History

Hemophilia was first described by a physician named Albucasis between 936 and 1013 AD in a medical book he published. He described the disease affecting males and causing major bleeding, even in small wounds. In the 1930's, it was believed hemophilia and other bleeding disorders were caused by platelets having defects, but Harvard researchers found that adding plasma would help blood clotting. In 1944, Dr. Pavlosky gave blood from two different hemophilia patients to each other, which helped the clotting. He discovered that each patient was deficient in a different type of protein. This meant there are two types of hemophilia: Hemophilia A and Hemophilia B. In 1965, Dr. Judith Pool discovered that thawing blood plasma left a precipitate of Factor VIII, which could be used to help clotting deficiencies. This became available in powder form by the 1970's. Unfortunately in the 1980's, it was found that blood treatments given to hemophilia patients could contain HIV, which led to many contracting the disease. In the 1990's treatments became better and safer. A recombinant factor VIII and IX were approved by the FDA. Today, preventative medications are used before a bleeding episode occurs.

Support

Besides Hemophilia Treatment Centers, there are many groups that seek to support and educate hemophilia patients.

National Hemophilia Foundation

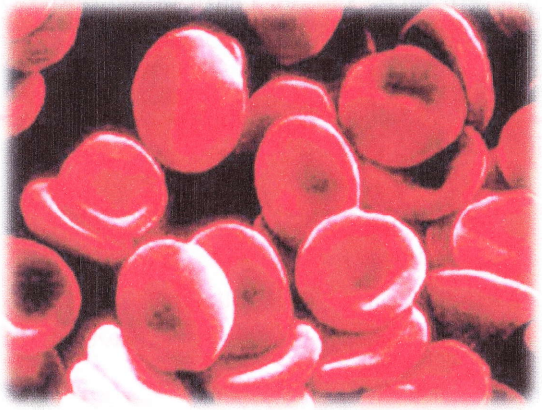
<http://www.hemophilia.org>

World Federation of Hemophilia

<http://www.wfh.org>

Those diagnosed with Hemophilia A (factor VIII deficiency) or Hemophilia B (factor IX deficiency), which are both X-linked recessive disorders, have multiple treatment options available that can either replace or help the body produce the deficient clotting factors. For those who have not been diagnosed, it is important to seek medical attention and advice if there is family history or if there is an episode of bleeding that does not stop for an extended period of time or leads to joint or internal pain.

Hemophilia



An X-linked recessive blood disorder

Clinical Features

Hemophilia is an X-linked recessive disorder affecting the blood's ability to clot.

There are clotting factor proteins in blood which help to stop bleeding. There are 13 different factors in all. Hemophilia patients have very little or no factor proteins present in their blood.

Symptoms include:

- Bleeding and excessive bleeding
- Bruising
- Bleeding into joints and joint pain
- Prolonged bleeding from wounds
- Blood in urine and stool
- Internal bleeding
- Death if bleeding cannot be stopped or if it affects a vital organ

There are two types of hemophilia: Hemophilia A and Hemophilia B. Hemophilia A occurs in 85% of those with hemophilia, making it the most common type. It is caused by a deficiency or lack of the factor VIII protein. Hemophilia B occurs in 15% of patients with hemophilia. It is caused by a deficiency or lack of the factor IX protein.

Diagnosis

To diagnose hemophilia, the doctor will look at the patient's personal medical history, family medical history, perform an examination, and do blood tests. One does not often suspect they have hemophilia until they have a bleeding episode or have family members affected.

The blood tests, also called a coagulation study, are designed to see the levels of the clotting factors and determine how long it takes for the patient's blood to clot. These will determine if the patient has the disorder, the type, and the severity of the condition. A mild case has 5 to 30% of the normal factor, a moderate case has 1 to 5%, and a severe case has less than 1%. Tests include partial thromboplastin time (PTT), normal prothrombin time, normal bleeding time, normal fibrinogen level, and a factor IX or VIII test.

Pregnant women that are carriers of hemophilia can have their child diagnosed within 10 weeks of becoming pregnant. There is also a "preimplantation diagnosis" method where a woman who is a carrier can have some of her eggs extracted and fertilized. The doctor will then select an embryo that does not have hemophilia and implant it in the patient. About one-third of babies diagnosed with hemophilia have no family history.

Treatment and Management

For those diagnosed with hemophilia, there are hemophilia treatment centers. These give support to those affected, including blood treatments, therapists, and education relating to hemophilia.

Hemophilia is treated using replacement blood clotting factors, which are injected into the patient's vein. The two main types are Plasma-Derived Factor Concentrates and Recombinant Factor Concentrates. The Plasma-Derived treatment contains clotting factors, antibodies, and albumin and comes directly from human plasma. It is tested and purified, then freeze-dried for use. The Recombinant treatment, which was approved by the FDA in 1992, is genetically engineered, prepared, and can be used at home as a treatment. It does not contain plasma or albumin, nor does it carry the risk of disease.

Another treatment option is DDAVP. It helps the body to release factor VIII because it is similar to a naturally occurring hormone. It comes in two different forms, one is injected into the vein, and the other is a nasal spray.

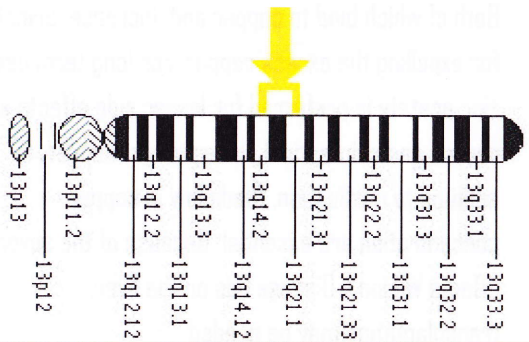
It is important to be aware of the source of human blood-based treatments due to risk of blood-borne disease. Patients should also stay up to date on hepatitis vaccinations.

