

AC 70 A  
Winter 2003

Professor Bob Goldberg

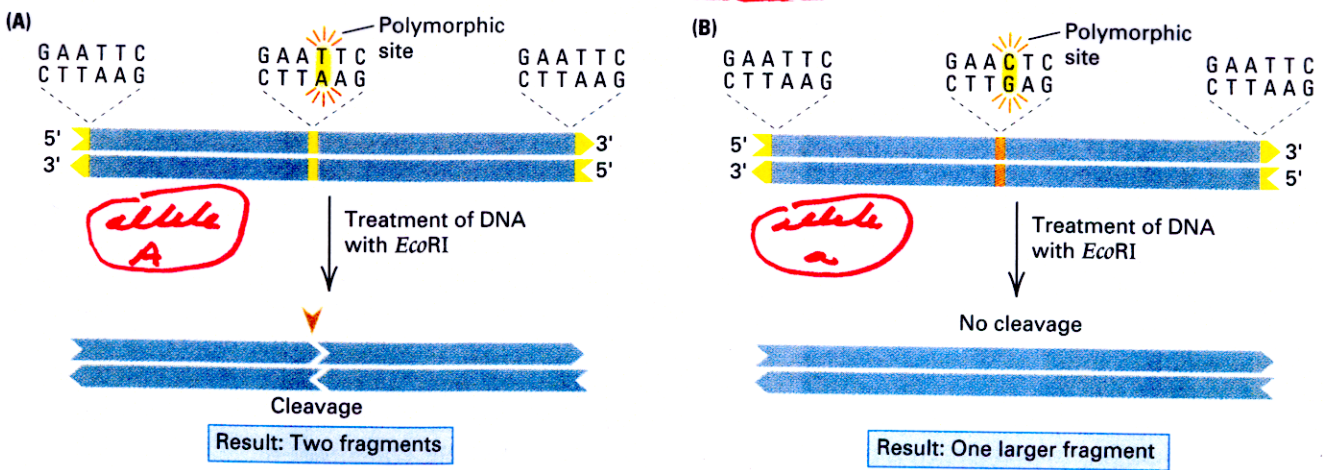
Learning Unit #7  
Detecting Changes in the  
Human Genome - Are there  
Races?

THEMES/CONCEPTS

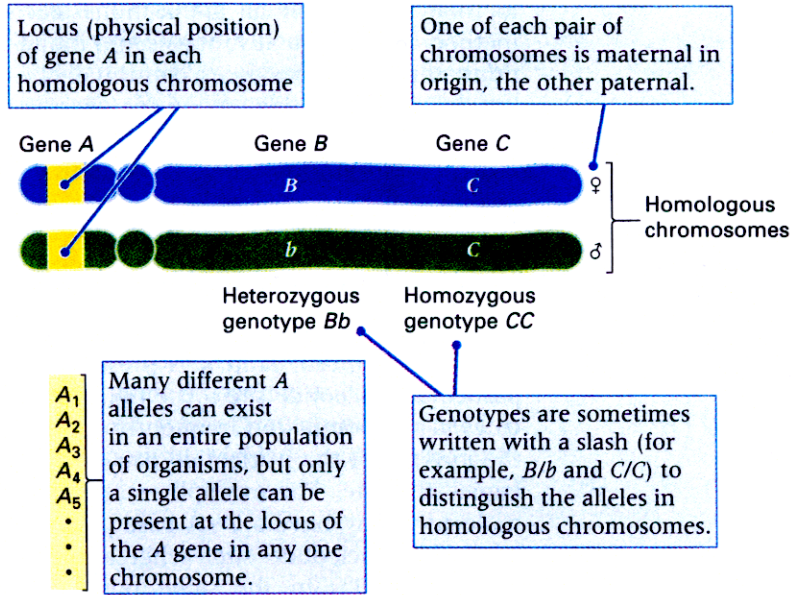
- ① Using RFLPs to detect SNPs
- ② Using RFLPs to Diagnose Disease Alleles
- ③ Positional Cloning Genes with SNPs
- ④ Detecting RFLPs with PCR
- ⑤ Using ASO's to Detect SNPs/DNA Fingerprints
- ⑥ BABZ/Pre-natal detection of Disease Genes
- ⑦ Ethical Issues in Genetic Testing
- ⑧ Human DNA Variation + Races -
- ⑨ Are there Races?

SNPs CAN BE DETECTED AS RFLPS IF PRESENT IN A RESTRICTION ENZYME SITE

Detect Polymorphism or Mutations at a Specific Locus



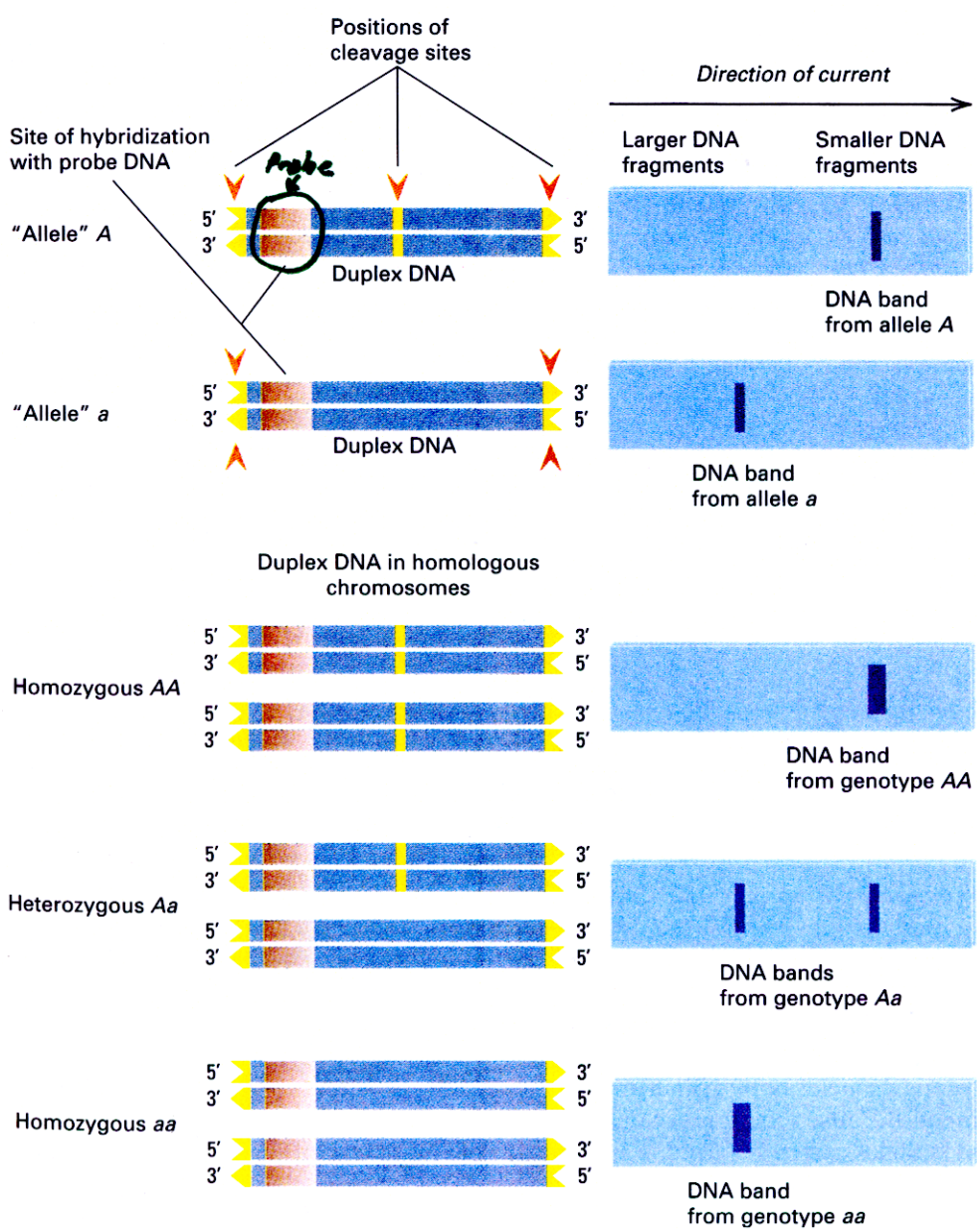
**Figure 2.23** A minor difference in the DNA sequence of two molecules can be detected if the difference eliminates a restriction site. (A) This molecule contains three restriction sites for *Eco*RI, including one at each end. It is cleaved into two fragments by the enzyme. (B) This molecule has an altered *Eco*RI site in the middle, in which 5'-GAATTC-3' becomes 5'-GAAGTC-3'. The altered site cannot be cleaved by *Eco*RI, so treatment of this molecule with *Eco*RI results in one larger fragment.



**Figure 2.22** Key concepts and terms used in modern genetics. Note that a single gene can have any number of alleles in the population as a whole, but no more than two alleles can be present in any one individual.



RFLPs/SNPs CAN BE USE TO detect ALLELIC VARIABILITY at a LOcus



Probe Specific for left half of DNA only  
∴ 1 band !!!

Pattern After Blotting

**Figure 2.24** In a restriction fragment length polymorphism (RFLP), alleles may differ in the presence or absence of a cleavage site in the DNA. In this example, the *a* allele lacks a restriction site that is present in the DNA of the *A* allele. The difference in fragment length can be detected by Southern blotting. RFLP alleles are codominant, which means (as shown at the bottom) that DNA from the heterozygous *Aa* genotype yields each of the single bands observed in DNA from homozygous *AA* and *aa* genotypes.

