Malattie genetiche

Comprendono tutte quelle condizioni patologiche a carico del patrimonio genetico. Possono essere ereditarie, e possono essere congenite.

Malattie ereditarie:
Derivano dai genitori, sono trasmesse attraverso le cellule germinali nelle diverse generazioni e sono quindi familiari. Non tutte le malattie ereditarie si manifestano al momento della nascita (ex. Corea di Huntington).

Malattie congenite:
Le malattie genetiche sono frequenti

Considerations for Determining Prevalence of Managed Care Enrollees with Genetic Risks/Diagnoses

Infants and Infant Deaths (Parents would be candidates for a genetic referral):
• 3-5% of all births result in congenital malformations
• 0.5% of all newborns have a chromosomal abnormality
• 7% of all stillborns (aborti) have a chromosomal abnormality
• 20-30% of all infant deaths are due to genetic disorders
• 30-50% of post-neonatal deaths are due to congenital malformations

Children and Adults (age 1 and above)
• 11.1% of pediatric hospital admissions are for children with genetic disorders
• 18.5% of pediatric hospitalizations are for children with congenital malformations
• 50% of individuals found to have mental retardation have a genetic basis for their disability
• 12% of adult hospital admissions are for genetic causes
• 15% of all cancers have an inherited susceptibility
• 10% of the chronic diseases (heart, diabetes, arthritis) which occur in the adult populations have a significant genetic component

http://www.kumc.edu/gec/prof/prevalnc.html
Le malattie genetiche sono frequenti

Another possibility for estimating members who may benefit from genetic services would be to consider the more common diagnoses, or reasons for referral, and estimate the prevalence of enrollees with, or at risk of, these conditions based on known incidence figures. For example:

- Down syndrome (1/600 live births and increases with advanced maternal age)
- Cystic Fibrosis (1/2500 Caucasian Americans)
- Fragile X syndrome (1/1,000 males and 1/800 female carriers of which 30% will be mentally retarded)
- Sickle cell disease (1/500 of African American births)
- Hemophilia - Factor VIII Deficiency (48/100,000 male births)
- Duchenne muscular dystrophy (1/5,000 male births)
- Hemochromatosis (1/450 individuals)
- Breast cancer (1/8 women of which 5-10% of will have a genetic predisposition)

One could apply these figures to the enrolled population to generate prevalence estimates for clients enrolled in a managed care plan. For example, assuming an enrolled population of 55,000, and that one half are female members, and recognizing the incidence of breast cancer of 1/8, an estimated 3400 members will develop breast cancer and 170-340 of these individuals will have a genetic basis for their disease. Their predisposition could be identified through a detailed family history obtained through a genetic evaluation and those high risk families may benefit from genetic testing for the known breast cancer genes

http://www.kumc.edu/gec/prof/prevalnc.html
**Malattie genetiche**

**Mutazioni Genomiche** (alterazione n° Cromosomi)
- Cromosomi Autosomici
- Cromosomi Sessuali
Non sono ereditarie

**Mutazioni Cromosomiche** (Alterazione Struttura Cromosomi)
- Traslocazioni
- Delezioni
Ereditarie e non ereditarie

**Mutazioni Geniche**
Delezioni, Inserzioni, Mutazioni Puntiformi, Espansione di Triplette
Possono essere EREDITATE in modo:
- MENDELIANO (singolo gene dominate/recessivo, cromosomi sessuali)
- NON MENDELIANO (Espansione triplette, mitocondriali)
Classificazione delle malattie ereditarie

• **Mendeliane** (mutazione di singoli geni con ampio effetto)

• **Multifattoriali** (genetici e ambientali)

• **Malattie da singolo gene con trasmissione non mendeliana** (es. espansione da triplette, malattie mitocondriali)
Malattie genetiche multifattoriali

• Risultanti dall’interazione fra le condizioni ambientali e un numero di geni partecipanti alla determinazione del fenotipo >1

• Il rischio di presentare un fenotipo clinico è proporzionale al numero di geni mutati ereditato

• Molte delle più comuni malattie (diabete, ipertensione, celiachia) hanno origine multifattoriale
11% of the genes in the genome are tested for clinically today

- Cystic Fibrosis (100%)
- Tay Sachs (100%)
- Breast Cancer (40-80%)
- Cardiomyopathy (55%)
- Type 2 Diabetes (25% to 33%)
- Alzheimer’s Disease (1.18% to 5.89%)

- Monogenic diseases
- Majority of disease risk by single gene
- Epigenetic disease (>1 gene + environment)
Scientists currently estimate that over 10,000 of human diseases are known to be monogenic. The single-gene or monogenic diseases can be classified into three main categories:

- Dominant
- Recessive
- X-linked

Dominant and recessive diseases are monogenic disorders that involve damage to only one gene copy. X-linked diseases are monogenic disorders that are linked to defective genes on the X chromosome.

Monogenic diseases are responsible for a heavy loss of life. It has been estimated that taken together, monogenic diseases may account for up to 40% of the work of hospital-based pediatric practice (Scriven, 1995).

Thalassaemia
Sickle cell anemia
Haemophilia
Cystic Fibrosis
Tay Sachs disease
Fragile X syndrome
Huntington's disease

Genes and Disease is a collection of articles that discuss genes and the diseases that they cause. These genetic disorders are organized by the parts of the body that they affect. As some diseases affect various body systems, they appear in more than one chapter.

With each genetic disorder, the underlying mutation(s) is discussed, along with clinical features and links to key websites. You can browse through the articles online, and you can also download a printable file (PDF) of each chapter.

From Genes and Disease you can delve into many online related resources with free and full access. For example, you can visit the human genome to see the location of the genes implicated in each disorder. You can also find related gene sequences in different organisms. And for the very latest information, you can search for complete research articles, and look in other books in the NCBI Bookshelf.

Currently over 80 genetic disorders have been summarized, and the content of Genes and Disease is continually growing.
Blood and Lymph Diseases

As most of the cells in the human body are not in direct contact with the external environment, the circulatory system acts as a transport system for these cells. Two distinct fluids move through the circulatory system: blood and lymph. Blood carries oxygen and nutrients to the body's cells, and carries waste materials away. Blood also carries hormones, which control body processes, and antibodies, to fight invading germs. The heart is the pump that keeps this transport system moving. Together, the blood, heart, and blood vessels form the circulatory system.