Key Facts

Copper is an essential element for proper cell function but an over abundance can be a bad thing.

Wilson's Disease is characterized by many different signs and symptoms caused by copper accumulating in the body, so multiple tests must be done to be sure. The Keyser-Fleischer rings are a good sign or Wilson's Disease but is not always the case. The disease is genetic (autosomal recessive, so males and females are at equal risk) so genetic screening should be offered to other family members.

13q14.3: Gene for ATP7B



Information

Information on Wilson's Disease

- Wilson's Disease Association
  www.wilsonsdiseaseaccosiation .org
- **NORD**, National Organization or Rare Diseases
  www.rairdiseases.org

Sources

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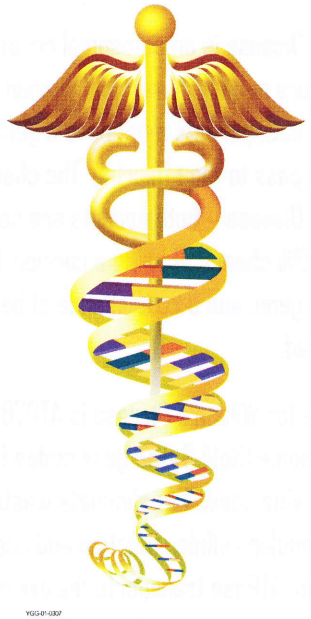
Matthew Archevald

Hepatolenticular Degeneration or Wilson's Disease



Kennesaw State University

What is Wilson's Disease?

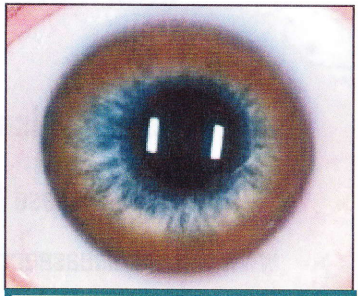
Wilson's Disease is a genetically inherited disorder in which the body does not excrete excess copper that is naturally consumed in the food that a person eats. The liver is the organ responsible for eliminating the excess copper in the body via bile. If excess copper is not eliminated properly it can damage the brain, liver and various other organs which could lead to a life threatening condition.

Wilson's Disease is an autosomal recessive disorder that occurs equally in men and women. To inherit the disease, both parents must have a gene mutation in order to pass to the offspring. The chance of having Wilson's Disease if both parents are carriers is 25%: with a 50% chance of being a carrier having only 1 affected gene, and a 25% chance of being genetically unaffected.

The gene for Wilson's Disease is ATP7B located on Chromosome 13q14.3. The gene codes for ATPase which is an enzyme needed to eliminate waste that could inhibit regular cellular function and copper is no exception. ATPase transports the excess copper from the liver to bile, then to the small intestine and eliminated in the feces.. When a person is affected with Wilson's Disease, this transport of excess copper is either insufficient or nonfictional entirely.

Signs & Symptoms

Because of the nature of the disease by the inability of the body to eliminate excess copper, some sighs and symptoms correlate well with the disease. A notable sigh of this disease are the Kayser-Flescher rings. These rust or silver colored rings are the result of copper accumulation on the iris around the pupil of each eye.



Kayser-Flecher rings of the eye is unique to Wilson's Disease

Other signs and symptoms include but not limited to:

- Jaundice (yellow skin or sclera of eyes)
- Cirrhosis (limited liver function from scarring)
- Difficulty walking
- Muscle stiffness
- Liver failure
- Splenomegaly and Hepatomegaly
- Neurosis (depression, psychosis, etc....)

Diagnosis & Treatment

Diagnosis:

Although the disease begins at birth, most persons affected by the disease show sighs between 6 and 20 years of age, but some will not show effects until as late as 40. The Kayser-Flescher rings are the most common sign for further testing and diagnosis. Most diagnostic testing begins with a 24 hour copper urine sample or by blood samples. Testing may continue with a brain scan (CAT or MRI), liver biopsy and genetic testing to identify the mutated gene. Finally, genetic screening of family members may be requested to determine if others in the family are affected.

Treatment:

There is no cure for Wilson's Disease. However, if diagnosed early, the symptoms can be managed and a patient can live a relatively normal life. Medication commonly taken include penicillamine and trientine. Both of which bind to copper and increase urination for expelling the excess copper. For long term use, zinc acetate is preferred for lesser side effects and reduce gastrointestinal absorption of copper. In addition to medication, foods low in copper concentration are essential. Because of the severe effects Wilson's Disease has on the liver, transplantation may be needed.

Treatment and Management:

There are no real treatments available for Oculodentodigital dysplasia, as it is caused by a deletion of genes. It is possible to take steps to repair some of the symptoms of the disorder. These steps include surgeries to correct the syndactyly of the fingers, as well as surgeries to alleviate some of the vision and hearing problems associated with the disorder. Hearing Aids may also help correct loss of hearing; and despite lower limb weakness, many individuals are able to walk with the help of a walker, braces, or crutches. While there are many options available to manage the symptoms of this disorder, these individuals will still be affected their entire lives. To help them learn to live with the effects of the disorder, support groups exist for both individuals affected by the disorder, as well as for their families.

Conclusion:

Oculodentodigital Dysplasia is an extremely rare genetic disorder resulting from a deletion on the q arm of chromosome 6.