As well as Genotypes

RFLPs CAN BE USED AS MARKERS FOR DISEASE GENES IF LINKED TO THE MUTANT ALLELE

Molecular Diagnosis of Human Diseases

Sickle Cell Anemia

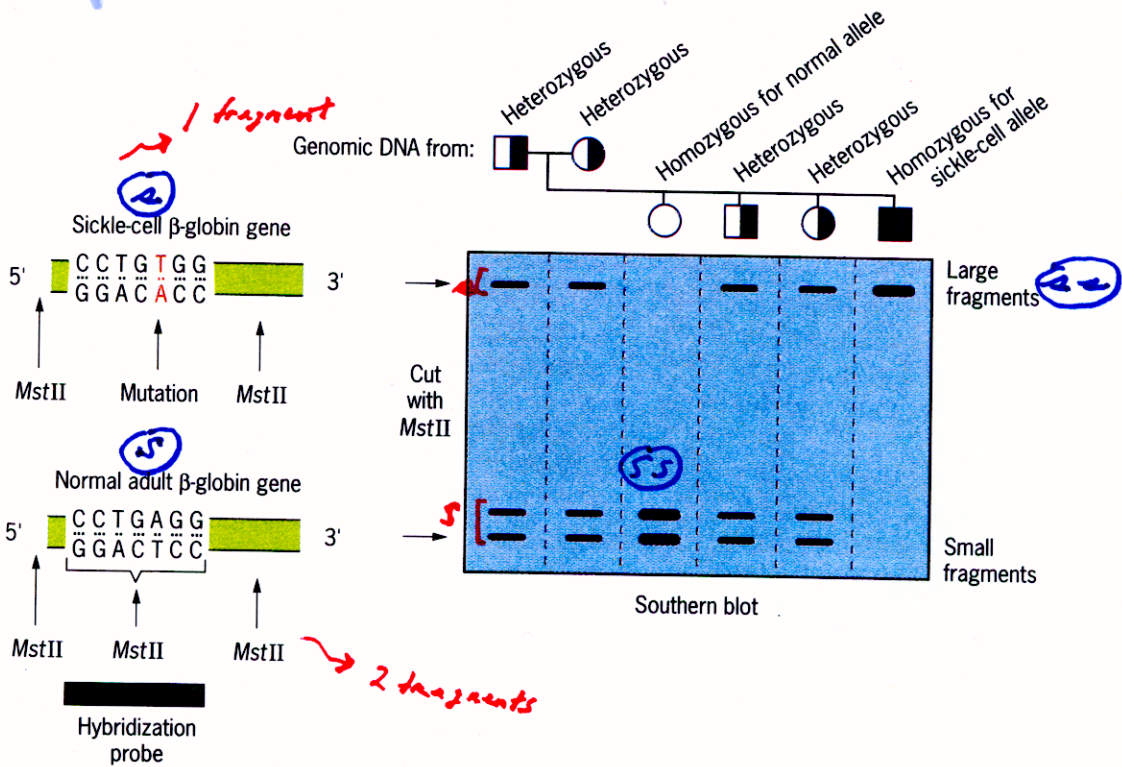


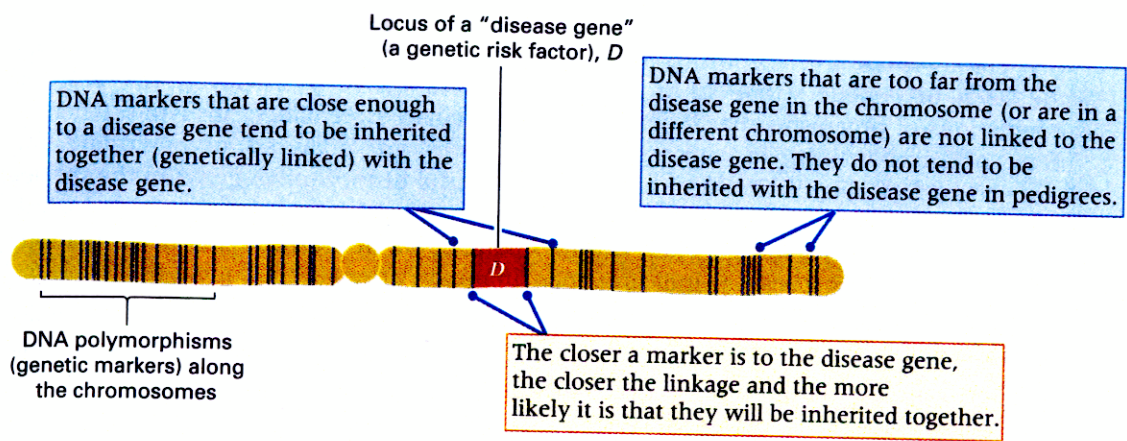
Figure 22.7 Detection of the sickle-cell hemoglobin mutation by Southern blot analysis of genomic DNAs cut with restriction enzyme MstII.

Marker is (IN) Gene!  $\therefore$  always linked with Phenotype!  
 $\therefore$  1 fragment at this locus is a marker for the normal allele.



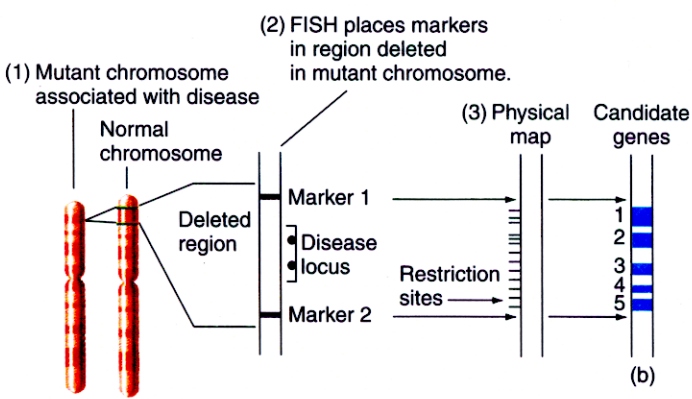
Markers tightly linked to disease gene can be used to identify what the disease gene is

Positional cloning in absence of known protein/gene product



**Figure 2.29** Concepts in genetic localization of genetic risk factors for disease. Polymorphic DNA markers (indicated by the vertical lines) that are close to a genetic risk factor (*D*) in the chromosome tend to be inherited together with the disease itself. The genomic location of the risk factor is determined by examining the known genomic locations of the DNA polymorphisms that are linked with it.

(a) Mapping a disease gene: a special case



(c) Examine expression of genes 1-5 in normal and diseased individuals.

| Gene | Expression |          |
|------|------------|----------|
|      | Normal     | Diseased |
| 1    | +          | +        |
| 2    | +          | +        |
| 3    | +          | -        |
| 4    | +          | +        |
| 5    | +          | +        |

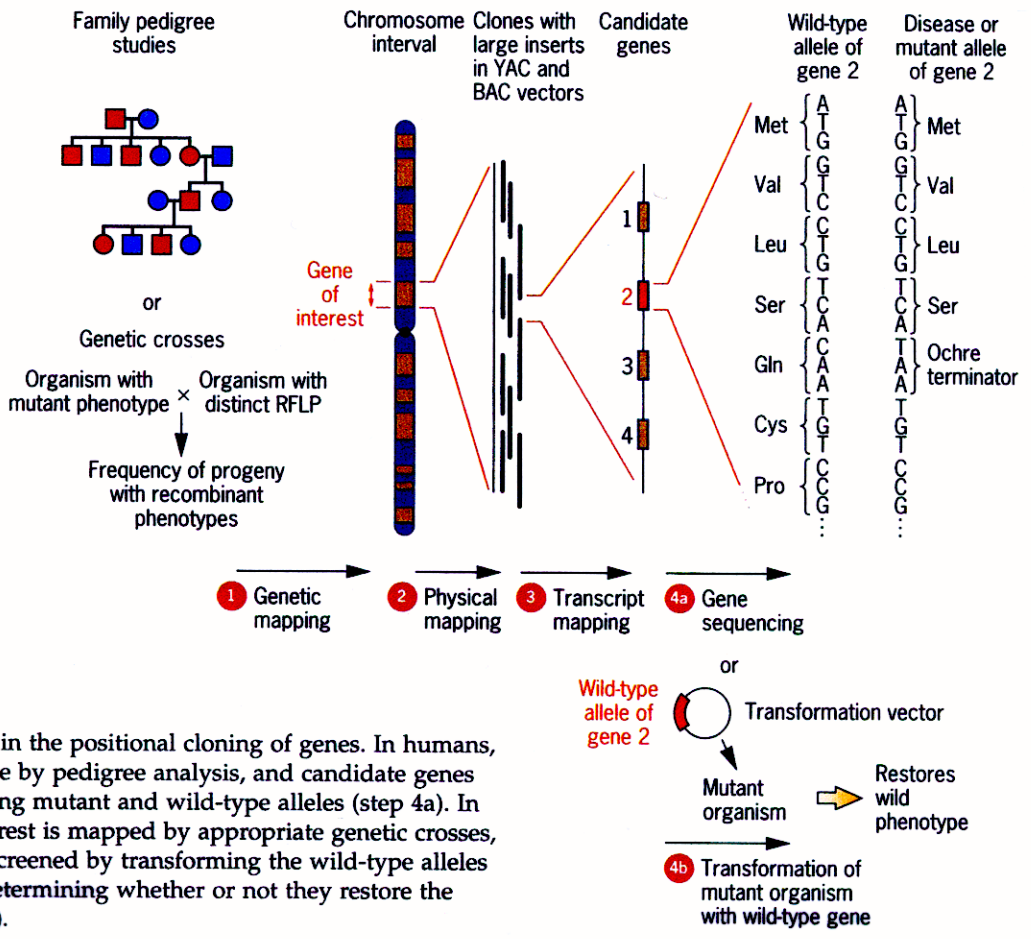
Conclusion: The tested diseased individual shows a correlation between the disease phenotype and the absence of expression from the number 3 gene.

