mutations seen in $\beta$ thalassemia
- AACAAA
- AATT$T$AA
- AATT$G$A
- AATAA$C$A

Image removed due to copyright restrictions.
Capping the 5’End.
Caps at the 5’end of eukaryotic mRNA include 7-methylguanylate (red) attached by a triphosphate linkage to the ribose at the 5’end.

Mutation in silent β thalassemia +1 A to C prevents cap formation
A Mutation in the Chain termination Codon Causes a Longer α Globin to be Produced; the Mutation also Causes Instability of the mRNA Leading to Reduced levels of Gene Expression

Image removed due to copyright restrictions.
Chart showing that reduced mRNA levels correlate with reduced globin expression.
DNA sequences such as \( \beta \) LCR and \( \alpha \) HS40 play a Key Role in Controlling Expression of Each Locus

Image removed due to copyright restrictions.
DELETION OF THE HS40 BOX LEADS TO INACTIVATION OF TRANSCRIPTION OF THE $\alpha$ GENE
Gene Sequences at a Distance from the Gamma Globin Chain Gene Affect Level of Expression

• Deletions of beta chain gene can lead to increased levels of gamma chain synthesis
Deletions which entirely eliminate the Beta Globin Gene Cause the Gamma Chain Genes to Remain On-- Hereditary Persistence of Fetal Hemoglobin (HPFH)
Worldwide Distribution of Globin Disorders
Epidemiology and the malaria hypothesis

Distribution of thalassemias, sickle cell disease, G6PD mirror worldwide distribution of malaria prior to 20th century.

Hypothesis (Haldane and others): heterozygous forms confer fitness - Thal trait, sickle trait, G6PD protective against death from cerebral falciparum malaria

Images removed due to copyright restrictions.
Maps showing the similar worldwide distributions of falciparum malaria and alpha-thalassemia.
Balanced Polymorphism

Malaria
AA

Thalassemia
aa
Hardy-Weinberg Equilibrium

- large population \[ A = p \]  
- no mutation \[ a = q \]  
- no selection \[ p + q = 1 \]  
- random mating \[ AA = p^2 \]  
- no migration \[ Aa = 2pq \]  
- [aa] = q^2 frequencies remain stable
The only reason that Hardy-Weinberg should not hold at conception is assortative mating.
Selection: Genetic Lethal Can Eliminate One Genetic Class at Some Point in Life

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
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<tbody>
<tr>
<td>At conception</td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2$</td>
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<tr>
<td>After lethal events</td>
<td>$p^2$</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>Aa</td>
<td>aa</td>
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<tr>
<td>--------------------------</td>
<td>------</td>
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<td>------</td>
</tr>
<tr>
<td><strong>At conception</strong></td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2$</td>
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<tr>
<td><strong>Early in life—</strong></td>
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<td>some lethal events</td>
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<tr>
<td>reduce aa class</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Later in life—</strong></td>
<td></td>
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<tr>
<td><strong>After all lethal</strong></td>
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<tr>
<td>events</td>
<td></td>
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<tr>
<td><strong>Can be as low as 0</strong></td>
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</tbody>
</table>
Balanced Selection: Genetic Lethal Can Eliminate More than One Genetic Class

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<td>At conception</td>
<td>$p^2$</td>
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<tr>
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<td>lethal events</td>
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<tr>
<td>reduce AA and aa</td>
<td></td>
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<tr>
<td>classes</td>
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<td>Later in life—more</td>
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<td>lethal events</td>
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<td>classes</td>
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<td></td>
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<tr>
<td>After all lethal</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>events</td>
<td></td>
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</tr>
</tbody>
</table>

- Early in life—some lethal events reduce AA and aa classes
- Later in life—more lethal events reduce AA and aa classes
- After all lethal events

Can be as low as 0
Age Related Allele Frequencies can Demonstrate Genetic Selection Operating on a Population

• Deviations from HWE as a function of age can demonstrate survival effects of alternative alleles at a locus
Genetic Selection Operating on a Population will Influence Allele Frequencies in Subsequent Generations

