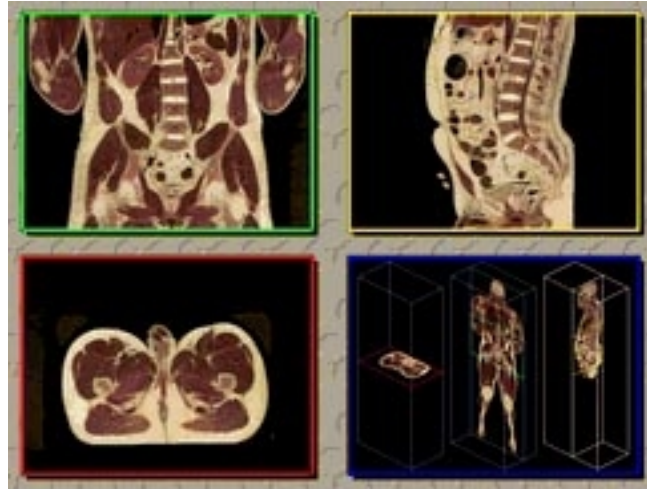


Male-Specific Diseases



Main Screen of Visible Human Explorer (Visible Man), Visible Human Project, National Library of Medicine.

What kind of biological mechanisms lie behind the formation of the different genders? Some scientists now conclude that cells from male and female organisms differ in ways that result from chromosomes, not hormones, and believe that every organ in the body — not just those related to reproduction — has the capability to respond differently on the basis of sex. For example, unique or gender-specific features of human biology have been found in skin, bone, heart and brain, to name just a few. In addition, many diseases are expressed differently in men and women.

Researchers are working to identify and understand differences related to the cause, prevention, treatment and impact of diseases and conditions which primarily affect men or women, or which affect men and women differently — with particular emphasis on gender and sex as key variables. Such differences can have a significant impact on the prevention, diagnosis and treatment of disease in both sexes.

Alport syndrome

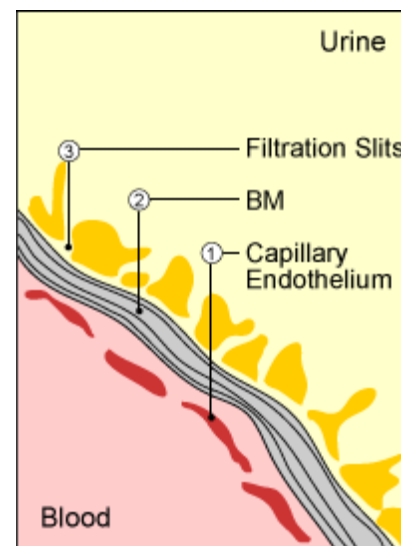
Alport syndrome (AS) is a genetic disease in which a collagen mutation affects the kidneys, the ears, and the eyes. The syndrome was named for Dr. Alport who in 1927 described a British family in which many members developed renal disease as well as deafness. He noted that affected men in the family died as a result of their kidney problems, whereas females were less affected and lived until old age.

It is now known that most cases of AS are caused by a mutation in the collagen gene *COL4A5*. This gene encodes for the alpha-5 chain of collagen type IV and is located on the X chromosome. Because women have two X chromosomes (XX), affected women usually have one normal copy and one abnormal copy of the gene. Men only have one copy of the X chromosome (XY). If they inherit the *COL4A5* mutation, this abnormal copy of the gene is the only copy they have and the effects are more severe.

Type IV collagen is found in basement membranes (BM), which are selective barriers between cells. In the kidney, the glomerular BM filters waste products into the urine while keeping useful molecules within the blood stream. In AS, the abnormal collagen disrupts this filter, leading to the loss of proteins and red blood cells into the urine. Blood in the urine (hematuria) is a sign common to

all types of AS. In the ear, abnormal collagen in the cochlea results in a progressive deafness in which the ability to hear high tones is lost first. Abnormal collagen can also affect the lens of the eye.

Currently, renal failure due to AS is treated by dialysis or, for some, renal transplantation. However, gene therapy may one day be able to provide a cure for AS by replacing the faulty *COL4A5* gene.



Filtration barrier in the kidney.

To enter urine, waste molecules pass through: 1, gaps between the lining of the blood vessel; 2, the BM; and 3, slits between epithelial cells. In AS, the BM deteriorates, allowing proteins and red blood cells to enter the urine.

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=alport+syndrome&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=461675&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=301050] catalog of human genes and disorders

Websites

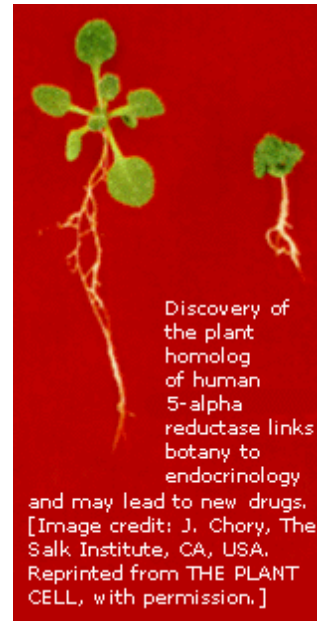
National Kidney Foundation [<http://www.kidney.org/general/atoz/content/alportsyn.html>] further information

GeneReviews [www.geneclinics.org/profiles/alport] a medical genetics resource

Male pattern baldness

5-alpha reductase is an enzyme that was first discovered in the male prostate. Here it catalyzes the conversion of testosterone to dihydrotestosterone, which in turn binds to the androgen receptor and initiates development of the external genitalia and prostate. The gene for 5-alpha reductase has been mapped to chromosome 5.