It is autosomal dominant and has a high penetrance but variable expression. Because of this, individual cases of the disorder can range from mild to severe. Because of the rarity of this syndrome it can be overlooked or misdiagnosed. The most common way to accurately diagnose this disorder is through genetic testing. Individuals with this disorder experience problems with teeth, eyes, limbs, and various other features. The symptoms of the disorder can be managed to some extent, through surgeries and corrective devices.

To help affected individuals deal with The persistent struggles of this disorder, support groups are available. These groups provide a comforting place for all involved with the disorder to discuss and learn more about this disorder. While there are many obstacles to overcome with this disorder, it is possible for those affected to live mostly normal and productive lives.

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Right Diagnosis. (2012) Symptoms of Oculodentodigital Syndrome. http://www.rightdiagnosis.com/o/oculodentodigital_syndrome/symptoms.htm.

Oculodentodigital Dysplasia

Written By Katrina Nobles for

Biology 3327: Medical Genetics

Kennesaw State University

April 10, 2012

Introduction:

In 1890, W.A. Bailey described a syndrome with microphthalmia and abnormalities of the teeth. In 1920, W. Lohmann described two patients with microphthalmus and camptodactyly of the fifth finger. Similar cases with incomplete features were reported over the ensuing years, and in 1957 Meyer-Schwickerath et al. introduced the term 'Dysplasia oculo-dento-digitalis'. In 1963, Gorlin et al. summarized the six known cases and defined the syndrome recognized today as Oculodentodigital Dysplasia. The disorder has been linked to a deletion on chromosome 6 of q22-q24. The entire region does not have to be deleted to be diagnosed as Oculodentodigital Dyslpasia. A deletion anywhere within this region will cause the characteristic phenotype and symptoms of this disorder.

This syndrome affects development of the face, eyes, limbs, and teeth. It is an extremely rare disorder with an incidence of only one in ten million.

Clinical Features:

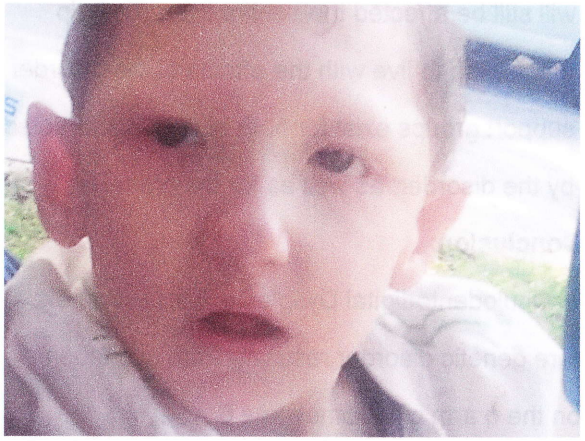
As mentioned in the previous section, this is an extremely rare disorder; in fact, there are only about 250 reported cases of Oculodentodigital Dysplasia reported worldwide. This is a congenital autosomal dominant disorder usually passed from parent to child. However, cases can arise from novel mutation. Cases can range from mild to severe as the disorder has a high penetrance but variable expression. This explains why the symptoms of the disorder that are expressed can vary widely, even within families. The most common phenotypes associated with the disorder are:

- Small teeth with many cavities, early tooth loss, and enamel hypoplasia
- Long, thin nose with small, thin nostrils
- Unusually small eyes- prone to poor eyesight, cataracts and glaucoma
- Short opening between eyelids
- Syndactyly of the fourth and fifth fingers, associated comptodactyly of the fingers
- Conductive deafness
- Craniofacial dysmorphism
- Various skeletal defects
- Mildly delayed mental development
- Lower limb weakness
- Fine, dry hair that is often curly

Due to the variability of expression in the disorder, any combination of these symptoms can be seen in an individual with Oculodentodigital Dysplasia, not all symptoms are present in all cases.

Diagnosis:

Some cases of Oculodentodigital Dysplasia are diagnosed at birth, but many cases go undiagnosed until adulthood and some are never diagnosed at all. Many times hand surgeons are the first to observe affected individuals when they seek treatment of the syndactyly of the fingers associated with this disorder. A few cases have been radiographically diagnosed when patients enter the hospital with similar symptoms. However, most cases of Oculodentodigital Dysplasia are diagnosed through genetic testing. As this disorder is so rare, advanced methods of diagnosing it have not been developed.



3 year old male diagnosed with Oculodentodigital Dysplasia through genetic testing.

Treatment & Disease Management

- Chemotherapy
- Radiation Therapy
- Lumpectomy
  - Remove lump
- Mastectomy
  - Complete breast removal

Support Groups

American Cancer Society

& National Cancer Institute

-www.cancer.org

Cancer Care

-www.cancercare.org

Conclusion

Breast cancer is a devastating genetic disease that affects countless families. Caused primarily by mutations in two tumor suppressor genes, BRCA1 and BRCA2, breast caner is difficult to prevent. Early detection however, now more possible than ever through mammography and cytogenetic testing, gives women a fighting chance at winning the uphill battle.

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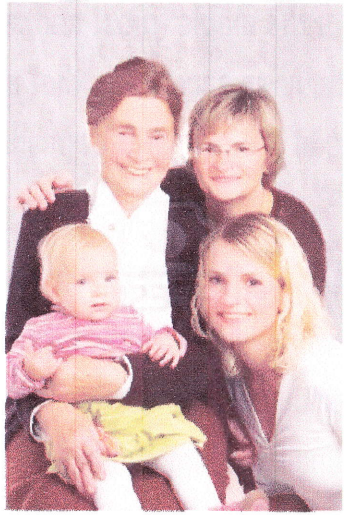
The Genetics of Breast Cancer

By: Hayley Getman



Introduction

The most common cause of breast cancer is a mutation in the genes BRCA1 & BRCA2 which are tumor suppressor genes. It is expressed in breast tissue cells, and functions to repair damaged DNA molecules. The gene was discovered in 1990 by King Laboratory at UC Berkeley.