- Reproductive fitness of each genotype class at the time of mating is the critical parameter in determining the genotype composition of the next generation
What matters for the next generation is the proportion of individuals in each genotype class at the time of mating and their relative effectiveness in mating—REPRODUCTIVE FITNESS

generation | p   | q   
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.66</td>
<td>0.33</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>0.25</td>
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</table>

gene pool
Fitness

fitness: proportion of offspring compared with “normal”

coefficient of selection = 1-F

F = 1, s = 0 if normal number of offspring
F = 0, s = 1 if lethal
Change in Allele Frequency Because of Reduced Reproductive Fitness

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2$</td>
</tr>
<tr>
<td>Fitness</td>
<td>1</td>
<td>1</td>
<td>1-s</td>
</tr>
<tr>
<td>In Next Generation</td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2(1-s)$</td>
</tr>
</tbody>
</table>
Even though selection may remove all homozygous recessives from the reproductive pool, heterozygote matings recreate this genotype class in the next generation.
Even after many generations the recessive allele remains at a significant frequency in the population but over time it gradually will drop to lower and lower population frequencies UNLESS
Heterozygote Advantage

When allele frequencies for the recessive allele remain high even after many generations despite negative selection of the recessive homozygote, then selection in favor of the heterozygote should be considered.

Examples: sickle cell anemia, thalassemia, cystic fibrosis, hereditary hemochromatosis, ccr5 deletion.
Epidemiology and the malaria hypothesis

Homozygote loss of fitness balanced by increased fitness of heterozygote

>200 million people are heterozygous carriers of thal mutations

~1 million with HbE/β0 thalassemia
tens of thousands with homozygous thal syndromes.

Images removed due to copyright restrictions.
Maps showing the similar worldwide distributions of falciparum malaria and alpha-thalassemia.
Graph showing the leading infectious killers in 1998, worldwide: acute respiratory diseases (3.5 million), AIDS (2.3 million), diarrheal diseases (2.2 million), malaria (1.1 million), and measles (0.9 million).
Malaria--Worldwide Impact

- **40% of the world's population** - mostly those living in the poorest countries - is at risk of malaria.
- Malaria causes between **300 - 500 million cases of acute illness** and over **1 million deaths** annually.
- **90% of deaths due to malaria occur in Africa**, south of the Sahara desert - mostly amongst young children.
- Malaria is the number one killer of young children in Africa, accounting for **1 in 5 of all childhood deaths**.
Species of Plasmodium which cause Malaria

- P. falciparum is the major killer among the four species of plasmodium which infect humans
- P. vivax, p. malariae and p.ovale cause serious illness but are not responsible for the high death rate caused by malaria in humans
Plasmodium falciparum has a very broad world wide distribution. It has a certain pattern of fevers. It is responsible for most malaria fatalities. Infected red blood cells develop surface 'knobs' which cause them to stick to endothelial cells (cells lining blood vessels). This causes blockages and brain and intestinal damage, often resulting in death, which can occur within a few days of infection. *P. falciparum* is especially dangerous to small children and to travellers from non-malarious areas. There is no dormant hyponozoite stage.
What about immunity?

- Adults from areas where malaria is endemic develop a form of partial immunity.
- This partial immunity develops slowly and only in response to repeated infections.
- In partially immune people, malaria parasites can often be found in the blood, but without clinical symptoms.
- Immunity is lost if exposure is not maintained. (after 6 months).
Malaria Pathology

- P. falciparum can cause repeated infections; immune response is very limited
- P. falciparum causes infected red blood cells to exhibit protruding knobs which stick to endothelial cells lining blood vessels
- Blockage of blood vessels in the brain causes cerebral malaria—a major cause of death
- Blockage of intestinal blood vessels also important in pathology
How the malaria life cycle in mosquitos determines where malaria will be most prevalent

In the part of the life cycle carried out in mosquitos, the embedded ookinete becomes an oocyst which grows rapidly and divides internally into sporozoites - the third asexual phase. The oocyst is the longest phase in the life cycle lasting between 8 and 35 days. How long this phase takes is acutely dependent on temperature.

The mosquito has to survive long enough for the oocyst to mature before it can infect anyone. So only elderly mosquitoes can pass on malaria and in the wild of course many mosquitoes never reach old age.

This is where temperature matters, the warmer the weather, the faster the oocyst can develop in the mosquito. Mosquito survival is probably the single most important factor in malaria transmission.
Demonstrating the protective effect of red cell mutations against *p. falciparum* infection

The observed malaria protective effect of common erythrocyte variants.