The lymphatic system (lymph, lymph nodes and lymph vessels) supports the circulatory system by draining excess fluids and proteins from tissues back into the bloodstream, thereby preventing tissue swelling. It also serves as a defense system for the body, filtering out organisms that cause disease, producing white blood cells, and generating antibodies.

The biochemical make up of lymph — the fluid found in the lymphatic vessels — varies with the site of origin. For example, lymph from bone marrow, spleen, and thymus have high concentrations of white blood cells for fighting infection, while lymph from intestines is high in fat that has been absorbed during digestion. Damage to the lymphatic and circulatory systems leaves the body more susceptible to sickness and infection, as well as to serious conditions such as cancer.

Diseases

• Anemia, sickle cell
• Burkitt lymphoma
• Gaucher disease
• Hemophilia A
• Leukemia, chronic myeloid
• Niemann-Pick disease
• Paroxysmal nocturnal hemoglobinuria
• Porphyria
• Thalassemia
Online Mendelian Inheritance in Man (OMIM; http://www.omim.org) lists the following phenotypes with Mendelian patterns of inheritance (reflecting mutations at a single locus):

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Autosomal</th>
<th>X Linked</th>
<th>Y Linked</th>
<th>Mitochondrial</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Gene description</td>
<td>13,685</td>
<td>668</td>
<td>48</td>
<td>35</td>
<td>14,436</td>
</tr>
<tr>
<td>+ Gene and phenotype, combined</td>
<td>105</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>109</td>
</tr>
<tr>
<td>= Phenotype description, molecular basis known</td>
<td>3,664</td>
<td>284</td>
<td>4</td>
<td>28</td>
<td>3,980</td>
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<tr>
<td>% Phenotype description or locus, molecular basis unknown</td>
<td>1,587</td>
<td>131</td>
<td>5</td>
<td>0</td>
<td>1,723</td>
</tr>
<tr>
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<td>1,748</td>
<td>118</td>
<td>2</td>
<td>0</td>
<td>1,868</td>
</tr>
<tr>
<td>Totals</td>
<td>20,789</td>
<td>1,203</td>
<td>59</td>
<td>65</td>
<td>22,116</td>
</tr>
</tbody>
</table>

Single-gene disorders represent one of the three major categories of genetic disease. **Mutations of single genes have been documented at almost 20% of the 22,000 genetic loci in the human genome that code for protein products.**
OMIM Entry Statistics

Number of Entries in OMIM (Updated December 20th, 2016):

<table>
<thead>
<tr>
<th>MIM Number Prefix</th>
<th>Autosomal</th>
<th>X Linked</th>
<th>Y Linked</th>
<th>Mitochondrial</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
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<td>35</td>
<td>15,447</td>
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<td>31</td>
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<td>0</td>
<td>1,612</td>
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<tr>
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<td>0</td>
<td>1,790</td>
</tr>
<tr>
<td>Totals</td>
<td>22,441</td>
<td>1,268</td>
<td>60</td>
<td>68</td>
<td>23,837</td>
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</tbody>
</table>
Single Gene Defects
(monogenic diseases)

Human Genes and Genomes

Leon E. Rosenberg and Diane Drobnis Rosenberg

Academic Press
ISBN 978-0-12-385212-0
Sir Archibald Garrod, the British physician who created the field of human biochemical genetics in 1902 by his study of alkaptonuria.

Alkaptonuria is an autosomal recessive aminoacidopathy characterized by accumulation of homogentisic acid (alkapton) in the urine resulting from congenital lack of the enzyme homogentisate 1,2-dioxygenase, which mediates an essential step in the catabolism of phenylalanine and tyrosine. It is manifested by elevated concentrations of homogentisic acid in the urine (which darkens on standing or with alkalinization), a peculiar discoloration of body tissues known as ochronosis, and arthritis.

We now know that it is caused by mutation in the homogentisate 1,2-dioxygenase gene (HGD) on chromosome 3q.

Prevalence 1-9/1.000.000
Examination of the structure of homogentisic acid, with its six-carbon phenyl ring, suggested to Garrod that it might be related to the amino acid phenylalanine and tyrosine, each with a phenyl ring as a major substituent.

\[
\begin{align*}
\text{HO} & \quad \text{CH}_2\text{--COO}^- \\
& \quad \text{OH}
\end{align*}
\]

Therefore, Garrod embarked on a series of feeding experiments in alkaptonuric patients and in healthy controls

• He fed homogentisic acid to patients and controls. Patients excreted all they ingested in the urine, controls excreted none

• He fed phenylalanine and tyrosine to patients and controls. Homogentisic acid excretion increased markedly in patients, controls excreted none
Garrod proposed that homogentisic acid was an intermediate in the pathway through which phenylalanine and tyrosine are broken down. He went on to propose that there must be an enzyme responsible for this breakdown of homogentisic acid and that enzyme was deficient in people with alkaptonuria.

He noted that affected patients were not infrequently the offsprings of first cousins or other consanguinous matings.

Fortuitously, he consulted William Bateson (who coined the word “gene”, which means “giving birth to” and the two men realized that alkaptonuria was behaving like a rare Mendelian recessive.

The defect was narrowed down to homogentisic acid oxidase (HGD) deficiency in a study published in 1958. The genetic basis was elucidated in 1996, when HGD mutations were demonstrated.
About one-third of these inborn errors are clinically harmless, another third result in severe dysfunction, and the remainder cause mild or moderate abnormalities.

On the right: clinical consequences of 332 well characterized inborn errors of metabolism.
Collectively, these mutations cause dysfunction of every class of protein present in human cells — structural, enzymatic, circulatory, membrane, transcriptional regulators etc. — and that these dysfunctions have been observed in every tissue and every cell type.

Some of these disorders are inherited as dominants traits, others are recessive, and still others are X-linked or mitochondrial.
Hemoglobin (Hb) is the iron-containing oxygen-transport metalloprotein in the red blood cells of all vertebrates (with the exception of the fish family Channichthyidae) as well as the tissues of some invertebrates.