**Figure 10.11 Positional cloning: From phenotype to gene.**

(a) Correlating the expression of a phenotype with one small segment of the genome. (1) Some diseases, such as Duchenne muscular dystrophy, are caused by a deletion. It is sometimes possible to observe directly the absence or shortening of a band in a chromosome from an affected individual as compared to the same chromosome from a healthy individual. Even when it is not possible to observe the deletion directly, the FISH protocol can detect it. (2) A marker in the deleted region will hybridize to the chromosome from the healthy individual, but not to the same chromosome from the diseased individual. Markers associated with the disease can be used in linkage analyses of families carrying mutant disease alleles that are not deletions. (3) When linkage analysis shows that a specific chromosomal region contains the disease locus, researchers can subject the marked region to physical analysis. (b) Investigators next analyze the region between recombination sites that define the smallest area within which the disease locus can lie for the presence of candidate genes (as described later in this chapter). (c) They then compare the structure and expression of each candidate gene in many diseased and nondiseased individuals. A correlation between a mutant structure or expression for a particular candidate gene and the disease phenotype can provide evidence that a particular gene is responsible for the disease phenotype. Proof of the association, however, requires further functional studies, which we describe later in this chapter.



# USING LINKED MARKERS TO IDENTIFY A DISEASE GENE

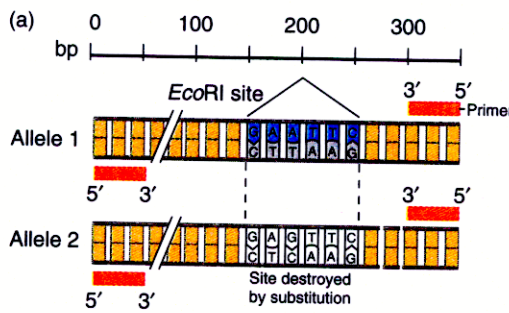


**Figure 21.8** Steps involved in the positional cloning of genes. In humans, genetic mapping must be done by pedigree analysis, and candidate genes must be screened by sequencing mutant and wild-type alleles (step 4a). In other species, the gene of interest is mapped by appropriate genetic crosses, and the candidate genes are screened by transforming the wild-type alleles into mutant organisms and determining whether or not they restore the wild-type phenotype (step 4b).

# RFLPs CAN BE detected USING PCR

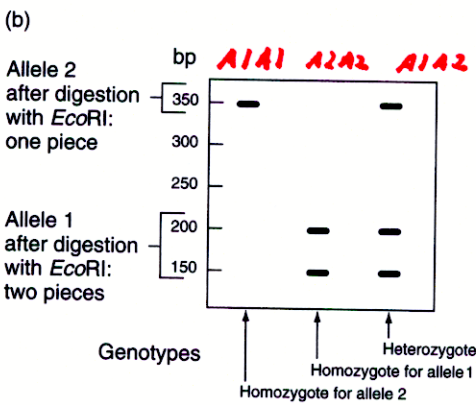
NO NEED FOR BLOT!  
ONLY NEED tiny amount of DNA

- ① AMPLIFY Gene Region containing the Polymorphism
- ② Digest with Relevant Restriction Enzyme
- ③ Visualize fragments directly on Gel!



→ 2 fragments (A2)

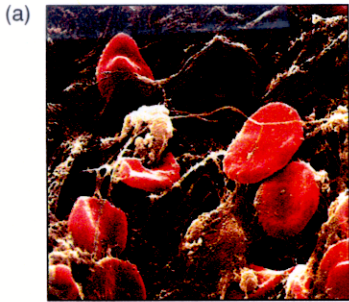
→ 1 fragment (A1)



**Figure 9.7** Restriction site polymorphisms can be detected most efficiently with PCR-based protocols. (a) PCR amplification of two alleles of a DNA locus with a restriction site polymorphism. Allele 1 has an EcoRI site that is eliminated in allele 2. The PCR products amplified from both alleles are identical in size. (b) Exposure of these PCR products to EcoRI causes cleavage of the allele 1 product but not the allele 2 product. Gel electrophoresis and ethidium bromide staining distinguish the three genotypes possible with the two alleles at this locus.

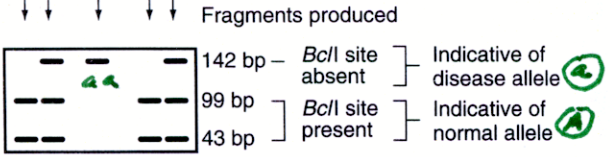
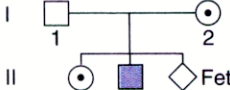
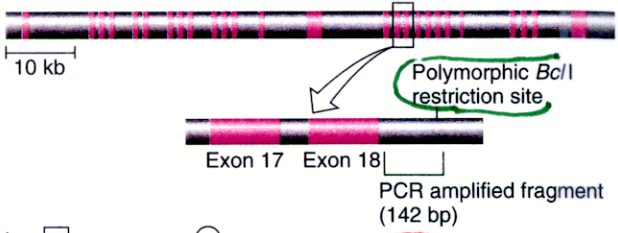
# USING RFLPs TO Detect a Mutant Factor VIII Gene

## A PCR Approach



**Figure 9.18 Diagnosis of hemophilia through the indirect detection of genotype at the factor VIII locus.** The factor VIII protein participates in a cascade of reactions that result in formation of a blood clot. (a) A polymorphic *Bcl* restriction site within intron 18 of the *factor VIII* gene has no effect on gene function but can provide a marker to follow the segregation of the gene from parents to children. (b) The family described by the pedigree has two healthy parents, but the mother is an obligate carrier of the disease mutation because she has passed this X-linked disease on to her son; her carrier status is signified by a circle with a dot in the middle. By comparing the RFLP pattern obtained from the mother's DNA with the pattern from her son's DNA, you can see that the disease allele is associated with the 142-bp *Bcl* restriction fragment, and the wild-type allele in the mother's genome contains a *Bcl* restriction site that causes this fragment to be cut into two pieces, one 43 bp and the other 99 bp in length. Using this information, you can determine that the firstborn sister is a carrier like her mother, while the male fetus will be disease free.

(b) Factor VIII gene



AAAA Aa Aa

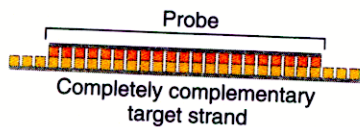


ASOs or Allele Specific Oligonucleotide Probes can be used to detect Specific Alleles/RFLPs/SNPs

This is the fastest/simplest approach to fingerprinting or monitoring disease loci - it utilizes PCR ⊕ Specific Annealing Conditions!

AT HIGH TEMPERATURE ONLY A PERFECT MATCH CAN ANNEAL SUCCESSFULLY! ONE MISMATCHED BASE PREVENTS HYBRID FORMATION!!!

(a) 1. 21-Base probe/target hybrid with no mismatches

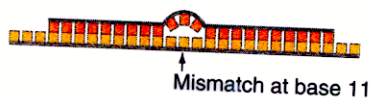


Raise temperature



Hybrid Perfect Match

2. 21-Base probe/target hybrid with middle mismatch



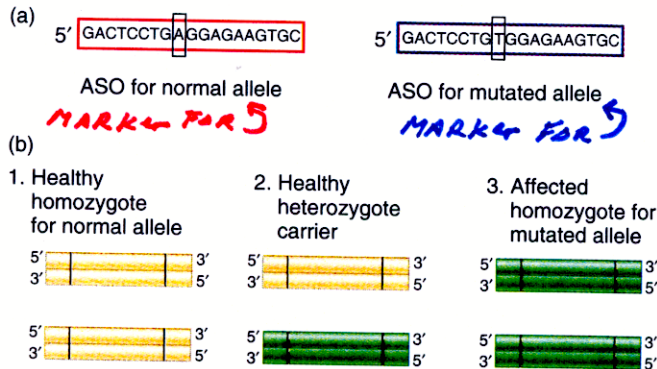
Raise temperature



NO Annealing Mismatch!

**Figure 9.8 Short hybridization probes can distinguish single-base mismatches, longer probes cannot.** (a) Researchers allow hybridization to occur between a short 21-base probe and two different target sequences. (1) A perfect match between probe and target extends across all 21 bases. When the temperature rises, this hybrid has enough hydrogen bonds to remain intact. (2) With a single-base mismatch in the middle of the probe, the effective length of the probe-target hybrid is only 10 bases. When the temperature rises, this hybrid does not have enough hydrogen bonds to remain intact, and it falls apart.