There are two types of breast cancer: (1) ductal carcinoma affecting the ducts that move milk from the breast to the nipple (most common), and (2) lobular carcinoma that affects the area of the breast that produces milk.

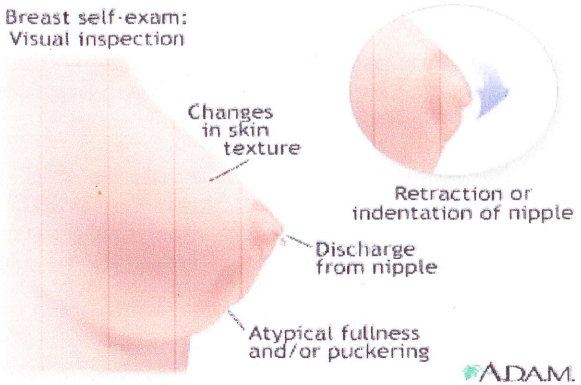
Genetic testing is available for women who want to know if they have a deleterious gene mutation. Genetic counseling is recommended.

Clinical Features

Breast cancer follows an autosomal dominant mode of inheritance. Of the women who inherit a mutated BRCA1 or BRCA2 gene, 60% will develop breast cancer versus only 12% in the general population.

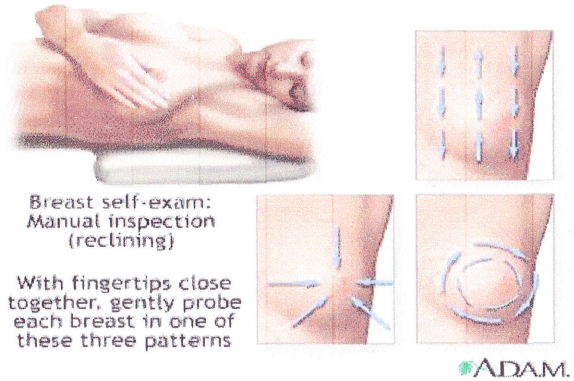
Symptoms

- Painless lump in the breast or armpit with hard, uneven edges
- Redness, dimpling, or puckering of breast or nipple.
- Fluid leakage from nipple.



Diagnosis

- Breast MRI
- Breast ultrasound
  - If lump is solid or fluid-filled
- Breast biopsy
- CT Scan
  - Determine if caner has spread
- PET Scan
- Mammography & Self-Examination
  - Preventative screening



Conclusion

NF1 and NF2 are both autosomal dominant genetic diseases caused by mutations in the neurofibromin gene or the schwannomin gene. NF is characterized by benign tumors, growths, and lesions in the skin, iris, and central nervous system. There are currently no cures for either but thanks to the rapidly advancing field of molecular genetics, more is being understood about the underlying causes of neurofibromatosis.

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Treatment and Disease Management

There is currently no cure for NF but treatments include surgery and chemotherapy, for the removal of tumors, as well as medication to help affected individuals deal with any pain they may experience. Most affected individuals are able to live a normal life with little to no impairment.

NF is inherited in an autosomal dominant fashion, therefore if an individual that is heterozygous for neurofibromatosis has children with an unaffected individual each offspring would have a 50% chance of inheriting NF. In the rare chance that an individual is homozygous for NF all of their offspring would be affected. Also, approximately 50% of NF1 cases are new cases caused by new mutations because the mutation rate at the neurofibromin gene is approximately 100 times higher than the average rate of mutation per locus in the human genome.

There are many support groups available for affected individuals, a few of which are listed below:

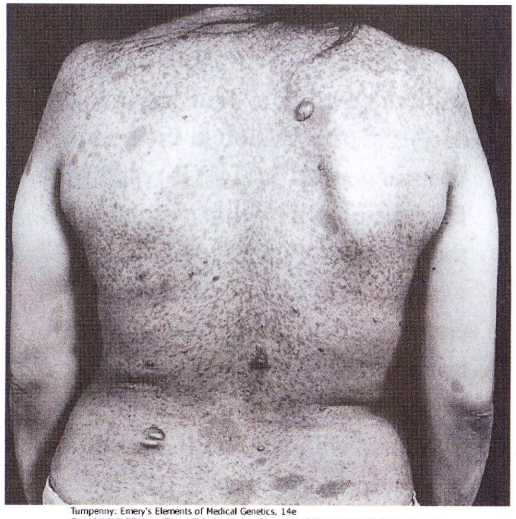
National Neurofibromatosis Foundation, Inc.

Neurofibromatosis, Inc.

The Neurofibromatosis Association

Neurofibromatosis

Jacob Sloan



Turnpenny: Emery's Elements of Medical Genetics, 14e
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An individual affected with NF showing café-au-lait spots and neurofibromata

Introduction

References to the clinical features of neurofibromatosis began showing up in medical journals as early as the eighteenth century but it was not until 1882 that Friedrich Von Recklinghausen, a German pathologist, contrived the term "neurofibroma". Two types of neurofibromatosis (NF), have been identified and are commonly referred to as NF1 and NF2. Both the NF1 and NF2 genes were mapped in 1987 using linkage analysis. A mutation in the neurofibromin gene (17q11.2) is responsible for causing NF1 while a mutation in the schwannomin gene (22q12.2), which acts as a tumor suppressor, causes NF2. Many different kinds of mutations in the previously mentioned genes have been found in individuals with NF, but the genotype-phenotype correlation is still unclear.