In mammals, the protein makes up about 97% of the red blood cells' (RBCs) dry content (by weight).

**Hemoglobin is a tetramer**: two alpha and two beta globin chains. Each globin chain contains a heme molecule
The human genome has **13 globin genes**: 

- 4 pseudogenes and 1 locus of unknown function
- The alpha genes are on chromosome 16.
- The beta genes are on chromosome 11
Time course of production of the several globin chains
Beta globin gene: only 1.6 Kb, composed of 3 exons and 2 introns. Gene expression controlled by a number of sequence motifs at or near the 5’ end of the gene (promoter + transcription factor sites)

Primary transcript edited by the usual addition of the cap site and of the polyA tail. Then, the transcript is spliced and the 2 introns are removed. The 3 exons are joined together to make beta-globin mRNA that exit the nucleus and is translated on cytoplasmic ribosomes to form the beta-globin protein, which contains 146 amino acid residues
Sickle cell anemia is caused by an abnormal type of hemoglobin called hemoglobin S.

Hemoglobin S is caused by a SNP in the 6° codon of the beta-globin gene (GAG -> GTG) leading to a glutamic acid to valine change often abbreviated Glu6Val. It is inherited as an autosomal recessive trait. Homozygotes (SS) almost always have serious clinical problems, whereas heterozygotes (AS) are usually healthy.

The Glu6Val mutation changes hemoglobin tetramers such that when deoxygenated in the tissues, they become insoluble and aggregate.

The prevalence of this disease varies among populations in direct relationship with malaria: in Nigeria 1 in 50 people has the SS genotype. Sickl e cell anemia occurs in 1/500 African Americans, 1/150,000 Europeans, 1/200,000 Asians.
Sickle Cell Anemia

In 1949 it became the first human disease to be understood at molecular level by Nobel Prize-winner Linus Pauling. It was the first disease in which the beta-globin chain was sequenced and a single amino acid substitution was shown. It was also the first human genetic system proving that the triplet genetic code was the same in humans as in simpler model organisms.

Normal red blood cells live about 120 days in the bloodstream, but sickled red cells die after about 10 to 20 days. Because they cannot be replaced fast enough, the blood is chronically short of red blood cells, leading to a condition commonly referred to as anemia.
**Missense mutations** «pock mark» the hemoglobin subunits. More than 75% in each chain have undergo substitutions. They often affect hemoglobin’s ability to form tetramers, carry oxygen or stability

**Red circles**
Amino acid residues at which functionally significant missense mutations have been observed

**Open circles**
Missense mutations of little or no functional significance

**Frameshift mutations** produce mRNA that is not translated properly, but their functional consequences depends on where the frameshift occurs in the mRNA
Haemophilia is a hereditary bleeding disorder, in which there is a partial or total lack of an essential blood clotting factor. It is a lifelong disorder, that results in excessive bleeding, and many times spontaneous bleeding, which, very often, is internal. Haemophilia is an X-linked recessive genetic pattern and is more common in males than females.
There are mainly **two types of Haemophilia**, they are Haemophilia A and Haemophilia B. Rarely there is another type of haemophilia known as haemophilia C.

- **Haemophilia A** is caused by the deficiency of clotting factor VIII
- **Haemophilia B** is caused by the deficiency of clotting factor IX (Christmas Factor)
- **Haemophilia C** is caused by the deficiency of clotting factor XI. In all the above cases, patient will have abnormal bleeding tendency.

**Incidence**
- **Haemophilia A**: 1:5000 males. It is four times more common than Type B.
- **Haemophilia B**: 1: 34,000 males.

**Haemophilia in girls is very rare condition.** This condition develops in girls only when both the X genes are defective. If a girl has one defective X gene and a normal X gene, she is not affected but her male children have 50% chance of getting the disease.
Cystic fibrosis (CF), also known as mucoviscidosis, is an **autosomal recessive** genetic disorder that affects most critically the lungs, and also the pancreas, liver, and intestine. It is characterized by **abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions**. **Difficulty breathing** is the most serious symptom and results from **frequent lung infections** that are treated with antibiotics and other medications. Other symptoms—including sinus infections, poor growth, and infertility—affect other parts of the body.
CF is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). This protein is required to regulate the components of sweat, digestive fluids, and mucus. CFTR regulates the movement of chloride and sodium ions across epithelial membranes, such as the alveolar epithelia located in the lungs.

Both CFTR copies must be missing for CF to develop, and therefore has autosomal recessive inheritance.

CF is most common among people of Central and Northern European ancestry, but occurs in many demographic groups around the world. The prevalence of CF is the rarest in Asia and the Middle East. Individuals with cystic fibrosis can be diagnosed before birth by genetic testing, or by a sweat test in early childhood. Ultimately, lung transplantation is often necessary as CF worsens.

Although it is severely underdiagnosed in Asia, existing evidence indicates that the prevalence of CF is rare. In the European Union 1 in 2000-3000 new borns is found to be affected by CF. In the United States of America the incidence of CF is reported to be 1 in every 3500 births.
The molecular genetic epidemiology of cystic fibrosis

Figure 2: Detection rate of CF-causing CFTR mutations

The detection rate of CF-causing CFTR mutations, i.e., the proportion of CFTR alleles derived from CF patients on which a mutation can be identified, are given for the different countries of the world. This detection rate for each country is the maximum detection rate obtained with any of the genotyping assays used. A color code is used for different detection rates, as shown in the inset. Detailed numbers of the detection rates are given in table 2. The countries marked with No data in the map refer to studies on which less than 100 CF cases were studied. They might, therefore, be less representative. For the regions colored in white, no data are available.

http://www.who.int/genomics/publications/en/HGN_WB_04.02_fig2.pdf
Tay Sachs disease

Tay-Sachs disease is an autosomal recessive disease in which harmful quantities of a fatty substance called Ganglioside GM2 accumulate in the nerve cells in the brain, leading to paralysis, dementia, blindness, psychoses, and even death.

Tay-Sachs is caused by mutations in both alleles of a gene (HEXA) on chromosome 15. HEXA codes for the alpha subunit of the enzyme β-hexosaminidase A. This enzyme is found in lysosomes, organelles that break down large molecules for recycling by the cell.