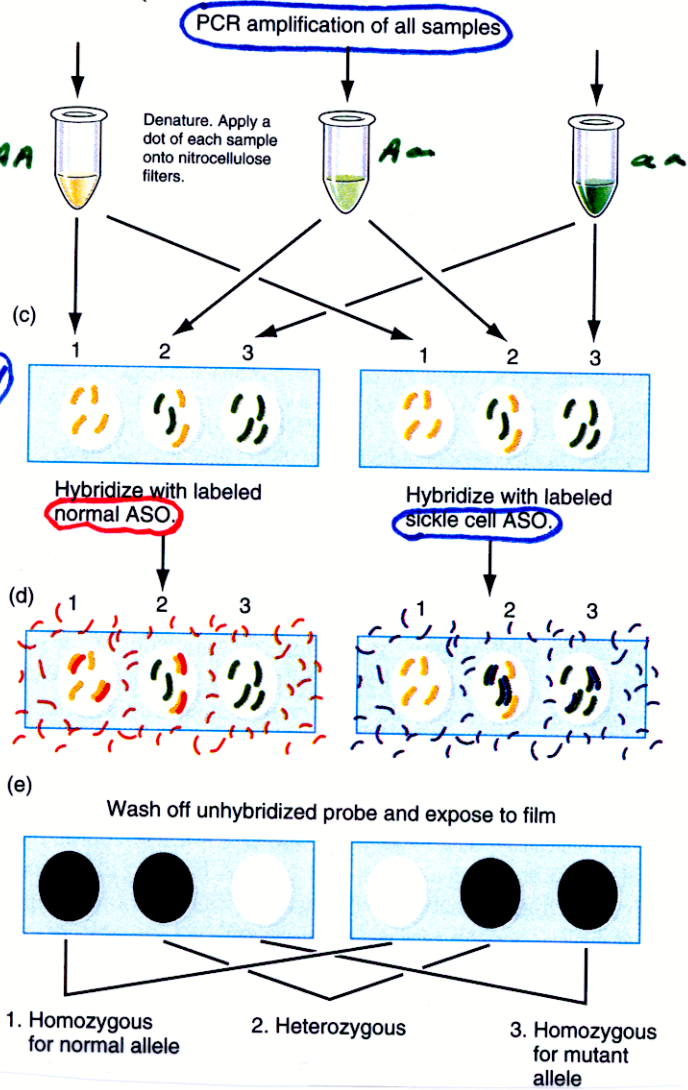
# USING ASOs to Detect sickle-cell ALLELES



PCR directly from cheek cell DNA or white blood cell DNA or Amniotic Fluid, etc.

**Figure 9.9 Using PCR with ASOs to determine genotype at the  $\beta$ -globin locus.** (a) Before performing the genotyping protocol, it is necessary to synthesize two oligonucleotides that differ at only a single base; one of these oligonucleotides is complementary to the wild-type  $\beta$ -globin allele, the other is complementary to the sickle-cell allele. These two synthetic DNA molecules serve as the ASOs for the sickle-cell genotype assay. (b) Genomic DNA samples obtained from individual people are subjected to PCR amplification with primers complementary to nonpolymorphic sequences that flank the base that mutates to cause sickle-cell anemia. (c) The amplified sample from each individual is divided into two aliquots that are blotted directly to filter paper. (d) One aliquot from each sample is hybridized to the wild-type ASO; the other aliquot is hybridized to the sickle-cell ASO. (e) Autoradiography indicates the  $\beta$ -globin genotype of each individual.

Amplified DNAs



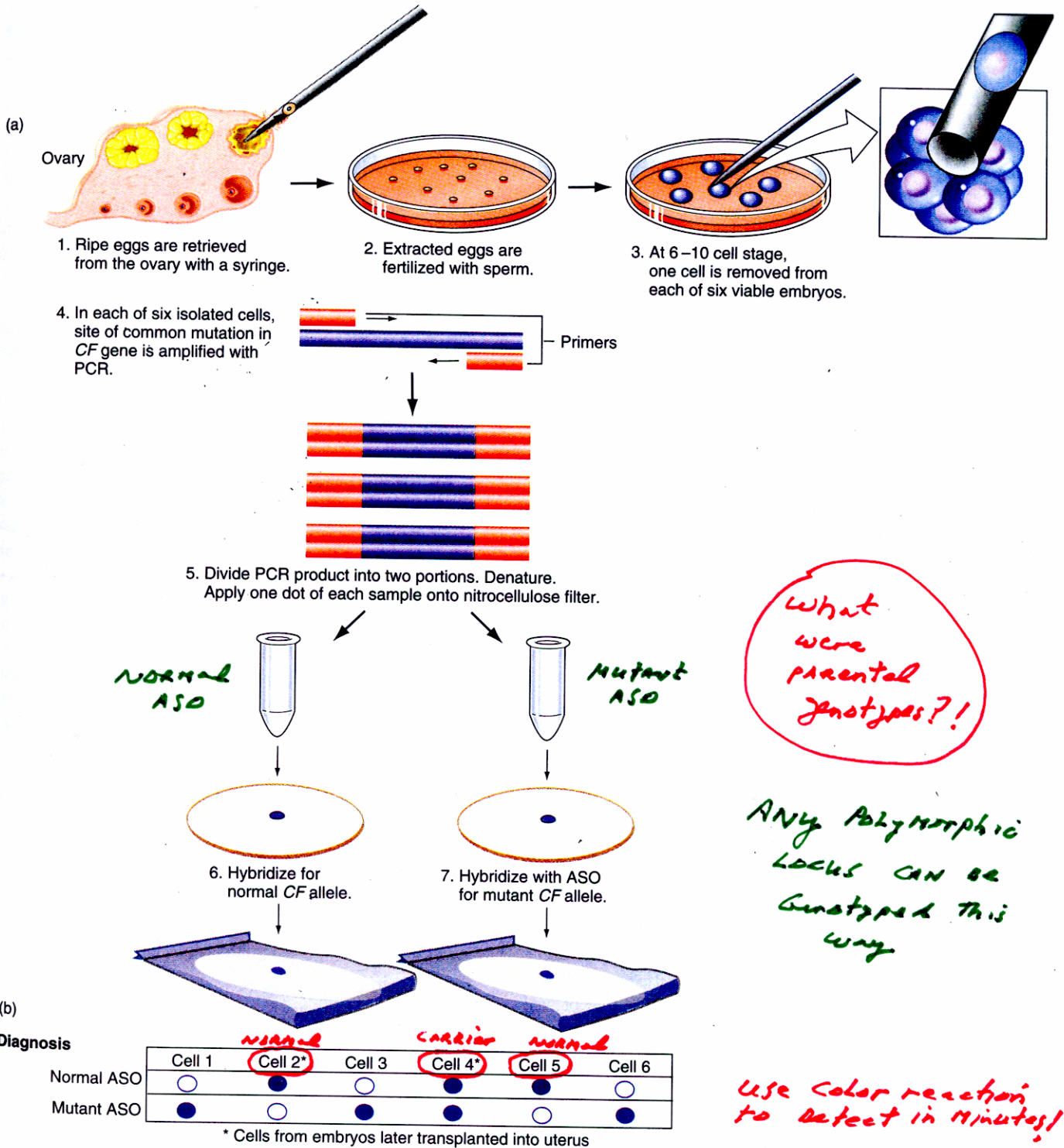
Note - Each ASO only reacts/hybridizes with a specific ALLELE!

CAN detect with a color reaction!

FAST, simple, inexpensive!

USE FOR DISEASE ALLELES & DNA FORENSICS!!  
 PATERNITY TESTS DONE THIS WAY!!!

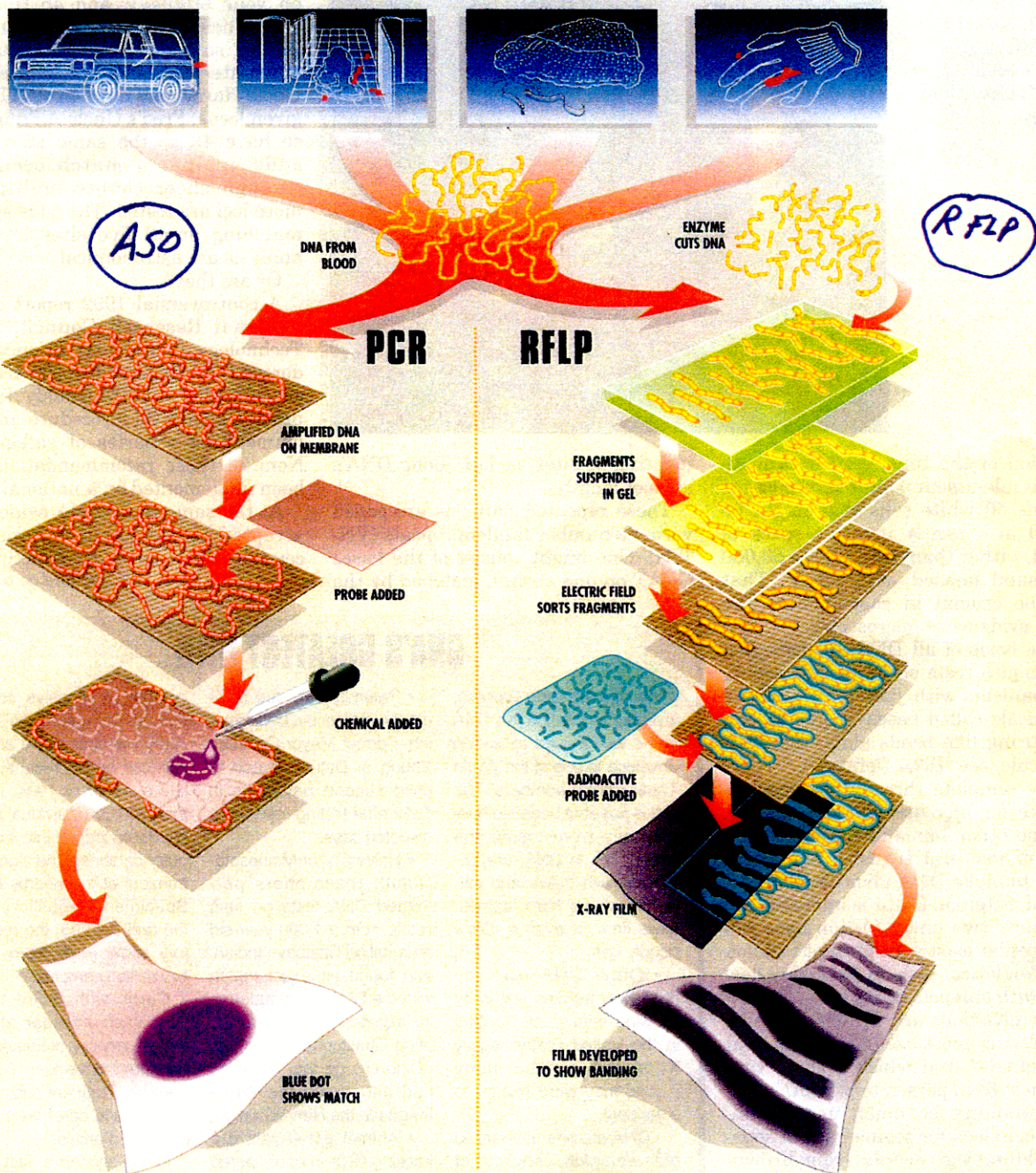
# Using ASOs + BABI test to Detect Mutant Cystic Fibrosis Alleles in Post-Fertilization EMBRYOS



**Figure 9.1** Detecting the cystic fibrosis genotype of embryonic cells. (a) *In vitro* fertilization and preimplantation diagnosis. (b) Cell 2 is homozygous for the normal allele; cell 4 is heterozygous for the CF mutation.