Clinical Features of NF1

NF1 is inherited in an autosomal dominant mode with an incidence of 1:3,000 with about 50% of cases being caused by new mutations. Individuals affected with NF1 can exhibit café-au-lait spots, neurofibromata, relative macrocephaly, and Lisch nodules. Café-au-lait begin appearing early in childhood and are characteristically small, pigmented skin lesions. Neurofibromata are small, benign growths that appear during adolescence or early adulthood and increase in number with age. Lisch nodules are small pigmented growths located in the iris. Small numbers of patients with NF1 develop more severe conditions such as epilepsy, scoliosis, or a tumor of the central nervous system.

Clinical Features of NF2

Similarly to NF1, the mode of inheritance for NF2 is autosomal dominant. The incidence for NF2(1:25,000-35,000) , however; is much less than that of NF1. Neurofibromata and café-au-lait spots can also be found in NF2 individuals, although these features are less common than in NF1 individuals. The most common feature found in NF2 cases is the formation of vestibular schwannomas, which are benign tumors that grow on the vestibular cochlear nerve, during early adulthood. Other tumors of the central nervous system are commonly found as well.

Diagnosis

The mapping of the NF1 gene and the NF2 gene has enabled mutational analysis to be a viable option for presymptomatic or prenatal diagnosis, however; most families decide not to undergo these tests because NF isn't a life threatening disease and mutational analysis can't determine the severity of the illness.

Example of Lisch nodules in a NF1 patient

Overview

Colon cancer or colorectal cancer (CRC) is the leading cause of cancer-related deaths in the United States according to the American Cancer Society. It is also the third common diagnosed cancer in both men and women. In 2012, 143,460 cases are expected to be diagnosed and 51,690 deaths are expected to occur [1]. You are at risk if you: are age 60 or older, African-American of eastern European descent, diet high in red/processed meats, inflammatory bowel disease, family history of colon cancer, and/or have a history of breast cancer. Individuals afflicted by colon cancer depicts the following symptoms: abdominal pain in the lower abdomen, blood in the stools as well as narrow stools, diarrhea, constipation, or other changes in bowel habits, and weight loss due to unknown reasons. However, early diagnosis can lead to a complete cure. For more information, please continue to explore...

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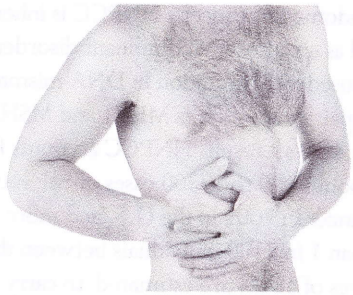
SUPPORT GROUPS

American Cancer Society
Colon Cancer Alliance
National Cancer Institute

The Syndrome Behind Colon Cancer

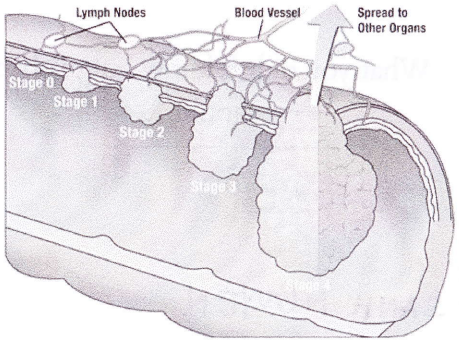


What you didn't know but probably should...

SANH NGUYEN

An aspect of Colon cancer

Symptoms related to colon cancer was first reported by the English pathologist, Alfred Scott Warthin in 1913. Later, Henry Lynch expanded upon it with greater detail by identifying the genetic disorder behind CRC known as hereditary nonpolyposis colorectal cancer (HNPCC) also known as "Lynch Syndrome" [2]. HNPCC is associated with increased risk to many forms of malignancy but particularly colorectal and endometrial cancer. HNPCC is inherited as an autosomal dominant disorder caused by a mutation in DNA mismatch repair genes such as MLH1 and MSH2 [3,4]. As a result, HNPCC accounts for about 1400 to 17300 cases of colorectal cancer in 2005 in the U.S. and more than 1 in 3100 individuals between the ages of 15-74 are estimated to carry a defective DNA mismatch repair gene associated with NPCC and are at risk in developing an NPCC-related cancer [5,6].

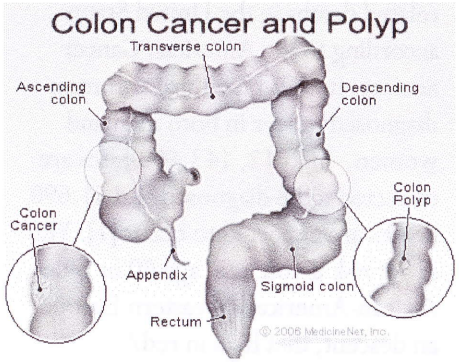


Diagnosis

Colon cancer diagnosis consists of a physical exam of the abdomen, colonoscopy, an internal examination of the colon and rectum by a tube-like instrument with a camera, and sigmoidoscopy, procedure to view the inside of the sigmoid colon and rectum. Screening for HNPCC are often performed by those who are diagnosed with colon cancer. Individuals who are at risk are diagnosed clinically such as tumor location or histology tests or laboratory through abnormal staining for mismatch proteins, or microsatellite instability (MSI). There are two clinical criteria that suggest diagnosis: Amsterdam and Bethesda. Amsterdam—3 relatives with HNPCC-related cancer, one is 1st degree relative of the other two, 2 successive generations affected, and 1 diagnosed before age 50. Bethesda—colorectal cancer diagnosed in patient under the age of 50, presence of HNCPP-related tumor, MSI like histology diagnosed in age under 60, more than one 1st degree relative with HNPCC tumor, and 2 or more relatives with HNPCC tumor regardless of age.