Normally, β-hexosaminidase A helps to degrade a lipid called GM2 ganglioside, but in Tay-Sachs individuals, the enzyme is absent or present only in very reduced amounts, allowing excessive accumulation of the GM2 ganglioside in neurons.

The progressive neurodegeneration seen in the varied forms of Tay-Sachs depends upon the speed and degree of GM2 ganglioside accumulation, which in turn is dependent upon the level of functional β-hexosaminidase A present in the body.
This disease is autosomal recessive.

Prevalence:

The frequency of the condition is much higher in Ashkenazi Jews of Eastern European origin than in others.

Approximately one in every 27 Jews in the United States of America is a carrier of the TSD gene. There is also a noticeable incidence of TSD in non-Jewish French Canadians living near the St. Lawrence River and in the Cajun community of Louisiana.

Among Jews of Sephardic origin and in the general, non-Jewish population, the carrier rate is about 1 in 250. There are certain exceptions. French-Canadian and the Cajun community of Louisiana have the same carrier rate as Ashkenazi Jews, one in 27. Also, individuals with ancestry from Ireland are at increased risk for the Tay-Sachs gene. Current research indicates that among Irish Americans, the carrier rate is about one in 50.
Fragile X syndrome

Fragile X syndrome is the most common inherited form of mental retardation currently known. Fragile X syndrome is a defect in the X chromosome and its effects are seen more frequently, and with greater severity, in males than females.

In Fragile X individuals, there is a mutation in one end of the FMR1 gene (the 5' untranslated region), consisting of an amplification of a CGG repeat. Patients with fragile X syndrome have 200 or more copies of the CGG motif. The huge expansion of this repeat means that the FMR1 gene is not expressed, so no FMR1 protein is made. Although the exact function of FMR1 protein in the cell is unclear, it is known that it binds RNA.

A similar nucleotide repeat expansion is seen in other diseases, such as Huntington disease.
Although it is a X-linked recessive trait with variable expression and incomplete penetrance, 30% of all carrier women are affected.

Prevalence:

According to the Fragile X association of Southern California, Fragile X syndrome is the single most common inherited cause of mental impairment affecting 1 in 3600 males and 1 in 4000 to 6000 females with full mutation worldwide. Some studies also suggest that fragile X affects 1 in every 2000 males and 1 in every 4000 females of all races and ethnic groups.

Studies have also revealed that 1 in 259 women of all races carry fragile X. The number of men who are carriers is thought to be 1 in 800 of all races and ethnicity. Carrier females have a 30% to 40+% chance of giving birth to a retarded male child and a 15 to 20% chance of having a retarded female.
Huntington disease (HD) is an inherited, degenerative neurological disease that leads to dementia. About 30,000 Americans have HD and about 150,000 more are at risk of inheriting the disease from a parent.

The HD gene, whose mutation results in Huntington disease, was mapped to chromosome 4 in 1983 and cloned in 1993. The mutation is a characteristic expansion of a nucleotide triplet repeat in the DNA that codes for the protein huntingtin.

Since people who have those repeats always suffer from Huntington disease, it suggests that the mutation causes a gain-of-function, in which the mRNA or protein takes on a new property or is expressed inappropriately.

With the discovery of the HD gene, a new predictive test was developed that allows those at risk to find out whether or not they will develop the disease. Animal models have also been developed, and we know that mice have a gene that is similar to the human HD gene.
As the number of repeated triplets - CAG - increases, the age of onset in the patient decreases. Furthermore, because the unstable trinucleotide repeat can lengthen when passed from parent to child, the age of onset can decrease from one generation to the next.
Huntington's is an autosomal dominant genetic disorder which means that if one parent carries the defective Huntington's gene, his/her offspring have a 50/50 chance of inheriting the disease. Everyone who carries the gene will develop the disease.

The function of the huntingtin gene, also called the HTT or HD (Huntington disease) gene, is unclear. It is essential for development, and absence of huntingtin is lethal in mice. In its wild-type (normal) form, it contains 6-35 glutamine residues. However, in individuals affected by Huntington's disease (an autosomal dominant genetic disorder), it contains more than 36 glutamine residues (highest reported repeat length is about 250).

Prevalence:

Huntington's disease (HD) affects males and females equally and crosses all ethnic and racial boundaries. It typically begins in mid-life, between the ages of 30 and 45, though onset may occur as early as the age of 2. Children who develop the juvenile form of the disease rarely live to adulthood.

In Western countries, it's estimated that about 5 to 7 people per 100,000 are affected by HD. A very high concentration of HD has also been found in the Lake Maracaibo region of Venezuela where the prevalence of HD is about 700 per 100,000.
Muscular dystrophy (MD) is a group of muscle diseases that weaken the musculoskeletal system and hamper locomotion. Muscular dystrophies are characterized by progressive skeletal muscle weakness, defects in muscle proteins, and the death of muscle cells and tissue.

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy among children. DMD occurs among approximately 1 in 3500 male births. This broad range reflects studies of different groups of individuals around the world. Usually, a person with DMD loses the ability to walk sometime during the period when he or she is 7 through 13 years of age, and can live into their 20s and 30s.

Becker muscular dystrophy (BMD) is a milder form of muscular dystrophy. BMD affects about 1 in 18,500 male births. Signs of BMD are similar to those for DMD. Typically, people with BMD lose the ability to walk after they are 16 years of age.

Together, DMD and BMD are called Duchenne/Becker muscular dystrophy (DBMD). Over time, the muscles of people with DBMD get much weaker because the lack of the dystrophin protein in muscle cells causes them to be fragile and easily damaged.

Thanks to advances in cardiac and respiratory care, life expectancy is increasing and many young adults with DMD attend college, have careers, get married and have children. Survival into the early 30s is becoming more common, and there are cases of men living into their 40s and 50s.
Duchenne muscular dystrophy is caused by mutations in DMD gene which codes for protein dystrophin. DMD gene is located on the short arm of the X chromosome (Xp21.2-p21.1).

DMD is inherited in an X-linked recessive pattern. Females will typically be carriers for the disease while males will be affected. Typically, a female carrier will be unaware they carry a mutation until they have an affected son.

