

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) can be used to test whether embryos have a defect before they are implanted into the mother. The first step is in vitro fertilization (IVF), where eggs are harvested from the woman and mixed with sperm in a culture dish. As the fertilized embryos develop, they can be inserted into the woman. For couples that are having a difficult time conceiving, this approach can sometimes result in pregnancy. For older women at higher risk for aneuploid fetuses or for couples at risk for a genetic disease, the cells of the developing embryos can be removed from the embryo and tested for abnormal chromosome number or the genetic disease trait. The cells in the early embryo are referred to as blastomeres. At the 8-cell stage a small glass capillary pipette can be inserted into the embryo and 1-2 cells can be sucked up into the pipette. These cells can then be tested. There are two types of tests that we will consider: fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR).

Fluorescence in situ hybridization (FISH)

Specific DNA sequences are produced that are labeled with a fluorescent dye. These labeled DNA “probes” are then incubated with the blastomeres. The labeled probes anneal to the specific sequences. Different DNA probes can be labeled with different colored dyes. The example that we used in class employed several probes labeled by different colors to detect several chromosomes. This approach can be used to detect aneuploid embryos. Only embryos with a normal number of chromosomes would be used for fertilization.

Polymerase chain reaction (PCR)

PCR is one of the most important techniques available in the study of genetics and was developed by a former Cal graduate student, Kerry Mullis. Professor Wilt has already covered PCR, but if you need to review the technique, it is described on page 270-273 of the textbook. Because PCR can be used to amplify any DNA sequence, the DNA from blastomeres can be amplified to screen embryos for genetic diseases. If a couple is at risk for having a child with sickle cell or Tay-Sachs disease, for example, the sequences of the hemoglobin or hexosaminidase gene that contain the mutation can be amplified from the blastomeres. This will identify the embryos that are homozygous for the mutation, heterozygous for the mutation and homozygous for the normal sequence. Only embryos that are normal can then be transferred to the mother.

Genetic Counseling (read pages 175-188)

Couples that are planning to have a child will meet with a genetic counselor if they are in a high-risk group. These groups include couples that have experienced multiple miscarriages, that have a family history of a genetic disease, that have a child with a genetic disease or that are members of a group that are at risk for a particular disease.

Genetic counselors help the couple construct family trees or pedigrees. They can order genetic tests and evaluate the results, and they can help the couple reach decisions about

the best course to take.

Construction of a pedigree can often identify a particular disease that runs in the family, and the genetic counselor will attempt to determine the mode of inheritance of the disease. If this can be done, the counselor can determine the probability that a parent is a carrier for the disorder and the probability that a child will be affected. In cases where the genetic disease is understood molecularly, a genetic test can be used to determine whether the parents carry the mutant allele. From a pedigree, the counselor will ask whether the trait is dominant or recessive, autosomal or X linked. We will consider the four types of mutations.

Autosomal recessive: By far the most common type of inherited mutation that affects health is autosomal recessive. We discussed this type of trait in the last lecture.

Autosomal dominant: Like autosomal recessive traits, autosomal dominant traits are expressed by males and females with equal frequency. The trait does not skip generations if it is completely penetrant. Hence, if neither parent is affected, the children will not be affected. Huntington's disease is an example. This is a progressive disorder of the central nervous system that affects 1 in 10,000 individuals in the U.S. The disorder usually begins to affect adults between the ages of 30-50 years old. Initial symptoms include irritability, clumsiness, depression and forgetfulness. These progress to more severe mental and physical impairment that leads to death.

X-linked recessive: Males usually express X-linked recessive traits. The sons of carrier females have a 50% chance of being affected. Affected males do not have affected children. Like autosomal recessive traits, the trait usually skips generations. Hemophilia is an X-linked recessive disorder that affected the royal families of Europe.

X-linked dominant: Disorders that are X-linked dominant are rare. Daughters, but not sons, can inherit the trait from their fathers. Daughters and sons can inherit the trait from their mothers. Like an autosomal dominant trait, the trait is present in each generation or is lost. Congenital Generalized Hypertrichosis is a strange medical syndrome that is inherited as an X-linked dominant trait. Affected individuals have hair growing on parts of their body that is usually devoid of hair. Some have speculated that this genetic syndrome could have contributed to the werewolf myth. Scientists are interested in this atavistic syndrome as understanding the gene that is mutated could shed light on how during our evolution we lost hair from parts of our body.

Eugenics (pp 314-315 in text)

Humans have been selectively breeding plants and animals for 10,000 years. In 1883, Sir Francis Galton, a British scientist, developed the idea that human traits could also be improved by controlled breeding. He advocated for an approach that would allow "the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable." Eugenics was born. Eugenics caught on in the US in the early 1900s. Charles Davenport, a Harvard-trained zoologist, started the Eugenics Record Office (ERO) at Cold Spring Harbor in Long Island. The ERO collected pedigrees and attempted to define

the genetics of human characteristics. In 1910, Davenport published a book "Eugenics: The Science of Human Improvement by Better Breeding," where he discusses both how both positive and negative traits could be bred. The idea of selecting for positive or fit traits led to silly "Fitter Family Contests" at state fairs. But the idea of negative selection, removing unfit individuals from the population, led to sterilization laws. The first law was passed in Indiana in 1907 and by 1924, 18 states had sterilization laws. These allowed for the sterilization of unfit individuals, primarily individuals with mental problems and epileptics.

In 1924, a Virginia court heard the case of Bell vs Buck. John Bell, the superintendent of the Virginia Colony for Epileptics and Feeble-minded where Carrie Buck was living, brought the case for her sterilization. The colony had been sterilizing patients and needed a law to allow the practice. Several witnesses, including employees of the ERO, claimed that Carrie was feeble-minded. The case was argued all the way to the Supreme Court, where Oliver Wendell Holmes presented the majority opinion in support of the colony. Carrie Buck was the first person sterilized under the new law on October 19, 1927. One of the reasons that Carrie was viewed as feeble-minded is she had an illegitimate child, Vivian. She was considered promiscuous, which was thought to be a sign of low intelligence, even though the child was the result of a rape. Carrie, her mother and her child were all considered to be feeble-minded. Carrie's daughter turned out to be an A student.

By 1935, 30 states had eugenic sterilization laws, and 21,000 people had been sterilized. Mental patients and epileptics could be sterilized, and patients were often told that they were having surgery but not that they were being sterilized. In 1942, the Supreme Court struck down a law allowing forced sterilizations of criminals. Yet, sterilization continued into the 1970s. In 2002, Virginia Governor Mark Warner officially apologized for the Buck vs Bell case, stating that the "eugenics movement was a shameful effort in which state government never should have been involved."

The science behind eugenics was largely discredited by the 1930s. In 1939, the Eugenics Records Office closed. But Eugenics was not dead. The seeds for the eugenics movement in Germany were planted in 1927 with the Kaiser Wilhelm Institute of Anthropology, Human Genetics, and Eugenics in Berlin. The Rockefeller Foundation funded the German Institute. In 1933, at the beginning of World War II, Hitler charged the medical profession with the task of implementing a national program of race hygiene, which permitted the sterilization of feeble-minded, mentally ill, epileptics, and alcoholics. Within a year, more than 50,000 sterilizations were ordered. Eventually, it became more economical to kill people instead of sterilizing them. The rationale establishing the purity of the Aryan race that Hitler developed came from his reading of the eugenics literature. The mechanics of mass killing used in the Nazi concentration camps were first developed in institutions for the mentally ill.