Treatment

Treatment for HNCPP often requires drastic measures. For example, the surgical removal of the entire colon, prophylactic colectomy may necessitate. The reason being is to ensure the needless occurrence of another colon cancer episode. However, there are options depending on the degree of the spread of the tumor such as total colectomy and ileorectal anastomosis, restorative proctocolectomy, proctocolectomy and ileostomy. Total colectomy and ileorectal anastomosis consists of the removal of the colon but 5 inches of the rectum is left remaining where it is surgically joined to the upper rectum. Restorartive proctocolectomy is the removal of the colon and rectum, leaving the anal canal and the anal sphincter muscles intact followed by a new rectum being made from the smaller intestine and attached to the anal canal. The final procedure, proctocolectomy and ileostomy, where both the colon and rectum are removed, patients then wear a bag to collect excrements.



CRC's most common cause is the mutation in DNA repair genes. Mutation at this site leads to HNCPP or Lynch Syndrome. Diagnosis of HNCPP follows the two guidelines, Amsterdam and Bethesda. With appropriate screening prevention of colorectal cancer may be possible with the detection by a colonoscopy examination at the onset. However, later stages of CRC requires surgical operation where the whole or partial removal of the colon and rectum.

Diagnosis:

Current methods used in the diagnosis of Alzheimer's require careful medical evaluation. These include:

-Thorough Medical History

-Mental Status Testing

-A Physical and Neurological Exam

-Tests such as blood tests and brain imaging are needed to rule out any other causes of dementia-like symptoms.

Other tests that may be conducted include:

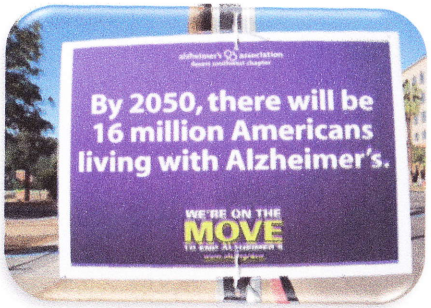
-Sequence Analysis of the entire coding region.

-Sequence Analysis of selected exons.

-FISH (Metaphase and/or Interphase) Analysis (primarily used for Duplication and/or deletion analysis for the genes involved).

*important note: having trouble with memory does not mean someone has Alzheimer's. Many health issues can cause problems with memory loss and thinking. Extensive Medical tests are required to diagnose a patient.

Figure 2: Alzheimer's Association Poster



Treatment and Disease Management

Current methods for disease treatment include drug and non-drug treatment that assist with cognitive and behavioral symptoms.

Some Drugs for memory loss and cognition include:

-Cholinesterase inhibitors (Aricept, Exelon, Razadyne, and Cognex)

-Memantine (Namenda)

Some drugs for Behavior Problems include:

-Antidepressants (Celexa, Prozac, and Zoloft)

-Anxiolytics (Ativan and Serax)

-Antipsychotics (Abilify, and Clozaril)

Conclusion:

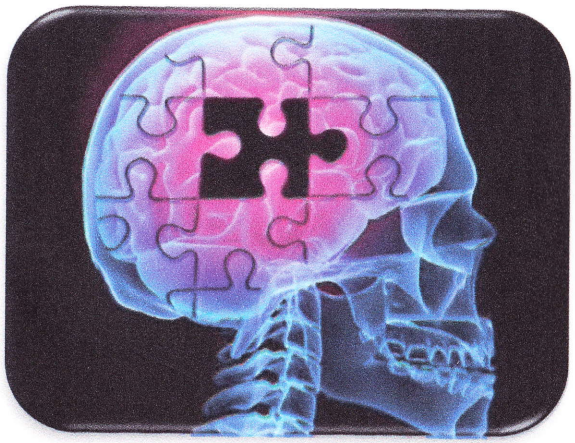
While there is no cure for the disease, many milestones have led to the diagnosis and treatment of this degenerative disease. More research is warranted to determine the true causes of this disease. While research has shown that at least four genes have been identified, the true nature of those genes requires more research for understanding the process and developing a cure. For more information about Alzheimer's Disease,please visit the following website:

National Institute of Health

ghr.nlm.nih.gov/condition/alzheimer-disease

Alzheimer's Association

http://www.alz.org



Alzheimer's Disease

William Dawkins

BIOL 3327

Medical Genetics

Dr. X. Hauge

Alzheimer's Disease

Alzheimer's disease is a progressive brain disorder that damages and eventually destroys brain cells, leading to memory loss, thinking, and other brain malfunctions. The disease is not part of normal aging. It usually develops slowly and gradually gets worse as more brain cells wither and die. The disease is currently fatal and has no cure.

History of Alzheimer's Disease

-1906: Dr. Alois Alzheimer describes "a peculiar disease" by linking microscopic brain changes in a patient named Auguste D., who had experienced profound memory loss, suspicions about family, and other worsening psychological changes. The patient's brain autopsy revealed dramatic shrinkage and abnormal deposits in and around the nerve cells.

-By 1984, beta-amyloid was identified. This peptide was reported to be "a novel Cerebrovascular amyloid protein", which was then identified as the primary component of Alzheimer's brain plaques and a prime suspect in triggering the nerve cell damage.

-By 1986, the Tau protein was identified as a key component of tangles, which is the second hallmark of Alzheimer's disease and another suspect in nerve cell degeneration.

