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Marfan syndrome

Marfan syndrome is caused by mutations in the FBN1 gene. These lead to abnormalities in the protein fibrillin, which is an essential component of connective tissues. The severity of the symptoms differs widely between different individuals with the defective gene. The syndrome often leads to eye defects, such as lens displacement and myopia. There is an increased risk of retinal detachment, glaucoma, and cataracts. Cardiovascular defects, such as an enlarged aorta and heart valve problems, are common, and can be life threatening. Medication, typically beta blockers, or surgery may be needed to reduce the risk of serious heart failure. Musculoskeletal disorders often occur: these include loose joints, protrusion or indentation of the sternum, and curvature of the spine. Those with the syndrome tend to be unusually tall and thin. Among the general population the risk of having Marfan's syndrome is about 1 in 5,000, although a parent with the syndrome has a 50:50 risk of their child inheriting the faulty copy of the gene, due to its nature as an autosomal dominant disorder. The disease seems to be spread evenly among all ethnic groups.

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Ehlers-Danlos Syndrome Type 4

Ehlers-Danlos Syndrome Type 4 is caused by mutations in the COL3A1 gene, which is one of a number of genes that control collagen production. The skin of those with the syndrome tends to bruise very easily. Blood vessels, the bowel, and the uterus have a high risk of perforations. Pregnancy is particularly risky for women with the syndrome. Sufferers tend to have highly visible blood vessels, particularly on the chest, and thin skin. The median age of death is about 48. The disease is autosomal dominant which typically requires at least one affected parent, and has a 50:50 chance of having the defect if one parent is affected. The occurrence of the syndrome is approximately 1 in 250,000 among the general population, and is equally prevalent among different ethnic groups.

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Familial Thoracic Aortic Aneurysm and Dissection (ACTA2)

Familial TAAD can be caused by mutations in the ACTA2 gene. This gene accounts for around 10-20% of cases of familial TAAD. The gene encodes for the protein α-2 actin, which is a component of smooth muscle cells in arterial walls. Along with the ACTA2 gene, other known and unknown genes can also cause familial TAAD. In patients with TAAD, the aorta increases in diameter, which may cause dissection, or blood flowing through the artery wall following a tear. Rupture of the artery may follow, often leading to rapid death. Surgery is often required where a significant thoracic aortic aneurysm occurs. Families with ACTA2 abnormalities are also more prone to occlusive vascular disease and livedo reticularis, a skin disease. With proper management, life expectancy for those with familial TAAD can approach that of the general population. The ACTA2 gene defects that cause familial TAAD are autosomal dominant. Typically, an affected person has one affected parent. However, it is possible for the defective gene to be carried without any TAAD occurring in a situation known as reduced penetrance. Overall, familial TAAD is estimated to cause roughly 20% of thoracic aortic aneurysms and dissections. Approximately 10,000 deaths per year occur due to TAAD in the USA; about 2,000 will be due to familial TAAD, giving around 200-400 deaths per year from ACTA2 defects, out of an overall USA total of around 2.6 million (0.01 to 0.02% of total deaths).

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Congenital Aneurysms (COL4A1)

Congenital aneurysms (widening of blood vessels) can be caused by mutations in the COL4A1 gene. This gene codes for the alpha-1 (IV) chain of type IV collagen. Defects in the gene can lead to cerebral aneurysms and strokes, due to a condition known as COL4A1-related brain small vessel disease. Damage to blood vessels can lead to various eye disorders. Defects in the gene can also cause porencephaly (fluid filled areas in the brain). A syndrome known as HANAC, hereditary angiopathy with nephropathy, aneurysms and muscle cramps, may also occur. Here, the kidneys are damaged, eye problems are common, aneurysms may occur in the brain and elsewhere, and the patient suffers frequent muscle cramps. The various conditions caused by COL4A1 defects all give increased risk of premature death, typically from strokes. The defective gene is autosomal dominant. Affected people typically have one affected parent. Diseases caused by defects in the COL4A1 gene are very rare. Less than 100 individuals with such diseases have been identified, all from Europe or North America.

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Familial Thoracic Aortic Aneurysm and Dissection (MYH11)

Familial thoracic aortic aneurysm and dissection, or familial TAAD, can be caused by defects in the MYH11 gene. The gene encodes for the myosin-11 protein, a contractile protein in smooth muscle. Cases of familial TAAD caused by defects in MYH11 are often associated with the condition Patent ductus arteriosus, or PDA, a congenital heart defect. The overall incidence of familial TAAD caused by MYH11 is low, accounting for only 1% of the total incidence of familial TAAD, which is itself only involved in around 20% of all cases of TAAD.