More recently, 5-alpha reductase was found in human scalp and elsewhere in the skin, where it carries out the same reaction as in the prostate. It is thought that disturbances in 5-alpha reductase activity in skin cells might contribute to male pattern baldness, acne, or hirsutism. The discovery of a plant homolog of human 5-alpha reductase may lead to new drugs, and the race is now on to find inhibitors of 5-alpha reductase.



Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=SRD5A1&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507201&org=1] related sequences in different organisms

The literature

Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=184753] catalog of human genes and disorders

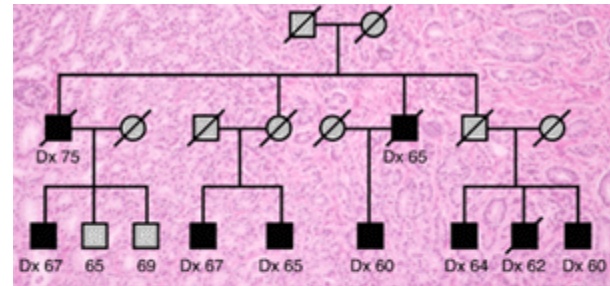
Prostate cancer

The second leading cause of cancer death in American men, prostate cancer will be diagnosed in an estimated 184,500 American men in 1998 and will claim the lives of an estimated 39,200. Prostate cancer mortality rates are more than two times higher for African-American men than white men. The incidence of prostate cancer increases with age; more than 75% of all prostate cancers are diagnosed in men over age 65.

Despite the high prevalence of prostate cancer, little is known about the genetic predisposition of some men to the disease. Numerous studies point to a family history being a major risk factor, which may be responsible for an estimated 5-10% of all prostate cancers.

One of the most promising recent breakthroughs may be the discovery of a susceptibility locus for prostate cancer on chromosome 1, called HPC1, which may account for about 1 in 500 cases of prostate cancer. The next step will be to clone the gene. Once researchers have the sequence, they will be able to search the databases to compare the

HPC1 sequence to previously characterized proteins from both humans and other animals. This should provide clues as to the function of HPC1 in the cell, and suggest potential starting points to find drug targets.



Hereditary prostate cancer (HPC) accounts for about 10% of all prostate cancer, and HPC1 is estimated to account for approximately 34% of these hereditary cases.

Background: histological section of a patient with HPC. Foreground: pedigree of a typical family demonstrating multiple affected individuals (solid boxes) whose disease links to the HPC1 region on chromosome 1. [With thanks to Jeffrey Trent and colleagues, NIHGR, NIH for supplying the image.]

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=prostate%20cancer&ORG=Hs&V=0] collection of gene-related information

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OMIM catalog of human genes and disorders

Websites

Fact sheet [www.nhgri.nih.gov/DIR/LCG/PROSTATE/pros_home.html] from the National Human Genome Research Institute, NIH

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania

GeneClinics [www.geneclinics.org/profiles/brca1/index.html] a medical genetics resource

SRY: Sex determination

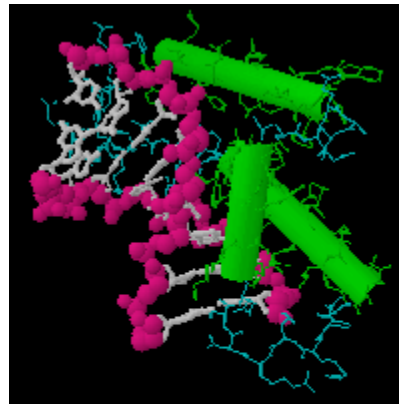
We have come a long way in our understanding of sexual dimorphism since 355 BC. In those days, Aristotle suggested that the difference between the two sexes was due to the heat of semen at the time of copulation: hot semen generated males, whereas cold semen made females. Thankfully, we now know a little more about the molecular events of sex determination.

Usually, a woman has two X chromosomes (XX) and a man one X and one Y (XY). However, both male and female characteristics can sometimes be found in one individual, and it is possible to have XY women and XX men. Analysis of such individuals has revealed some of the molecules involved in sex determination, including one called SRY, which is important for testis formation.

SRY (which stands for sex-determining region Y gene) is found on the Y chromosome. In the cell, it binds to other DNA and in doing so distorts it dramatically out of shape. This alters the properties of the DNA and likely alters the expression of a number of genes, leading to testis formation. Most XX men who lack a Y chromosome do still have a copy of the SRY region on one of their X chromosomes.

This copy accounts for their maleness. However, because the remainder of the Y chromosome is missing they frequently do not develop secondary sexual characteristics in the usual way.

Since human SRY is similar to SRY of mice, a model of SRY function has been developed in mice. This has been particularly important in discovering the interactions of SRY with other genes in male sex determination.



SRY (green) binds to DNA (pink) and distorts its shape. In so doing, it regulates genes that control the development of the testes.

Important Links

Gene sequence

Genome view see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=SRY&ORG=Hs&V=0] collection of gene-related information

BLink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507225&org=1] related sequences in different organisms

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Research articles online full text

Books online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=480000] catalog of human genes and disorders