-By 1987, the drug Tacrine was launched in clinical trials as the first drug to target symptoms of Alzheimer's. The first deterministic Alzheimer's gene was also identified as being associated with a rare, inherited form of the disease located on Chromosome 21 coding for Amyloid Precursor Protein (*APP*), being the "parent" molecule from which Beta-amyloid is formed.

-1993: Alzheimer's risk factor gene (*APOE-e4*) is identified (Chromosome 19), in which encodes for Apolipoprotein-E. The e-4 allele of this gene raises the risk for developing the disease.

Clinical Features of the Disease:

Hallmark changes of Alzheimer's Disease include:

-Plaques, or microscopic clumps of beta-amyloid peptides in the brain.

-Tangles, or twisted microscopic strands of the Tau protein in the brain.

-Loss of connections among brain cells is responsible for memory, learning, and communication failure.

-Inflammation results from the brain's attempt to limit the lethal effects of these changes occurring.

-Eventual death of brain cells and severe tissue damage and shrinkage.

Clinical Symptoms:

-Most common early symptoms include difficulty remembering newly learned information due to Alzheimer's changes initially occurring in the part of the brain that affects learning capability.

-As the disease progresses, disorientation, mood, and behavioral changes; deepening confusion about events, time, and place; suspiciousness of family, friends, and professional caregivers; difficulty speaking, swallowing, and walking can occur.

Mode of Inheritance

Alzheimer's disease is transmitted in an Autosomal Dominant fashion, meaning that one copy of the affected gene is all that is necessary to increase the risk of developing the disease.

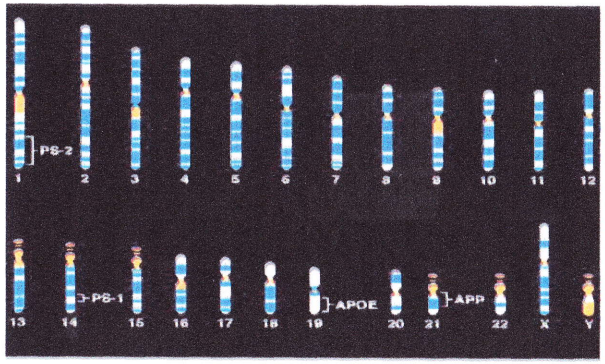
Genes involved:

Most cases of early-onset Alzheimer's (occurring between the ages of 30 to 40 years) are thought to be due to gene mutations passed from parent to child. Current research indicates that early-onset results from mutations in any one of the following genes: *APP* (21q21.2), *PSEN1* (14q24.3), or *PSEN2* (1q31-q42). See Figure 1 for Chromosome Map.

Late-onset of the disease (occurring after the age of 65) is not well understood, and is thought to be related to variations in one or more genes in combination with life style and environmental factors. The *APOE* (19.13.2) gene is identified as the risk factor determinant, especially when the *e4* allele is present. While one copy of the allele increases the risk factors, 2 copies of the allele will greatly increase the risk for development of the disease; however, it is important to note that simply carrying the allele only increases the risks and does not determine the development of the disease.

Down syndrome is seen having a higher correlation to early-onset development (30-40 years of age), due to having three copies of the *APP* gene located on Chromosome 21; however, Down Syndrome cases only account for less than 1% of all Alzheimer's cases.

Figure 1: Gene Locations



CLINICAL FEATURES

About one-third of people with TSC inherit the mutation from a parent who also has TSC through dominant inheritance. Parents who are carriers of an abnormal gene have a 50/50 chance of passing that gene on to their offspring. The remaining two-thirds of people with TSC have *de novo* or sporadic TSC. In other words their parents do not show any signs or symptoms of TSC but one of either TSC gene in the parents is mutated to the abnormal form. In this case, it is not likely that the parents will have another child with TSC because it is sporadic.

Current estimates indicate about 1 in 6,000 babies born will have tuberous sclerosis complex and there are one million people affected worldwide. People with mild forms of TSC may go on to live to adulthood and work in competitive industries like law studies and the medical field.

DIAGNOSIS

For individuals with milder forms of tuberous sclerosis complex, diagnosis may never occur because the person may never exhibit any signs or symptoms. But babies can be diagnosed after receiving a brain MRI or CT Scan, renal ultrasound, echocardiogram of the heart, EKG, eye exam and a Wood's Lamp evaluation of the skin. Genetic testing is available to detect deletions using Multiplex-Ligation Probe Amplification (MLPA). PCR and DNA sequencing can also be done to determine risk and/or locate defects in the gene.

STAY INFORMED

Tuberous Sclerosis Alliance

art for a cure

step forward to cure tuberous sclerosis complex

UNLOCK THE CURE

There are a number of organizations available to anyone who has questions about tuberous sclerosis or would like to become a part of the teams working toward a cure. For more information:

- Visit www.tsalliance.org
- Call **1-800-225-6872**
- E-mail: **info@tsalliance.org**

TS Alliance
801 Roeder Road, Suite 750
Silver Spring, Maryland 20910

What You Need to Know

Tuberous Sclerosis Complex (TSC)

Jasmine Johnson

INTRODUCTION

What is Tuberous Sclerosis Complex (TSC)?

TSC, also known as Bourneville's disease and Epilola, was discovered in the 1880s by a French scientist named Bourneville. TSC is an incurable genetic disorder caused by a mutation in one of two genes, TSC1 or TSC2. These genes are responsible for regulation of negatively control mTOR, a protein that acts as a central regulator of tumor cell division, blood vessel growth, cell metabolism and neuronal migration/wiring.