# FINGERPRINTING WORKS



being tested and transfer their radioactivity selectively to those fragments.

Finally, the membrane is placed over standard X-ray film. Radiation emitted from the P-32 gradually exposes the film and gives a precise picture of the DNA fragments.

But the process takes time. The P-32 is so weak that this approach is like sitting in your dentist's chair for two weeks to get an X-ray of

your molars. And each of the five loci must be exposed sequentially. The ten weeks of waiting for the X-ray film to be exposed accounts for most of the time it takes to complete an RFLP fingerprint.

Once the film is developed, it's inspected by the scientist conducting the test and at least one other expert. In addition, it is scanned into a computer for precise measurement and

comparison against known samples of DNA.

If lines and bars from the known and unknown DNA samples don't match, this is conclusive evidence that they came from different people.

If the X-ray codes do match, some experts will argue that they almost certainly came from the same person. And other experts will challenge that conclusion.—J. S.



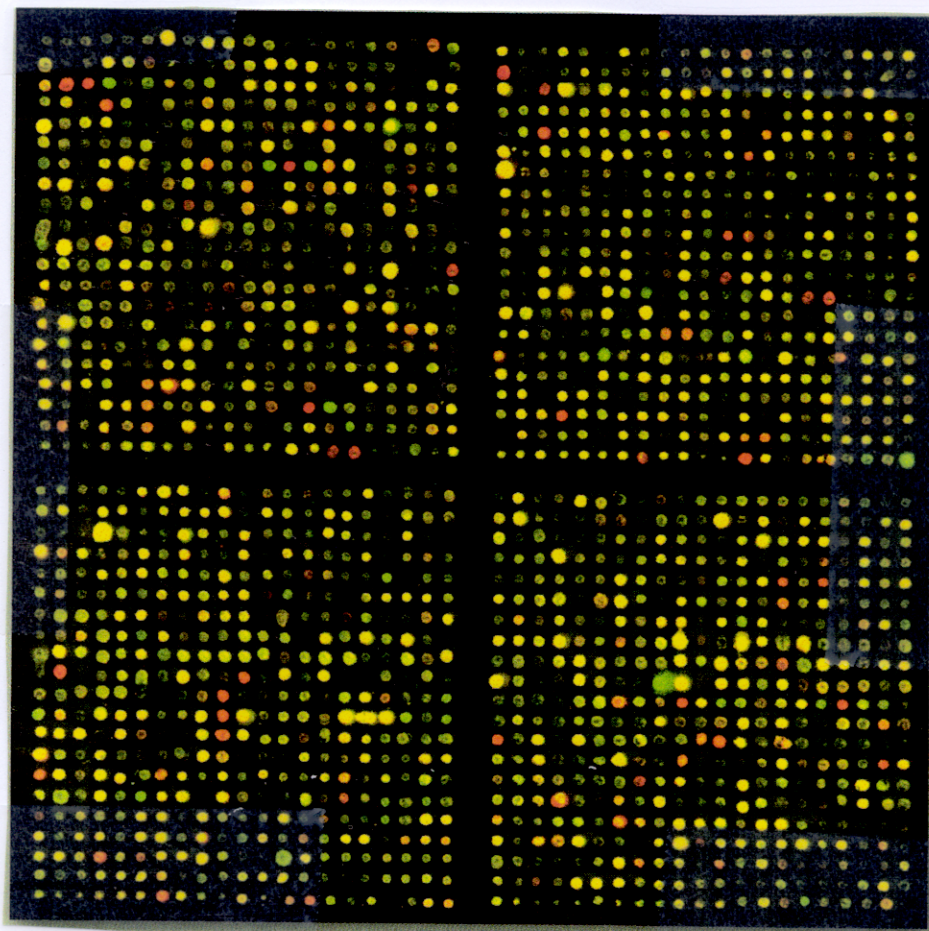
# DIFFERENT PROCEDURES TO DETECT SNPs / ALLELIC POLYMORPHISMS

**TABLE 9.2 Protocols for Detecting Single-Base Variations**

| Protocol  | Advantages  | Disadvantages   | Main Uses  |
|---|---|---|--|
| RFLP analysis<br>By Southern blots and labeled probes               | No requirement for sequence information                     | Requires a large amount of DNA  | Genotyping in the <u>absence of sequence information</u>                               |
| By restriction enzyme digestion and electrophoresis of PCR products | Rapid; no blotting and hybridization                        | Substitution must affect restriction site; requires sequence information from locus | Rapid analysis of restriction site polymorphisms among individuals within a population |
| PCR analysis using ASOs   | No need to run a gel; can detect all single-base variations | Must know sequence of alternative alleles   | Standard genotyping  |

⊕ Direct Sequencing - but not practical for routine work!

GENOME CHIPS WILL BE USED FOR Genotyping

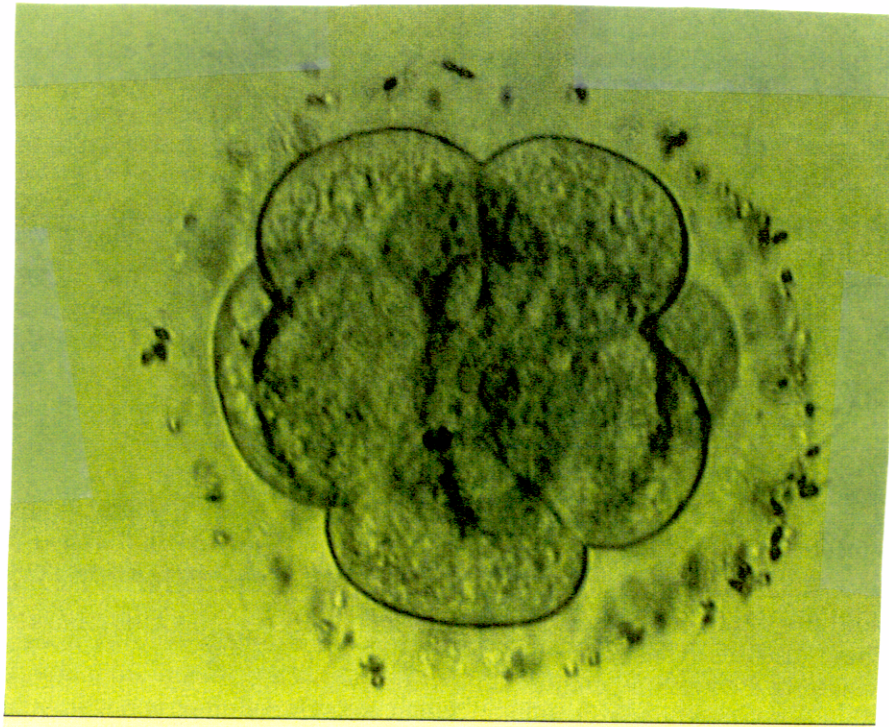


They work like ASOs but use MANY probes at a time

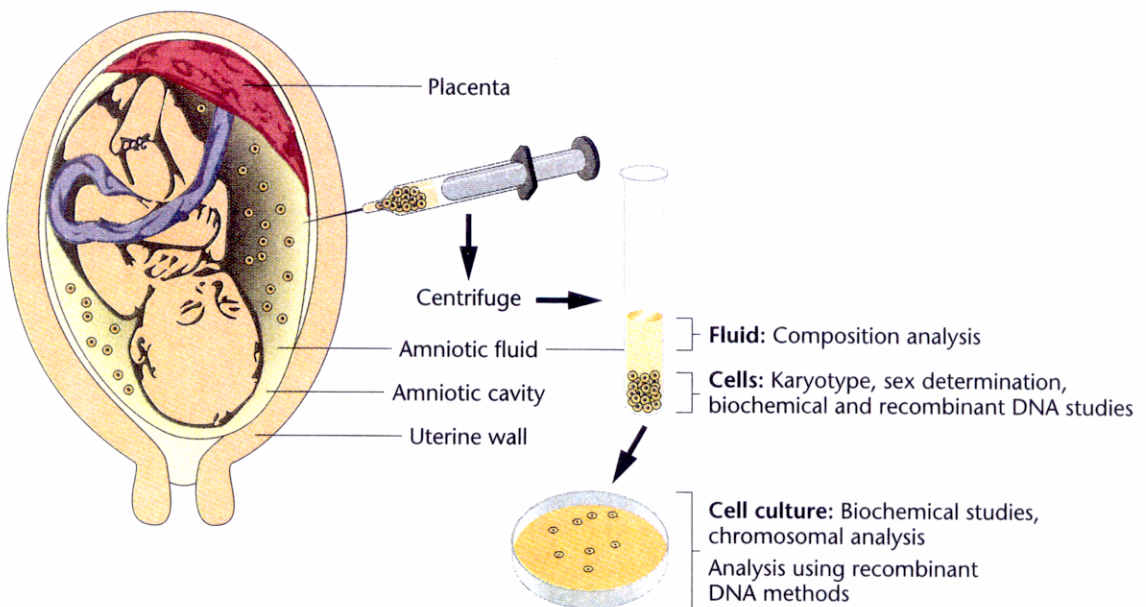
Genotyping of The Future



ASOS CAN BE USED TO DETECT Disease Genes in Single Embryo Cells OR DURING Pregnancy



An eight-cell human pre-embryo.