<table>
<thead>
<tr>
<th></th>
<th>In vitro</th>
<th>Phagocytosis</th>
<th>In vivo</th>
<th>References</th>
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<tbody>
<tr>
<td></td>
<td>Invasion/Growth</td>
<td>Phagocytosis</td>
<td>Case-control</td>
<td></td>
</tr>
<tr>
<td><strong>HbAS</strong></td>
<td>↓ invasion/multiplication (low O₂ conditions)</td>
<td>↑ susceptibility to phagocytosis</td>
<td>Protection: severe malaria (60-90%); mortality (55%)</td>
<td>Willcox <em>et al.</em> (1983a); Aidoo <em>et al.</em> (2002); Ayi <em>et al.</em> (2004)</td>
</tr>
<tr>
<td><strong>HbAC</strong></td>
<td>normal</td>
<td>N/A</td>
<td>Reduced risk: clinical malaria (29%); severe malaria (47-80%)</td>
<td>Friedman <em>et al.</em> (1979); Agarwal <em>et al.</em> (2000); Modiano <em>et al.</em> (2001)</td>
</tr>
<tr>
<td><strong>HbCC</strong></td>
<td>↓ multiplication; altered knob formation</td>
<td>↑ susceptibility to phagocytosis</td>
<td>Reduced risk of clinical malaria (90%)</td>
<td>Fairhurst <em>et al.</em> (2003); Mockenhaupt <em>et al.</em> (2004a)</td>
</tr>
<tr>
<td><strong>HbAE</strong></td>
<td>↓ parasite invasion (25%)</td>
<td>↑ susceptibility to phagocytosis</td>
<td>Reduced risk of complications (6.9x reduced odds)</td>
<td>Yuthavong <em>et al.</em> (1990); Hutagalung <em>et al.</em> (1999); Chotivanich <em>et al.</em> (2002)</td>
</tr>
<tr>
<td><strong>HbEE</strong></td>
<td>↓ invasion/multiplication</td>
<td>↑ susceptibility to phagocytosis</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>α-Thalassaemia</strong></td>
<td>↓ Normal invasion multiplication</td>
<td>No difference from controls</td>
<td>Reduced risk of severe malaria (risk = 0.4 - 0.66)</td>
<td>Allen <em>et al.</em> (1997); Pattanapanyasat <em>et al.</em> (1999); Mockenhaupt <em>et al.</em> (2004b)</td>
</tr>
<tr>
<td><strong>β-Thalassaemia</strong></td>
<td>inconclusive</td>
<td>↑ susceptibility to phagocytosis</td>
<td>Protection against hospital admission with malaria (50%)</td>
<td>Willcox <em>et al.</em> (1983b); Ayi <em>et al.</em> (2004);</td>
</tr>
<tr>
<td><strong>G6PD deficiency</strong></td>
<td>↓ growth under oxidative stress</td>
<td>↑ susceptibility to phagocytosis (ring stage)</td>
<td>Protection of F(htz) against non-severe malaria; Protection of M and F(htz) against severe malaria (50%)</td>
<td>Gilles <em>et al.</em> (1967); Bienzle <em>et al.</em> (1972); Ruwende <em>et al.</em> (1995); Cappadoro <em>et al.</em> (1998)</td>
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<td><strong>PK deficiency</strong></td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Min-Oo <em>et al.</em> (2003);</td>
</tr>
</tbody>
</table>

↓, decrease; ↑, increase; M, male; F, female.

Figure by MIT OpenCourseWare. After Min-Oo and Gros, 2005.
High Frequency of Alpha Thalassemia Alleles in Regions of the World with High Incidence of Falciparum Malaria

Map of global incidence of alpha-thalassemia alleles.
High Frequency of Beta Thalassemia Alleles in Regions of the World with High Incidence of Falciparum Malaria

Image removed due to copyright restrictions.
Map of global incidence of beta-thalassemia alleles.
Different βThalassemia mutations are most common in different populations

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>Description</th>
</tr>
</thead>
</table>
| Mediterranean  | IVS-1, position 110 (G → A)  
Codon 39, nonsense (CAG → TAG) |
|                | IVS-1, position 1 (G → A) |
|                | IVS-2, position 745 (C → G) |
|                | IVS-1, position 6 (T → C) |
|                | IVS-2, position 1 (G → A) |
| African        | −29, (A → G)  
−88, (C → T)  
Poly(A), (AATAAA → AACAAA) |
| Southeast Asian| Codons 41/42, frameshift (−CTTT)  
IVS-2, position 654 (C → T) |
| Indian sub-continental | −28, (A → G)  
IVS-1, position 5 (G → C)  
619-bp deletion  
Codons 8/9, frameshift (+G)  
Codons 41/42, frameshift (−CTTT)  
IVS-1, position 1 (G → T) |
Why do different human populations have different allele frequencies for many genetic loci?