Sources

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Familial Thoracic Aortic Aneurysm and Dissection (MYLK)

Familial thoracic aortic aneurysm and dissection, or familial TAAD, can be caused by defects in the MYLK gene. The gene encodes for the myosin light chain kinase protein found in smooth muscles. In patients with TAAD, the aorta increases in diameter, and dissection (blood flowing through the artery wall, following a tear) may occur at some point. In cases of TAAD caused by MYLK gene defects, it appears that dissection may occur without significant widening of the aorta. Rupture of the artery can follow, often leading to rapid death. Surgery is often required where a significant thoracic aortic aneurysm occurs. With proper management, life expectancy for those with familial TAAD can approach that of the general population. The incidence of familial TAAD caused by MYLK is low, accounting for only 1% of the total incidence of familial TAAD. Overall, familial TAAD is estimated to cause roughly 20% of thoracic aortic aneurysms and dissections. Approximately 10,000 deaths per year occur due to TAAD in the USA, so about 2,000 will be due to familial TAAD, giving around 20 deaths per year from MYKL defects, out of an overall USA total of around 2.6 million (0.001% of total deaths).

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Arterial Tortuosity Syndrome (SLC2A10)

Arterial tortuosity syndrome (ATS) is caused by mutations in the SLC2A10 gene. The gene encodes for the protein GLUT10, which is believed to help regulate cell proliferation. Those with the syndrome have unusually long, often twisted, arteries which are prone to aneurysm (bulging), stenosis (constriction), and dissection (blood flowing through the torn artery wall). Arterial rupture, or constriction of the blood supply to vital organs, can lead to early mortality. Many sufferers die as children, although others may survive longer. Other symptoms of the syndrome include: elastic skin, very mobile or restricted joints, and various hernias. Sufferers tend to have elongated faces, widely spaced eyes (hypertelorism), and small chins. Arterial tortuosity syndrome is an extremely rare condition: only about 100 cases have been reported worldwide. The genetic abnormality is recessive, requiring one faulty gene from each parent. No evidence has shown more prevalence in any particular ethnic group.

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Loeys-Dietz Syndrome Type I (TGFBR1)

Loeys-Dietz Syndrome Type I is caused by mutations in the TGFBR1 gene. Other types of the syndrome are caused by faults in other genes. The TGFBR1 gene encodes the production of the TGF-β receptor 1 protein, which is believed to be involved in regulating cell proliferation. Those with the syndrome are liable to arterial aneurysms and tortuosity, along with hypertelorism (large distance between the eyes), cleft palates, and bifid (split) uvulae. Early mortality can occur due to arterial rupture. Loeys-Dietz Syndrome Type I is a rare condition, only found so far in a fairly small number of families. It is not yet possible to estimate its overall prevalence, or whether it is more common in particular ethnic groups. The Type 1 syndrome is believed to be the most common form of Loeys-Deitz syndrome. The defective gene is autosomal dominant, typically requiring at least one affected parent.

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Familial TAAD and Loeys-Dietz Syndrome Type II (TGFBR2)

Familial Thoracic Aortic Aneurysm and Dissection (Familial TAAD) and Loeys-Dietz Syndrome Type II can both be caused by different mutations in the TGFBR2 gene. The TGFBR2 gene encodes for the TGF-β receptor type 2, which is believed to be involved in the regulation of cell proliferation. Other types of Loeys-Dietz syndrome are caused by faults in other genes. Those with the syndrome are liable to arterial aneurysms and tortuosity, along with hypertelorism (large distance between the eyes), cleft palates, and bifid (split) uvulae. It is estimated that about 4% of the total cases of familial TAAD are due to mutations in the TGFBR2 gene. In patients with TAAD, the aorta increases in diameter, and dissection (blood flowing through the artery wall, following a tear) may occur at some point. Rupture of the artery may follow, often leading to rapid death. Surgery is often required where a significant thoracic aortic aneurysm occurs. With proper management, life expectancy for those with familial TAAD can approach that of the general population. The two conditions are separate: familial TAAD doesn't give rise to the other symptoms seen with Loeys-Dietz Syndrome Type II. Loeys-Dietz Syndrome Type II is a very rare condition, only found so far in a fairly small number of families. It is not yet possible to estimate its overall prevalence, or whether it is more common in particular ethnic groups. The defective gene is autosomal dominant, typically requiring at least one affected parent. Familial TAAD comprises about 20% of the overall cases of TAAD. About 10,000 people in the USA die each year from TAAD, so around 2,000 of these will be due to familial TAAD, hence there are roughly 80 deaths per year from TAAD from TGFBR2 defects.

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CYSTIC FIBROSIS AND CF-RELATED DISORDERS

Cystic Fibrosis (CFTR)

Cystic Fibrosis is caused by defects in the CFTR gene. The gene encodes for the protein cystic fibrosis transmembrane conductance regulator, which is involved in chloride ion transport and hence mucus production. Sufferers have breathing difficulties, due to sticky mucus buildup in the lungs. They also have severe digestive problems, since pancreatic enzymes are blocked from entering the small intestine, the main locus of nutrient absorption. Male sufferers are normally infertile, due to the lack of functioning vas deferens tubes which lead to the urethra. Diabetes and liver disease are common complications that often develop over time. The mean projected survival time for children born with the condition in the USA in 2010 was estimated at 37 years for women and 40 years for men. The inheritance of the defective gene is autosomal recessive, typically requiring both parents to be asymptomatic carriers of the mutated gene. The condition is relatively common among Caucasian Americans, with an incidence of about 1 in 2,500 to 1 in 3,500. The figures are about 1 in 4,000 to 10,000 for Hispanic Americans, 1 in 15,000 to 20,000 for African Americans, and 1 in 100,000 for Asian Americans. It is estimated that 1 in 29 Caucasian Americans carry the defective gene asymptomatically. The figures are 1 in 46 for Hispanic Americans, 1 in 65 for African Americans, and 1 in 90 for Asian Americans.