Mutations in TSC2 tend to be more severe than those in TSC1. Tuberous sclerosis complex can affect many organs but effects are primarily found in the brain & central nervous system, skin, heart, kidneys, eyes, and even teeth. TSC can cause non-cancerous tumors in these organs; although non-cancerous, the tumors produced can have serious effects such as blocking the flow of blood and spinal fluid. Other signs and symptoms of TSC include:

- Cortical tubers on the brain* (can cause seizures)
  - Seizures occur in 60-90% of individuals with TSC & some may develop epilepsy
- Sub-ependymal giant cell astrocytomas (SEGAs) brain tumors which can cause blockage & may require removal
- Cardiac rhabdomyomas (tumors of the heart) usually found during infancy & childhood
- Benign* & malignant angiomyolipomas (tumors of the kidney)
- Cysts
- Renal cell carcinoma
- hypomelanotic macules*
- shagreen patch*
- Fibromas (fibrous growths around the fingernails & toenails)
- facial angiofibromas

Most common signs & symptoms*

TREATMENT & DISEASE MANAGEMENT

There is currently no cure for tuberous sclerosis complex, however there are many support groups and organizations as well as treatments for individuals living with the disease. Early intervention can have many benefits in helping with symptom management.

Some current treatment options available include the following:

- For seizures: vigabatrin and other antiepileptic drugs; sometimes epilepsy surgery is required
- Neurosurgery
- mTOR inhibitors
- Genetic counseling is available

FIGURE 1. Signs & Symptoms

Hypomelatonic macules

CONCLUSION

Tuberous sclerosis complex is a life-long disease which can be managed and allow individuals to live well-rounded, successful and independent lives. There are a number of treatments available to TSC patients and an equivalent amount of supporting organizations to help people living with TSC.

References

1. Gene reviews™, 1993-2006. "Roberts syndrome" http://www.ncbi.nlm.nih.gov/books/NBK84258/

Rick Ejifoma
4/10/12
Biol 3327

Looking into Roberts syndrome

Information/Diagnosis/ Treatment

What you should know about Roberts disease.

Introduction

Roberts syndrome (also known as *pseudothalidomide syndrome*) a very rare genetic disorder that causes mild to severe prenatal retardation or disruption of cell division leading to severe malformations of the bones in the skull, face, arms and legs, it also results in low birth weight. It was named after John B. Roberts, who first described the syndrome in 1919. In 1995, Hugo Vega and Miriam Gordillo, two Colombian geneticists studied DNA samples from 15 families affected by Roberts syndrome. Using the information collected from the samples they were able to determine the identity of the gene mutation responsible for Roberts Syndrome. It was discovered to be a mutation of the ESCO2 gene on 8th chromosome (Gordillo et al., 2006).

Clinical Features

Some features of Roberts syndrome are retarded growth, limb malformations such as bilateral symmetric tetraphocomelia (shortened arms and legs), hypomelia (incomplete development), oligodactyly (fewer than 5 fingers or toes on each limb), syndactyly (fused fingers or toes), clinodactyly (curved pinky finger) and elbow and knee flexion contractures. Some craniofacial (skull) abnormalities are a bilateral cleft lip and/or palate (a gap running from the inner mouth to the nasal cavity), micrognathia (undersized jaw), hypertelorism (abnormal spacing between the eyes), exophthalmos (bulging eyes) and Microbrachycephaly (smaller than normal head size).

The prevalence and incidence of the disease is not known, but less than 150 cases have been reported. Roberts syndrome is an autosomal recessive disease, the child must inherit one copy of the defective gene from each parent which makes the parents heterozygous carriers of a mutant allele. They are asymptomatic and do not express the mutation so their phenotype is normal. Siblings of an affected individual have a 25% chance of being affected, 50% chance of being a carrier and a 25% chance of being unaffected and not a carrier. Two pregnancies of affected individuals have been reported, one resulting in the birth of an unaffected girl and the other was a second-trimester miscarriage. The offspring of an affected individual are obligate carriers. Each sibling of the parents of an affected individual has a 50% chance of being a carrier (Gordillo et al., 2006).

Diagnosis

Cytogenetic testing is the main method for laboratory diagnosis. Cytogenetic preparations are stained with Giemsa or C-banding techniques to show abnormal premature centromere separation and separation of the heterochromatic region in most chromosomes across all metaphases. Through molecular genetic testing, *ESCO2* is the only gene known to be associated with Roberts Syndrome. Prenatal diagnosis for Roberts syndrome is possible through cytogenetic testing of fetal cells and ultrasound examination to track growth and evaluate the formation of the limbs, organs and other structures of patients at risk for Roberts Syndrome (Gordillo et al., 2006).

Sequence analysis for ESCO2 has also been done; all individuals with a cytogenetic diagnosis of Roberts syndrome have had mutations in *ESCO2*. However, testing carriers for Roberts syndrome requires previous identification of the disease in the family along with cytogenetic testing and ultrasound examination (Gordillo et al., 2006).

Treatment and Disease management

Surgery is available to correct the cleft lip and abnormal limbs. Prosthetic limbs are available as attachments to replace missing or truncated limbs. There is special education and therapy for speech assessment and development of affected individuals. Ophthalmologic (ear), cardiac (heart) and renal (kidney) anomalies can be screened for monitored by trained professionals. Genetic counseling can be provided to families of affected individuals to explain the risks for each family member, cause, signs and symptoms. Organizations such as Consumer Resources provide information and support to readers to raise awareness (Gordillo et al., 2006).

Conclusion

Although extremely rare, Roberts syndrome can have severe, even fatal consequences for those individuals that are suffering from this disease. While great progress has been made in identification and treatment for this disease, this brochure provides valuable information about this devastating disease.