**FIGURE 21.6** The technique of amniocentesis. The position of the fetus is first determined by ultrasound, and then a needle is inserted through the abdominal and uterine wall to recover fluid and fetal cells for cytogenetic and/or biochemical analysis.



EMBRYO SPLITTING CAN LEAD TO QUADRUPLETS IN PRIMATES

Fig. 1. Embryo splitting and development of non-human primates after embryo transfer. A zona-free eight-cell stage rhesus embryo, fertilized in vitro, is dissociated into eight individual blastomeres by mechanical disruption in  $Ca^{2+}$ - and  $Mg^{2+}$ -free medium. Two dissociated blastomeres are transferred into each of four empty zonae (A), thereby creating the four quadruplet embryos, each with two of the eight original cells (B). Split embryos are scored daily for development and structural normalcy, and embryos showing signs of compaction are selected for transfer 1 to 3 days after splitting. Endocrine profiles are traced daily and implantation is confirmed by ultrasound on day 31 after transfer. A miscarried pregnancy in which the fetus is absent though the placenta appears normal (C), and the quadruplet pregnancy with normal fetal development (D) that resulted in the birth of Tetra (Fig. 2) resulted from the transfer of two quadruplet embryos each to two surrogates. Bar in (A) and (B), 120  $\mu$ m; in (C) and (D), 5 cm.

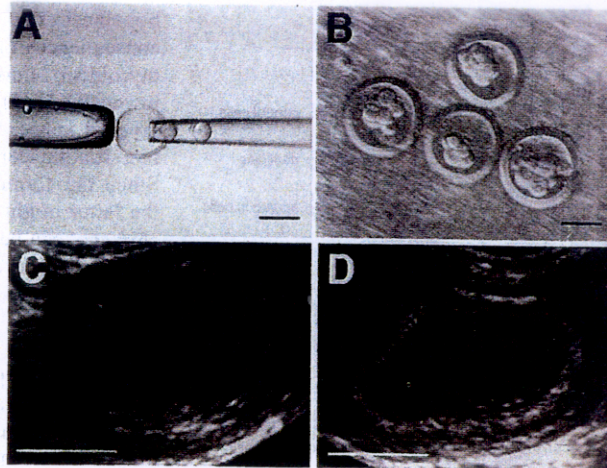


Fig. 2. Tetra, a nonhuman primate quadruplet cloned from an eight-cell embryo by splitting.

Humans? ASO/BABI Test  $\rightarrow$  good embryo  $\rightarrow$  split into 3 (2 cells each)  
 implant 1  $\rightarrow$  daughter  $\rightarrow$  40yo  $\rightarrow$  implant a second (gives birth to her daughter/sister!!  
 Twin!!!



## Social and Ethical Issues Surrounding Preimplantation Embryo Diagnosis

- In 1990, Germany passed a law that prohibits preimplantation embryo testing.
- A 1993 report from Canada's Commission on Reproductive Technologies warns against allowing market forces to determine the use of reproductive technologies. It also calls for creation of a permanent regulatory and licensing body to govern all aspects of the new reproductive practices, including sperm banks and *in vitro* fertilization.
- In 1994, France and Norway passed legislation that limits genetic testing to situations in which the results are medically therapeutic, and authorizes governmental bodies to establish the criteria for defining "therapeutic" in this context. These laws prohibit the use of genetic testing for sex selection and normal trait enhancement.
- In 1994, a U.S. National Institutes of Health advisory panel issued guidelines for federally funded research on embryos. These guidelines allow the use of preimplantation embryo testing for disease diagnosis and accept the practice of determining an embryo's gender to diagnose a sex-linked disease, such as hemophilia A. The guidelines do not accept sex selection for any other reason. An oversight committee

would monitor compliance with the guidelines to ensure the scientific qualifications of federally funded researchers as well as the likelihood that their studies will produce "significant scientific or clinical benefit" that cannot be "otherwise accomplished by using animals or unfertilized gametes."

At the same time, the United States had more than 300 privately run, unregulated *in vitro* fertilization clinics, commonly referred to as IVF Centers. Most of these centers were willing to do whatever a paying client requested, including sex selection and analysis of the genetic susceptibility for complex traits whose inheritance is not yet well understood.

This range of responses to the issues generated by the new reproductive technologies shows a diversity of approaches based on national culture and history. It also reflects international apprehension about the potential for misuse and abuse of the new technologies. Here are some of the main concerns.

### When Should the Tests Be Used?

The couple in our opening story whose firstborn suffered from cystic fibrosis faced a medical problem. Preimplantation diagnosis could help them have a second child unaffected by the disease. With no cure at present for CF and no therapy that allows CF-affected

people to look forward to a life of normal length, this is an example of medically therapeutic testing. Most governmental committees and bodies argue against testing for any other reason, but commercial clinics do not. Moreover, if postnatal therapies for cystic fibrosis, such as nasal sprays that introduce a normal CFTR protein into the respiratory tissues or protocols that insert normal *CF* genes in the cells of the lungs and nasal passages, become available, some medical practitioners may no longer consider preimplantation diagnosis a preferred therapy.

### How Should the Tests Be Carried Out?

The couple in our opening story began by consulting a genetic counselor and then worked with medical practitioners associated with a university laboratory. Most geneticists agree that counseling before a procedure should foster an open discussion of all the issues (including the possibility that the tests might give false negatives); and that long-term follow-up should be part of the process. The preimplantation testing itself, like other forms of genetic testing, should be carried out by highly trained personnel in licensed laboratories. These accredited laboratories operate according to professional standards and have scientific and ethical review boards that monitor all work.

### Who Should Have Access to the Technology?

The combination of *in vitro* fertilization and preimplantation testing cost \$6000 to \$10,000 in 1994. Should the government provide tests for people who cannot afford them? How should society decide this issue? (A related discussion of access to medical technology appears in the Genetics and Society box in Chapter 1.)

### Should Parents Have the Right to Make Any Genetic Decision?

If, for instance, they decide to have a child affected by a genetic disease, should they bear all financial responsibility for its care, or should some form of universal health insurance provide help?

### Who Should Have Access to Test Results?

Just the parents? The parents and eventually the child? The parents, the child, and certain community institutions, such as schools? Some combination of these plus commercial enterprises such as insurance companies and places of employment? (We discuss this same question of privacy in relation to other types of genetic testing in the Genetics and Society boxes in Chapters 1 and 2.)

### What Constitutes a Human Individual?

Cultural and religious beliefs, rather than scientific knowledge and social customs, are the basis for answers to this question. Some people see preimplantation diagnosis as an alternative to abortion that allows a couple to make a decision before pregnancy, and thus a life, begins. Others argue that even at the eight-cell stage, a preimplantation embryo is the equivalent of a human being, and rejection of an embryo is the equivalent of killing a human being.

Although there are no simple solutions to these complex issues, geneticists around the world agree on the need for continuous discussion and tight oversight of the development of the new reproductive technologies.



# Genetic Testing Issues

- ① Privacy?
  - Who should know - spouse, children, employer, insurance company? *if carrier?*
  - Who should tell - person, Dr., testing lab.
  - Results when insurer's know/employer's know?
  
- ② Voluntary vs. Mandatory Testing?
  - What is precedent? State laws?
  - Results - Sickle-cell / Cystic Fibrosis PKU?
  - Test for my reason - information? Eugenics?
  
- ③ Regulation?
  - Who monitors tests? Over-the-counter
  - Who licenses testing labs & ensures quality/accuracy?
  - Who can have access to tests? Costs?
  
- ④ Health Insurance?
  - Who pays for genetic diseases?
  - If known before birth? Carriers?
  - How assess rates/prisks?
  - Will Society pay for genetically "inferior" if testing available?
  - Community Rating? Universal Health Insurance.
  
- ⑤ Penetrance/Expressivity Problem?
  - What to do if disease not manifested 100%? How deal with information?
  - Insurance Issues?



# Genetic Testing Issues Continued

⑥ What laws govern Parental Rights to Test & Perhaps use BABI Test to Enhance?  
*who protects genetic rights of zygote? does it have any?*

⑦ How use Association Studies that Test for Complex Traits?  
*How use probabilities for "getting" the disease? who gets disease? we all carry genes for some disease? Environmental factors?*

⑧ What does history tell us?  
*Sickle-Cell Testing!  
Cystic Fibrosis Testing?  
Tay-Sachs Testing?  
HMO's? Employers?*

⑨ What Laws Protect us from Genetic Discrimination?  
*Any? America's Disabilities Act. Carriers?*

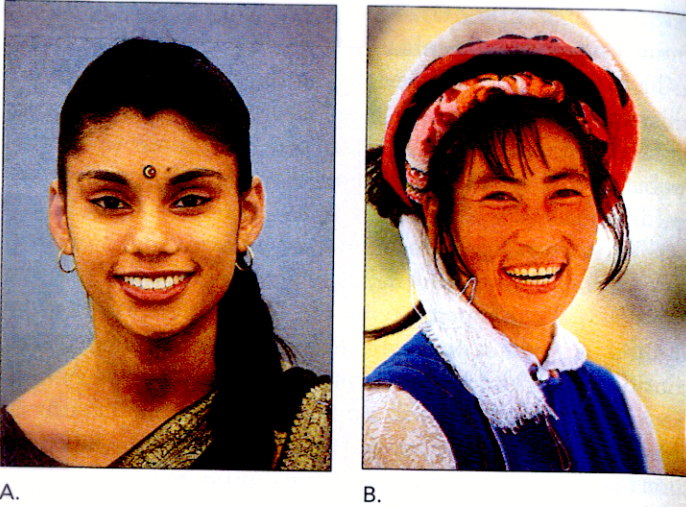
⑩ What about Testing for Enhancement/Eugenics?