The son of a carrier mother has a 50% chance of inheriting the defective gene from his mother. The daughter of a carrier mother has a 50% chance of being a carrier or having two normal copies of the gene. In all cases, the father will either pass a normal Y to his son or a normal X to his daughter.

Female carriers of an X-linked recessive condition, such as DMD, can show symptoms depending on their pattern of X-inactivation.
The Dystrophin gene responsible for the disease was identified by **positional cloning**.

It was known that the casual gene was on the X chromosome because the disease was inherited as an X-linked trait. Linkage studies had placed it somewhere on the short arm (p) which is 60 Mb and encodes 400 genes.

Therefore, the researchers went from disease to its map position on the chromosome to identification of the gene and then to defining its function.
Dystrophin is the largest human gene, about 2.3 million bases (Mb) long. It contains 79 exons and occupies more than 1% of the X chromosome. The dystrophin protein is extremely large as well: 420 kiloDaltons (kDa).

Dystrophin is involved in the contractile apparatus of muscle proteins, where it interacts with the cytoskeleton. The majority of mutations in DMD patients are large or small deletions that affect the reading frame in the dystrophin gene.
Detection of dystrophin by immunofluorescence. Note the intense staining around the periphery of normal muscle fibers.
Amyotrophic lateral sclerosis (ALS), often referred to as "Lou Gehrig's Disease," is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed.

A-myotrophic comes from the Greek language. "A" means no or negative. "Myo" refers to muscle, and "Trophic" means nourishment—"No muscle nourishment." When a muscle has no nourishment, it "atrophy"es or wastes away. "Lateral" identifies the areas in a person's spinal cord where portions of the nerve cells that signal and control the muscles are located. As this area degenerates it leads to scarring or hardening ("sclerosis") in the region.

About 90% of patients with adult-onset ALS have no family history of ALS and present as an isolated case in their family. This is called sporadic ALS (SALS), and although there is likely a genetic predisposition involved, SALS is not directly inherited. The remaining 10% of people with ALS have a family member with ALS, and this is referred to as familial ALS (FALS).

There are several inheritance patterns, but the most common for FALS is autosomal dominant. The most common genes currently known to be associated with FALS include SOD1, TDP-43, FUS and the more recently discovered C9ORF72 and UBQLN2. Other genetic causes of ALS affect relatively few people. Nonetheless, understanding how they cause the disease may offer large insights into the disease process. These genes include VCP (valosin-containing protein), alsin, senataxin, and angiogenin and optineurin.
C9ORF72. This gene, discovered in 2011, is the most common genetic cause of ALS. (Its name refers to the position of an “open reading frame” on chromosome 9). Mutations in this gene account for between 25% and 40% of all familial ALS cases (depending on the population), and also approximately 4% to 6% of sporadic cases. As noted above, these apparently sporadic cases are in fact genetic. The gene mutation appears to act in a dominant manner. How this gene causes ALS is unknown, and is the subject of a great deal of intense research.

Cu/Zn Superoxide Dismutase 1 (SOD1). Mutations in SOD1 were first described in 1993, and SOD1 was the first gene known for ALS. It accounts for about 10% of familial ALS, or 1.5% to 2% of all ALS. It is inherited in a dominant manner. How SOD1 mutations cause ALS is unknown. It is clear that disease is not due to lack of function of the protein, since deleting the gene in animal models doesn’t cause ALS. Instead, it appears to take on some new toxic function, possibly related to an increase in the tendency of mutant SOD1 molecules to aggregate and form clumps in motor neurons. It is also possible that SOD1 causes ALS through actions in nearby cells called astrocytes, not in motor neurons themselves. Astrocytes help maintain motor neurons, and SOD1 mutation may impair their ability to do so. Read more about SOD1.

TDP-43. TAR DNA binding protein 43 (TDP-43) was linked to ALS in 2008. Mutations in TDP-43 cause a dominant form of ALS. The normal role of the TDP-43 protein includes binding to RNA, the genetic messenger molecule. Mutations in the TDP-43 gene cause the TDP-43 protein to mislocalize in motor neurons, away from the nucleus where it is normally found, and into the cytoplasm (the material surrounding the nucleus), where it aggregates into clumps that can be seen under the microscope. Even in ALS not caused by TDP-43 mutations, the protein is found in these aggregates, suggesting it may play a pivotal role in many forms of ALS.

FUS. Fused in sarcoma (FUS) was also discovered to play a role in ALS in 2008. Like TDP-43, it is inherited in a dominant manner. It is also an RNA binding protein, and may play a similar normal role in the cell. FUS and TDP-43 may in fact interact as part of their normal function.

Ubiquilin-2. Ubiquilin-2 was linked to ALS in 2011. Unlike all other known ALS genes, the ubiquilin-2 gene resides on the X chromosome. Despite this, both men and women develop ALS due to ubiquilin-2 mutations. The normal function of the protein is to help degrade damaged or defective proteins in the cell. It is likely that mutations in the gene interfere with this function, and may lead to accumulation of harmful material within the cell.
Familial Hypercholesterolemia

The body is unable to remove low density lipoprotein (LDL, or "bad") cholesterol from the blood. This results in high levels of LDL in the blood. High levels of LDL cholesterol make you more likely to have narrowing of the arteries from atherosclerosis at an early age. Those with familial hypercholesterolemia are more likely to have a family history of high cholesterol and heart disease at a younger age than normal.

Blood tests may show:

- **High levels of total cholesterol**
  - Greater than 300 mg/dL in adults
  - Greater than 250 mg/dL in children
- **High LDL levels**
  - Greater than 170-200 mg/dL in children
  - Greater than 220 mg/dL in adults
- **Normal triglyceride levels**
Men who have familial hypercholesterolemia have heart attacks in their 40's to 50's, and 85 percent of men with the disorder have a heart attack by age 60. Women who have familial hypercholesterolemia also have an increased risk for heart attack, but it happens 10 years later than in men (so in their 50's and 60's).

It is inherited in families in an **autosomal dominant manner**.

The altered gene (gene mutation) that causes familial hypercholesterolemia is located on chromosome 19. It encodes for a protein called LDL receptor (LDLR) that is responsible to clear up LDL from the blood stream. One in 500 individuals carries one altered gene causing familial hypercholesterolemia. More rarely, a person inherits the gene mutation from both parents. **Individuals who are homozygous have a much more severe form of hypercholesterolemia, with heart attack and death often occurring before age 30.**
Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver.