- Genetic drift
- Founder effects
- Mutation
- Selection
Genetic Drift

- fluctuation in gene frequency due to small size of breeding population
- fixation or extinction of allele possible
Genetic Drift
Founder Effect

- high frequency of gene in distinct population
- introduction at time when population is small
- continued relatively high frequency due to population being “closed”
initial population

"bottleneck" where new population is derived from small sample

new population with high frequency of mutant allele
POSITIONAL CLONING

• RESOLUTION IN FAMILY ANALYSIS IS LIMITED BY THE NUMBER OF FAMILY MEMBERS YOU CAN COLLECT

• BUT IF THE AFFECTED INDIVIDUALS IN A POPULATION CAN BE TREATED ESSENTIALLY LIKE A LARGE FAMILY, THEN INCREASED RESOLUTION CAN BE ACHIEVED
What if you want better resolution than the families collected can give?

• Linkage disequilibrium can sometimes be used to pinpoint position of disease gene

• Linkage disequilibrium uses meioses that happened many generations in the past to increase the resolution of genetic mapping
Linkage Disequilibrium Can Be Used to Identify the Position on a Chromosome Most Likely to Contain the Disease Gene Because of a Shared Chromosomal Haploype Among Affected Individuals

An explanation for linkage disequilibrium between a disease locus, such as cystic fibrosis, and a closely linked marker locus. Frequencies of haplotypes reach equilibrium if the marker locus is far enough away from the disease locus for many crossovers to have occurred during evolution, since the time of the original mutation. For markers very closely linked to the disease locus, little recombination has occurred, and thus the distribution of alleles observed in chromosomes with the CF mutation will be different from that observed in normal chromosomes.

Figure by MIT OpenCourseWare.
Haplotype
An associated set of alleles at two or more genetic loci on a chromosome which are inherited together over multiple generations because the recombination rate between them is very low relative to the number of generations considered.

Linkage disequilibrium
If the alleles at a pair of loci are looked at jointly in a large number of individuals, the presence of a particular allele at one locus may be correlated with the presence of a particular allele at the other locus; when this occurs the two loci are in linkage disequilibrium. One major reason for two loci to show linkage disequilibrium is that the two loci are very close together on a chromosome and the mutation to give rise to one of the alleles has happened recently enough that genetic recombination has not yet caused the new mutant allele to be associated with the two alleles at the other locus with equal frequency; i.e. they form a haplotype.
The principle of positional cloning--affected individuals in a family share a chromosomal segment which includes the mutation causing the disease--Supposing many patients are actually related to each other even though we do not know this for certain

Descendants with disease allele carry region of identity to ancestor and to each other

Linkage disequilibrium and haplotype analysis can be used to identify location of disease gene if many individuals with disease are actually related to a common ancestor
THE RELATIONSHIP BETWEEN DNA VARIANTS ON A CHROMOSOME AND THE FUNCTIONAL “DISEASE ALLELE” ARE A PRODUCT OF THE HISTORY OF MUTATIONS TO CREATE THE CHROMOSOMAL HAPLOTYPE.

Emergence of Variations Over Time

Common Ancestor

Disease Mutation

Variations in Chromosomes Within a Population
Linkage Disequilibrium Between Marker KM 19 and cystic fibrosis

<table>
<thead>
<tr>
<th></th>
<th>ALLELE 1</th>
<th>ALLELE 2</th>
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<tbody>
<tr>
<td>CF CHROMOSOMES</td>
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<td>228</td>
</tr>
<tr>
<td>NORMAL CHROMOSOMES</td>
<td>284</td>
<td>66</td>
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Linkage Disequilibrium Between Marker XV2C and cystic fibrosis

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<tr>
<td>CF CHROMOSOMES</td>
<td>235</td>
<td>109</td>
</tr>
<tr>
<td>NORMAL CHROMOSOMES</td>
<td>17</td>
<td>141</td>
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