# Genetic Testing Issues

A clinically-oriented  
list

- ① Diagnostic genetic testing
- ② Predictive / Presymptomatic Genetic Testing
- ③ Genetic Testing of Children - diagnostic vs. predictive
- ④ Late-onset Disorder pre-symptomatic testing
- ⑤ Genetic Testing & Privacy
- ⑥ Genetic testing & Insurance
- ⑦ Over-the-Counter Testing
- ⑧ Population Screening for carriers
- ⑨ Newborn Screening (e.g., PKU)
- ⑩ Pre-Natal Genetic Screening
- ⑪ Outcomes of Genetic Counseling

Are There  
Human Races  
or  
Human Beings?



**Figure 14-4** People from different geographic regions vary in such traits as height, blood type, skin color, and facial features. A. An Indian woman. B. An ethnic minority woman from China. (A, Superstock; B, Paul Greblunas/Tony Stone Images)

### What Are Human “Races”?

We all know that the human species varies in appearance and in physiology geographically. People of Indian descent, for example, are recognizably different from those of Chinese descent. We can look at the shape of the nose, the eyes, and the ears, for example, and we see differences (Figure 14-4). We can look at the distribution of individual alleles and see differences. Fifty-one percent of Nigerians have type O blood, compared to only 30 percent of Japanese. Twenty percent of Russians have type B blood, while the Amerindians of Lima, Peru, have no detectable levels of type B blood at all.

Nineteenth-century anthropologists struggled to classify human groups into a few major races. Some systems identified only 12 races, while other systems listed 30 or more. One problem was that no matter how anthropologists classified humans, there always seemed to be tribes or nations that would not fit into any known group. The Basques, who live in the Pyrenees mountains between France and Spain, for example, appear European. Yet their language and culture are unlike any other in the world, and some researchers once argued that they are direct descendants of Stone Age Europeans. Similarly, the Bushmen are unique among African groups in both appearance and physiology (Figure 14-5).

A more serious problem with the grouping of humans into races is that most groups do *not* stand out from those around them; they blend. Because groups of humans inevitably mix, through migration, warfare, and trade, human “races” are never pure. Both the Japanese and British, for example, take pride

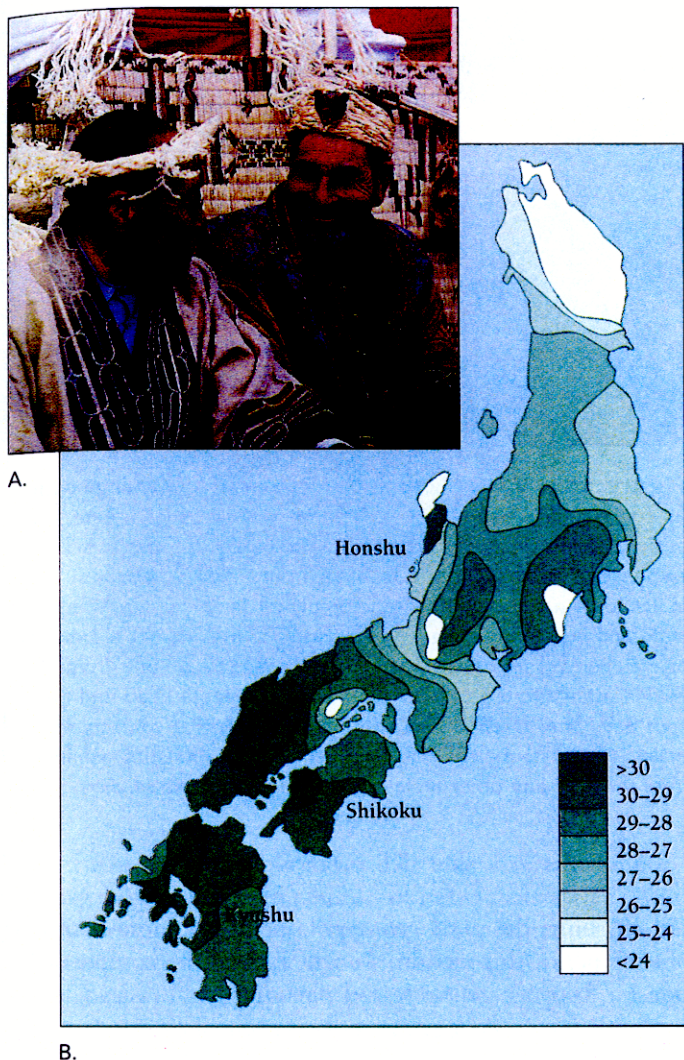
in the purity of their island races. Yet the Japanese are a grade mixture of Korean and Ainu north islanders (a people of possibly European descent). This mix shows up in the distribution of blood types from one end of Japan to the other (Figure 14-6).

The British are even more of a melting pot than the Japanese. The Bronze Age Beaker Folk mixed with the Indo-European Celts in the first thousand years B.C. In the next thousand years, the Angles, the Saxons, the Jutes, and the Picts arrived, followed by the Vikings and their descendants, the



**Figure 14-5** Classifying humans into a few discrete races has been unsuccessful. Named races frequently include markedly distinct peoples. A. A Bushman from Namibia. B. A rubber plantation foreman from the Ivory Coast. (A, M.P. Kahl/Photo Researchers, Inc.; B, Charles O. Cecil/Visuals Unlimited)





**Figure 14-6** Variation in blood group A in modern Japan. A. Even the Japanese, a relatively homogeneous island race, show variation that demonstrates intermarriage with other groups. Populations closest to mainland Korea have the greatest concentration of A alleles. Populations closest to Hokkaido have the lowest concentrations of A alleles. B. In Hokkaido lives a remnant population of Ainu, sometimes called the “hairy Ainu.” The Ainu, who were once a white minority in Japan, are considered primitive by other Japanese. The Ainu had white skin, abundant body hair, and round eyes. Descendants of Causasoid peoples from northern Asia, the Ainu once lived on all four of Japan’s major islands. Today they live only in the north. Intermarriage and cultural assimilation by the Japanese have made the traditional Ainu virtually extinct. (A, Superstock; B, from *Human Diversity* by Lewontin © 1982 by Scientific American Library. Used with permission of W.H. Freeman and Company)

French Norman invaders. In the last century, Africans, Indians, Pakistanis, and others have lent spice to this already heady mix.

If the Japanese and the British, seemingly isolated by geography, are well mixed, most mainland groups represent a true continuum of traits. In fact, studies of the distributions of different alleles have convinced researchers that human

rac<sup>es</sup>—in the biological sense—do not exist. This is because, in humans, genetic variation within populations is greater than that between nations or races. Of all human genetic variation, 85 percent is variation among the individuals within a country or a continent. Another 6 percent is variation among populations from the same continent. Only about 9 percent of all DNA reflects genetic differences among peoples (“rac<sup>es</sup>”) from different continents. The greatest genetic variation among humans is found in Africa. If a disaster killed everyone on Earth except for those living in Africa, the human species would still retain at least 91 percent of its genetic diversity. Less than 9 percent of all genetic diversity would be lost.

In practice, we focus on the small numbers of traits (for example, skin color and eye shape) that vary geographically—a subset of the 9 percent—and we use just those few traits to identify groups of people who differ from us more in their cultural practices than in their genetic constitutions.

Recent work, for example, shows that many differences in skin and hair color reflect variations in a single gene. That gene specifies the structure of a protein, called MC1R. MC1R affects our response to a hormone that regulates the balance of different types of skin pigments (melanins). Caucasians who tan well, for example, have the same form of MC1R that is present in Africans.

Researchers suggest that variations in skin color represent adaptations to different amounts of sunlight. A mere handful of variants are probably responsible for the most obvious traits that have historically been used to distinguish human “rac<sup>es</sup>.” As geneticists Mary Claire King and Kelly Owens state, “The myth of major genetic differences across “rac<sup>es</sup>” is . . . worth dismissing with genetic evidence.”

As we consider some peculiarities of Brazilian history and social structure, we can construct a model to explain why Color should indeed be a poor predictor of African ancestry at an individual level. Most Africans have black skin, genetically determined by a very small number of genes that were evolutionarily selected (5, 6). Thus, if we have a social race identification system based primarily on phenotype, such as occurs in Brazil, we classify individuals on the basis of the presence of certain alleles at a small number of genes that have impact on the physical appearance, while ignoring all of the rest of the genome. Assortative mating based on Color, which has been shown by demographic studies to occur in Brazil (22, 33), will produce strong associations among the individual components of Color. Indeed, we detected the presence of such positive associations at highly significant levels in the Queixadinha population (data not shown). On the other hand, we expect that any initial admixture association between Color and the PSAs will inevitably decay over time. It is easy to see how this combination of social forces could produce a population with distinct Color groups and yet with similar levels of African ancestry. Let us take as an example, the historically common Brazilian mating of a white European male with a black African slave woman: the children with more physical African features would be considered black, whereas those with more European features would be considered white, even though they would have exactly the same proportion of African and European alleles. In the next generation, the light-skinned individuals would assortatively tend to marry other whites and conversely the darker individuals would marry blacks. The long-term tendency would then be for this pattern to produce a white group and a black group, which would, nonetheless, have a similar proportion of African ancestry.