Statins have some side effects including a mildly increased risk of diabetes and abnormalities in liver enzyme tests. Additionally they have rare but severe adverse effects, particularly muscle damage, and some doctors believe they are over-prescribed.

As of 2010, a number of statins are on the market: atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altocor), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor) and simvastatin (Zocor). Several combination preparations of a statin and another agent, such as ezetimibe/simvastatin, are also available.

The best-selling statin is atorvastatin which by 2003 became the best-selling pharmaceutical in history. The manufacturer Pfizer reporting sales of US$12.4 billion in 2008.
L'imprinting genomico o imprinting genetico indica una modulazione della espressione di una parte del materiale genetico: tale modifica può riguardare l'uno o l'altro dei due corredi parentali. Si tratta di un meccanismo di regolazione genica che riguarda circa un centinaio di geni conosciuti, molti di questi hanno un ruolo rilevante nel differenziamento e nello sviluppo.

Nella spermatogenesi parliamo di imprinting paterno, mentre nell'ovogenesi di tipo materno. La diversa metilazione di un determinato locus genico costituisce una sorta di "impronta", la quale impone l'espressione di uno solo dei due alleli di quel determinato locus genico, ossia quello della madre o quello del padre.

Alla fecondazione lo zigote perde la metilazione in quasi tutto il genoma, i geni sottoposti ad imprinting vengono esclusi da questo fenomeno, in quanto la metilazione in questo caso è impiegata per segnalare la provenienza parentale del gene. In seguito, prima dell'impianto della blastocisti avviene una prima fase di metilazione. Durante la formazione dei tessuti embrionali si ha una metilazione attiva e durante il differenziamento delle gonadi c'è un pattern di metilazione specifico per lo sviluppo dell'ovaio o del testicolo. Questo processo è detto anche riprogrammazione epigenetica.

Un errato imprinting genomico rende peculiari alcune malattie che risultano quindi ereditabili solo se la mutazione occorre sul gene paterno o materno in casi rispettivamente di imprinting materno e paterno. A titolo d'esempio bisogna citare la sindrome di Prader-Willi, la sindrome di Angelman e la sindrome di Russel-Silver.
Espressione differenziale di materiale genetico a seconda che esso sia stato trasmesso dal padre o dalla madre.

I geni soggetti a imprinting sono presenti in duplice copia, ma di essi viene espressa una sola copia

Espressione monoallelica di geni biallelici
Concetto contrario alle leggi di Mendel secondo le quali l’origine materna o paterna di un’informazione non ne influenza l’espressione (equivalenza degli incroci reciproci)

• Geni soggetti a imprinting paterno -> la copia fornita dal padre viene silenziata
• Geni soggetti a imprinting materno -> la copia fornita dalla madre viene silenziata
pedigree di una malattia dovuta ad un gene soggetto ad imprinting materno (è attiva solo la copia fornita dal padre)

il rapporto maschi : femmine tra gli affetti è 1:1, una femmina malata non trasmette MAI la malattia, che può ricomparire però nei suoi nipoti
Prove dell’esistenza dell’imprinting

esperimenti di trapianti di pronuclei nel topo: creazione di zigoti androgenetici e ginogenetici

**ZIGOTI GINOGNETICI**
2n cromosomi TUTTI di derivazione **FEMMINILE**

**ZIGOTI ANDROGENETICI**
2n cromosomi TUTTI di derivazione **MASCHILE**

**CONTROLLI**
ZIGOTI OTTENUTI CON TRASFERIMENTO DI PRONUCLEI
2n cromosomi, n forniti da UN **MASCHIO** E n da una **FEMMINA**

**EMBRIONI ABORTIVI** – STRUTTURE EXTRAEMBRIONARIE PRESSOCHÉ ASSENTI, EMBRIONE QUASI NORMALE

**EMBRIONI ABORTIVI** – IPERPLASIA DEL TROFOBLASTO, EMBRIONE PRESSOCHÉ ASSENTE

**EMBRIONI NORMALI** – LA MANIPOLAZIONE DI PER SÉ NON IMPEDISCE IL NORMALE SVILUPPO
• Molto spesso i geni soggetti a imprinting sono riuniti in **cluster** contenenti geni ‘imprintati’ nella madre e geni ‘imprintati’ nel padre

• I due cluster omologhi mostrano **metilazione differenziale** (ma non sempre la metilazione è a carico dell’allele non espresso)

• Nei cluster sono in genere presenti sia geni strutturali (il loro prodotto finale è una catena polipeptidica) sia geni che producono RNA non codificanti
Sindrome di Beckwith-Wiedemann (BWS)

Malattia dovuta a un gene soggetto a imprinting materno (è attiva solo la copia fornita dal padre) causata da acquisizione di funzione. Il gene mappa in 11p15

Nei soggetti normali è espressa solo la copia paterna

La duplicazione sul cromosoma paterno ha come conseguenza un raddoppiamento del prodotto genico ed insorgenza della malattia

La duplicazione sul cromosoma materno è senza conseguenze perché la copia sovranumeraria non viene espressa
Sindrome di Beckwith-Wiedemann (BWS)

Una mutazione nel centro di imprinting impedisce il silenziamento del gene in cis

La mutazione è sul cromosoma paterno → non si hanno conseguenze fenotipiche perché la copia che non può essere spenta è comunque destinata ad essere espressa

La mutazione è sul cromosoma materno → l’individuo è malato perché ha due copie attive del gene
Sindrome di Prader-Willi (PWS) - malattia dovuta ad assenza della funzione del ‘gene’ PWS (si tratta di vari geni che per semplicità vengono qui considerati come un unico gene), ‘gene’ soggetto ad imprinting materno (è espressa solo la copia fornita dal padre) che mappa in 15q11-13

Sindrome di Angelman (AS) - malattia dovuta ad assenza della funzione del gene AS, gene soggetto ad imprinting paterno (è espressa solo la copia fornita dalla madre) che mappa in 15q11-13

Entrambe le malattie possono essere dovute a:

1. delezione dell’intera regione cromosomica 15q11-13;
2. disomia uniparentale (UPD) (materna nella PWS, paterna nella AS);
3. errore di imprinting
4. solo per la sindrome di Angelman: mutazione nella copia materna del gene AS

La delezione è sul cromosoma Paterno → assenza della funzione del ‘gene’ PWS, si ha *Sindrome di Prader-Willi*.