Our study makes clear the hazards of equating color or race with geographical ancestry and using interchangeably terms such as white, Caucasian, and European on one hand, and black, Negro, or African on the other, as is often done in scientific and medical literature (34, 35).

ONLY A SMALL Proportion of Human Gene Diversity Due to Differences in "RACES"

| Gene             | Total $H_{species}$ | Proportion                        |                                  |               |
|------------------|---------------------|-----------------------------------|----------------------------------|---------------|
|                  |                     | Any population Within Populations | Within Races between Populations | Between Races |
| Hp               | .994                | .893                              | .051                             | .056          |
| Ag               | .994                | .834                              | —                                | —             |
| Lp               | .639                | .939                              | —                                | —             |
| Xm               | .869                | .997                              | —                                | —             |
| Ap               | .989                | .927                              | .062                             | .011          |
| 6PGD             | .327                | .875                              | .058                             | .067          |
| PGM              | .758                | .942                              | .033                             | .025          |
| Ak               | .184                | .848                              | .021                             | .131          |
| Kidd             | .977                | .741                              | .211                             | .048          |
| Duffy            | .938                | .636                              | .105                             | .259          |
| Lewis            | .994                | .966                              | .032                             | .002          |
| Kell             | .189                | .901                              | .073                             | .026          |
| Lutheran         | .153                | .694                              | .214                             | .092          |
| P                | 1.000               | .949                              | .029                             | .022          |
| MNS              | 1.746               | .911                              | .041                             | .048          |
| Rh               | 1.900               | .674                              | .073                             | .253          |
| ABO              | 1.241               | .907                              | .063                             | .030          |
| Mean $\bar{X} =$ |                     | .854                              | .083                             | .063          |

MORE Genetic diversity within a Population than between!!!

Due to small # genes

Source: R. C. Lewontin, *Genetic Basis of Evolutionary Change* (Columbia University Press, 1974).

SAME POPULATION     
 SAME RACE     
 DIFFERENT RACES  
 0.854                      0.083                      0.063

Note: 85% of Human Genetic Variation occurs  
 ① within Populations between individual people irrespective of "race"

② Remaining Variation (15%) split evenly between different populations (geographies) of same "race" (8%) & between different "races".

③ only 6% of Human Genetic Diversity is due to differences Between Races!  
of the 25% Total Polymorphisms



# CONCLUDE

① If 85% of human genetic variation occurs between individual people within any given population (localized).

② And if only 7% of human genetic variation occurs between races (naïve allele specific to a race)

③ Then losing all "races" except one retains 93% of human genetic variation!!!!

$$[85\% + (15\% - 7\%)] = 93\%$$

85% genetic variability = between individuals within population

8% genetic variability = between different populations of same race

7% genetic variability = between races

Humans highly heterozygous or hybrids!

④ Genetic Variability re-occurring all the time by mutation!



# What is a "Race"?

① Localized or Inbred Population that has a higher frequency of alleles at a very small number of gene loci

But does this definition hold up?

→ affecting a few physical features - !!!

② High frequency alleles of one "race" are present at lower frequency in other races - that is all humans have the SAME genes - only differ in FORM

③ Heterozygosity (Variation) high in all human populations - NONE homozygous at all loci!

④ Most genes in humans identical in all individuals + populations

∴ What is a "pure" race? / Master Race: NOT representative of most gene loci

⑤ Genes affecting Variation in skin color, hair form, facial features

"Race" Classification is Arbitrary & NOT Science-Based

**RACE BY RESISTANCE**  
 Traditionally we divide ourselves into races by the twin criteria of geographic location and visible physical characteristics. But we could make an equally reasonable and arbitrary division by the presence or absence of a gene, such as the sickle-cell gene, that confers resistance to malaria. By this reckoning, we'd place Yemenites, Greeks, New Guineans, Thai, and Dinkas in one "race," Norwegians and several black African peoples in another.

could define "race" by a variety of criteria!

genes -  
 geographic population. After in a small % of genes giving rise to phenotypic diversity

but -  
 only a small % of total gene variation



PEOPLE WHO POSSESS AN ANTIMALARIA GENE...

AND THOSE WHO DON'T.

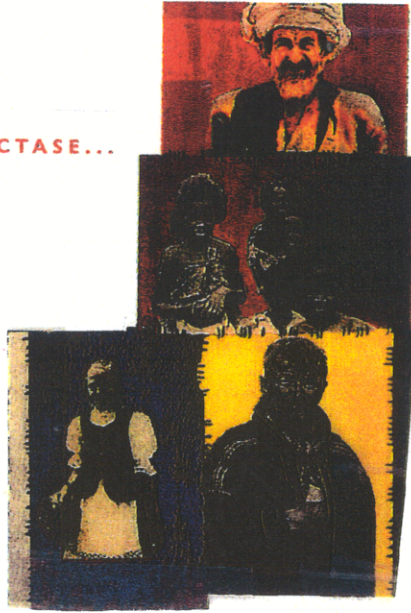




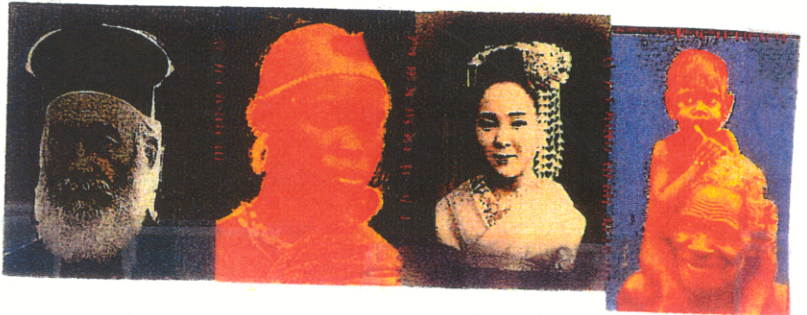
## RACE BY DIGESTION

We could define a race by any geographically variable trait—for example, the retention in adulthood of the enzyme lactase, which allows us to digest milk. Using this as our divisive criterion, we can place northern and central Europeans with Arabians and such West African peoples as the Fulani; in a “lactase-negative race,” we can group most other African blacks with east Asians, American Indians, southern Europeans, and Australian aborigines.

PEOPLE WHO POSSESS LACTASE...



AND THOSE WHO DON'T.



## RACE BY FINGERPRINTS

Probably the most trivial division of humans we could manage would be based on fingerprint patterns. As it turns out, the prevalence of certain basic features varies predictably among peoples: in the "Loops" race we could group together most Europeans, black Africans, and east Asians. Among the "Whorls" we could place Mongolians and Australian aborigines. Finally, in an "Arches" race, we could group Khoisans and some central Europeans.

## ARCHES



## RACE BY GENES

One method that seems to offer a way out of arbitrariness is to classify peoples by degree of genetic distinctness. By this standard the Khoisans of southern Africa would be in a race by themselves. African blacks would form several other distinct races. All the rest of the world's peoples—Norwegians, Navajo, Greeks, Japanese, Australian aborigines, and so on—would, despite their greatly differing external appearance, belong to a single race.

But clearly only 6% of genetic diversity accounted for by "race" — what genes/traits used!?



# CONCLUSION

- ① Races are Arbitrary "Entities"  
Established by using "Arbitrary" Criteria  
→ Can be Culturally "generated" — denied! leading to  
disastrous social consequences!
- ② Yes — there is genetic diversity between  
"race" or relatively "inbred"  
geographical populations → lead to  
physical differences.
- ③ Physical differences due to very small #  
of genes —  
↓ ↓ ↓ ↓
- ④ Molecular Biology shows that there are  
only minor differences between genomes of  
different people or groups of people —  
*The Unity Far Exceeds the Differences  
@ Gene Level*  
Political Consequences? Unity Emphasis!  
We are ALL The SAME  
BUT Different!! You now know why!

How did we get into serious "Trouble" with the "Race" Concept?



- Linnaeus 1758
- Blumenbach 1795
- "Inventor" of modern Racial Classification
- Caucasian - Europe, Asia, Africa (adjacent)
- Mongolian - other Asian inhabitants
- Ethiopian - dark-skinned Africans
- American - Native populations of new world
- Malay - Polynesians, Australian abor

Linnaeus - Neutral geography-based classification (4 "races")

Johan Friedrich

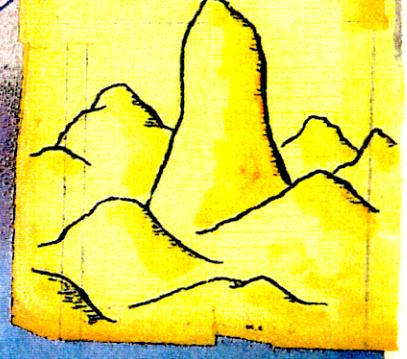
Blumenbach - All "races" originated from one place - origin, but subjectively stated that European or Caucasian (he named this "race") was the supposed most "beautiful" race - even though he felt races were equal in all respects & "argued" with people who didn't! A contradiction!  
5 "races" & Qualitative Judgment of which the most "beautiful"  
 collected skulls!!!



Blumenbach Changed Linnaean Neutral System to a hierarchical system of departure

from European Ideal (His) of Beauty

Mount CAUCASUS



Consequences of Blumenbach's Professorial Ideas?

Nº 1

CAUCASIANS  
Original  
primal  
"race"



Native Americans



Malays  
MELANESIAN  
AFRICANS



Mongolians



Africans  
Ethiops



1795