La delezione è sul cromosoma Materno → assenza della funzione del gene AS, si ha *Sindrome di Angelman*. 
Disomia Uniparentale Paterna (UPD) → assenza funzionale del gene AS → **Sindrome di Angelman**

Disomia Uniparentale Materna → assenza funzionale del ‘gene’ PWS → **Sindrome di Prader-Willi**

Mutazione nel centro di imprinting sul cromosoma P che non può essere «resettato» e che viene trasmesso con un’impronta di tipo Materno → assenza funzionale del gene PWS → **Sindrome di Prader-Willi**

Mutazione nel centro di imprinting sul cromosoma M che non può essere «resettato» e che viene trasmesso con un’impronta di tipo Paterno → assenza funzionale del gene AS → **Sindrome di Angelman**
Genomic Imprinting
(Prader-Willi and Angelman Syndromes)

Sono attivi solo:
• Un set di geni Prader-Willi (paterni)
• Un set di geni Angelman (materni)

Uniparental Disomy
Stesso risultato delle delezione
La sindrome di Angelman riguarda tutte le razze ed entrambi i sessi. È stata descritta per la prima volta da Harry Angelman, pediatra inglese, nel 1965. L'incidenza è stata stimata fra 1 su 12.000 e 1 su 25.000.

Poiché l'incidenza della sindrome di Prader-Willi è stata stimata in 1 su 10.000, resta da spiegare perché quella relativa alla sindrome di Angelman sia inferiore. Una possibile causa (anche se non unica), considerata anche la maggior gravità della sindrome, è che siano maggiori i casi di aborto spontaneo.

La sindrome di Prader-Willi è, per certi versi, l'opposto della sindrome di Angelman: in quest'ultima, infatti, è il cromosoma 15 materno a non funzionare correttamente.
Prader-Willi/Angelman Syndrome

- Nella PWS il gene materno è silenziato perché sotto imprinting, mentre quello paterno è deleto.
- La regione in questione è sul cromosoma 15 (15q11-q13).
- La PWS è strettamente correlata con la Sindrome di Angelman (AS), che è causata da imprinting paterno e delezione del gene materno caratterizzata da movimenti ripetitivi, simmetrici, atassici e da una disposizione all'allegria, al riso frequente.
Il DNA genomico mitocondriale è circolare, costituito da ~ 16000 b.p. e codifica per gli enzimi della fosforilazione ossidativa.

Ovociti: 200.000-300.000 copie di mt DNA
Spermatozoi: perdono i mitocondri nella fertilizzazione
Eteroplasmia: coesistono molecole di mtDNA mutate e normali
Caratteristiche dell’ mtDNA

- POLIPLASMIA
- ETEROPLASMIA
- EFFETTO SOGLIA
- SEGREGAZIONE MITOTICA
- EREDITÀ MATERNA
In ogni cellula sono presenti molti mitocondri ed ogni mitocondrio contiene multiple copia del suo genoma (eccetto piastrine e ovulo non fertilizzato) → migliaia di copie mtDNA / cell.

Durante la divisione cellulare i mitocondri vengono distribuiti casualmente alle cellule figlie e quindi la genetica mitocondriale è più simile alla genetica di popolazione che alla genetica mendeliana.

In tessuti normali tutte le copie di mtDNA sono identiche → omoplasmia.

Nel caso di una mutazione del mtDNA questa può colpire tutte le copie oppure essere presente solo in una percentuale di genomi → eteroplasmia.

Generalmente i polimorfismi neutrali sono omoplasmici mentre la maggior parte delle mutazioni-malattia sono eteroplasmiche
**EFFETTO SOGLIA**
L’espressione clinica delle mutazioni del mtDNA è determinata dalla *relativa proporzione wild type / mutato* in un determinato tessuto; è necessario un numero minimo di copie per danneggiare il metabolismo energetico di un determinato organo o tessuto (valore relativo e non assoluto) (SNC, cuore, muscolo, rene e ghiandole esocrine) (bilancio energetico).

**SEGREGAZIONE MITOTICA**
Durante la divisione cellulare la proporzione di genomi mutati può variare per *deriva* nelle cellule figlie, con conseguente cambiamento fenotipico.

**Eteroplasmia + effetto dose → eccezioni fenotipiche all’eredità matrilineare.**
• Mutazioni puntiformi o delezioni.

• ♀ malata può trasmettere la malattia a tutti i figli (♂ e ♀). La mutazione é nella cellula uovo.

• ♂ malato non trasmette la malattia alla progenie. Lo spermatozoo perde i mitocondri

• Malattie progressive dei muscoli, cuore, SNC (es. Neuropatia ottica ereditaria di Leber)

Figura 5. Principali organi e tessuti colpiti dalle malattie mitocondriali
Malattie mitocondriali

- Malattia Di Alpers - Polidistrofia cerebrale progressiva infantile.
- Sindrome Di Barth - Cardiomiopatia Infantile Mortale.
- Mancanza Della Carnitina: Malattie con disturbo della demolizione degli acidi grassi - Codice di esenzione: RCG070.
- Carenza della CPT (carnitin-palmitin-trasferasi).
- Mancanza Del Compresso I - carenza di NADH deidrogenasi (NADH-CoQ riduttasi).
- Mancanza Del Compresso II - Carenza di succinato deidrogenasi.
- Mancanza Del Compresso III - Carenza di Ubiquinone-citocromo c ossidoriduttasi.
- Mancanza Del Compresso IV/Mancanza Del Cox.
- KSS - sindrome di Kearns-Sayre (sporadica) - Codice di esenzione: RF0020.
- MILS - Sindrome di Leigh ereditata per via matrilineare Codice di esenzione: RF0030.
- MERFF - Epilessia mioclonica, con le fibre ragged-rosse - Eredità materna o sporadica - Codice di esenzione: RF0020.
- MDS La sindrome da deplezione del DNA mitocondriale - Codice di esenzione: RN0710.
- MNGIE: - Codice di esenzione: RN0710.
- Mancanza di CPT I
- Mancanza di CPT II
- Acidosì lattica.
- LCAD - Mancanza A catena lunga Della Deidrogenasi Dell'Acilico-CoA
- LHON
- La neuropatia ottica ereditaria di Leber (LHON).
- Mancanza Della Carbossilasi Del Piruvato.
- Mancanza Della Deidrogenasi Del Piruvato.
- Malattia di Alzheimer: il cinque per cento circa dei malati anziani presenta la stessa mutazione del DNA mitocondriale.
- La sindrome da deplezione del DNA mitocondriale (MDS).

http://www.webalice.it/prati_50/malattiemito.htm
**Sindrome Di Barth - Cardiomiopatia Infantile Mortale.**
La sindrome di Barth è una malattia metabolica caratterizzata da cardiomiopatia dilatativa, più raramente di tipo ipertrofico, neutropenia, miopatia scheletrica, difetto di crescita. Successivamente alla sua caratterizzazione clinica e biochimica, il gene-malattia è stato mappato in Xq28, utilizzando il clonaggio posizionale; l'analisi mutazionale ha identificato il gene G4.5. Sono state identificate oltre 20 mutazioni.

**CPEO - Sindrome Esterna Progressiva Cronica Di Oftalmoplegia.**
Sindrome oftalmoplegica esterna cronica progressiva. E' caratterizzata da una debolezza progressiva dei muscoli oculari e del muscolo elevatore della palpebra superiore
Causa: Mutazione puntiforme del DNA mitocondriale: A3243G (la più comune)
La maggior parte di questi quadri clinici è dovuta a mitocondriopatie, ma la causa della disfunzione mitocondriale è variabile (mutazioni puntiformi, delezioni del DNA mitocondriale, mutazione di geni nucleari, con effetti sul DNA mitocondriale, come la timidina fosforilasi nella MNGIE).

**MELAS**
Nella sindrome di MELAS (Encefalomiopatia mitocondriale con Acidosi Lattica ed episodi di ictus ), ai sintomi clinici i associano, in modo più o meno incostante, emiparesi, emianopsia, deficit motorio, emicrania, vomito, demenza, convulsioni, sordità, diabete, disturbi della memoria. La mutazione più frequente è A3243G del tRNA per la Leucina del DNA mitocondriale.
**KSS - sindrome di Kearns-Sayre**

Insorge prima dei 20 anni. Comporta oftalmoplegia, ptosi, retinite pigmentosa, segni associati a miopatia, disturbi della conduzione cardiaca, iperproteinorrachia. Nei casi sporadici possono essere presenti altri sintomi come sordità, cardiomiopatia, crisi epilettiche, disturbi del transito intestinale, ipoparatiroidismo, ritardo nella crescita, diabete, insufficienza renale. **Queste patologie sono associate ad ampie delezioni eteroplasmiche del DNA mitocondriale, la più frequente delle quali è lunga 4,9 kilobasi.** Il rapporto tra la percentuale degli organelli mutati/non mutati può essere molto elevato e quando raggiunge la soglia del 60% circa (ad es: nel muscolo) determina un fenotipo patologico con deficit a carico dei complessi della catena respiratoria, anomalie istochimiche, "Ragged Red Fibers".

**NARP**

La sindrome Neuropatia, Atassia e Retinite Pigmentosa (**NARP**) è clinicamente eterogenea, ma spesso è caratterizzata dalla combinazione tra neuropatia sensoriale-mоторia, atassia cerebellare e cecità notturna. **La sua prevalenza è stimata in circa 1/12.000.** La sintomatologia clinica comprende: retinopatia precoce "sale e pepe"; retinite pigmentosa; pupille "pigre"; nistagmo; cecità; debolezza muscolare prossimale; ritardo di sviluppo; atrofia cortico-spinale; demenza; ipoacusia; convulsioni; atassia; neuropatia sensoriale; debolezza muscolare prossimale neurogena. La sindrome **NARP è una malattia ad eredità materna, dovuta alla mutazione 8993T>G nel gene del mtDNA, MTATP6, che codifica per la subunità 6 dell’ATPasi.** La mutazione 8993T>G comporta un cambio aminoacidico dalla leucina 156, altamente conservata, in arginina (L156R), e causa un grave deterioramento della sintesi dell’ATP mitocondriale, che riduce l'energia e produce la morte cellulare, in particolare nei tessuti che dipendono fortemente dal metabolismo della fosforilazione ossidativa, come il cervello e la retina.
Red hair is a recessive genetic trait caused by a series of variants in the melanocortin 1 receptor (MC1R), a gene located on chromosome 16. As a recessive trait it must be inherited from both parents to cause the hair to become red. Consequently there are far more people carrying the variant for red hair than people actually having red hair. In Scotland, approximately 13% of the population are redheads, although 40% carry at least one variant.

There are many kinds of red hair, some fairer, or mixed with blond ('strawberry blond'), some darker, like auburn hair, which is brown hair with a reddish tint. This is because some people only carry one or a few of the several possible MC1R variants. The lightness of the hair ultimately depends on other mutations regulating the general pigmentation of both the skin and hair.
Skin and hair pigmentation is caused by two different kinds of melanin: eumelanin and pheomelanin. The most common is eumelanin, a brown-black polymer responsible for dark hair and skin, and the tanning of light skin. Pheomelanin has a pink to red hue and is present in lips, nipples, and genitals. The mutations in the MC1R gene imparts the hair and skin more pheomelanin than eumelanin, causing both red hair and freckles.

Redheads have very fair skin. This is an advantage in northern latitudes and very rainy countries, where sunlight is sparse, as lighter skin improves the absorption of sunlight, which is vital for the production of vitamin D by the body. The drawback is that it confers redheads a higher risk for both sunburns and skin cancer.

Studies have demonstrated that people with red hair are more sensitive to thermal pain and also require greater amounts of anesthetic than people with other hair colours. The reason is that redheads have a mutation in a hormone receptor that can apparently respond to at least two different hormones: the melanocyte-stimulating hormone (for pigmentation) and endorphins (the pain relieving hormone).
Map of red hair frequency in Europe