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Cystic Fibrosis (SCNN1A)

Cystic Fibrosis is caused by defects in the CFTR gene, however defects in the SCNN1A gene can give similar symptoms. The SCNN1A gene encodes for a subunit of the epithelial sodium channel protein. In some cases a mutation on the CFTR gene may act together with a mutation on the SCNN1A gene to give a cystic fibrosislike disease. Patients have breathing difficulties due to sticky mucus that builds up in the lungs. They may also have severe digestive problems since digestive enzymes from the pancreas are blocked by thick mucus. Male sufferers may be infertile, due to the lack of functioning vas deferens tubes which transfer sperm to the urethra. Diabetes and liver disease are common complications that often develop over time. However, some of the symptoms may be absent with non-typical cystic fibrosis. Non-typical cystic fibrosis from SCNN1A mutations is a rare disease, but may be underreported. No reliable estimates are available for its prevalence.

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Cystic Fibrosis (SCNN1B)

Cystic Fibrosis is caused by defects in the CFTR gene, however defects in the SCNN1B gene can give similar symptoms. The SCNN1B gene encodes for a subunit of the epithelial sodium-channel protein. In some cases a mutation on the CFTR gene may act together with a mutation on the SCNN1B gene to give a cystic fibrosislike disease. Sufferers have breathing difficulties, due to sticky mucus buildup in the lungs. They may also have severe digestive problems, since digestive enzymes from the pancreas are blocked from entering the small intestine, the main location of nutrient absorption. Male sufferers may be infertile, due to the lack of functioning vas deferens tubes which lead to the urethra. Diabetes and liver disease are common complications that often develop over time. However, some of the symptoms may be absent with non-typical cystic fibrosis. Non-typical cystic fibrosis from SCNN1B mutations is a rare disease, but may be underreported. No reliable estimates are available for its prevalence.

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Cystic Fibrosis (SCNN1G)

Cystic Fibrosis is caused by defects in the CFTR gene, however defects in the SCNN1G gene can give similar symptoms. The SCNN1G gene encodes for a subunit of the epithelial sodium-channel protein. In some cases a mutation on the CFTR gene may act together with a mutation on the SCNN1G gene to give a cystic fibrosis-like disease. Sufferers have breathing difficulties, due to sticky mucus buildup in the lungs. They may also have severe digestive problems, since digestive enzymes from the pancreas are blocked from entering the small intestine, the main locus of nutrient absorption. Male sufferers may be infertile, due to the lack of functioning vas deferens tubes which lead to the urethra. Diabetes and liver disease are common complications that often develop over time. However, some of the symptoms may be absent with non-typical cystic fibrosis. Non-typical cystic fibrosis from SCNN1G mutations is a rare disease, but may be underreported. No reliable estimates are available for its prevalence.

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Cystic Fibrosis (CA12)

Cystic Fibrosis is caused by defects in the CFTR gene. However, defects in the CA12 gene can lead to individuals with high sweat chloride concentrations. Such high levels are normally indicative of cystic fibrosis, but in these cases the other symptoms of classical cystic fibrosis are not present: there is no evidence of lung disease or poor pancreatic function leading to digestive problems. Usually males with classical cystic fibrosis are sterile, but since the CA12 related condition has mainly been described in children, it's not clear whether it's normally associated with male sterility. The CA12 gene encodes for the carbonic anhydrase 12 enzyme. Children with the condition had low levels of sodium (hyponatremia), high levels of potassium (hyperkalemia), suffered from dehydration, and failed to thrive in the first year. Normal growth usually resumes after one year of age. Elevated sweat chloride levels from mutations in the CA12 gene is an extremely rare disease. Initial studies focused on a group of related Bedouin in Israel, but it is not known if the condition is more common in any particular ethnic group. The condition is autosomal recessive, which typically requires an affected child to have two asymptomatic carrier parents.

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NON-SYNDROMIC HEARING LOSS

Nonsyndromic Hearing Loss & Deafness (COL11A2)

Non-syndromic hearing loss can be caused by mutations in a number of genes, including the COL11A2 gene (referred to as DFNA13 hearing loss). This gene encodes for part of Type XI collagen. Type XI collagen plays a vital role in the inner ear, thus mutations in COL11A2 can lead to poor hearing, as the collagen fibrils in the ear lack their normal structure. Patients with this non-progressive deficiency find it particularly difficult to hear mid-level frequencies, while retaining the ability to detect low and high frequencies. Initial studies focused on two families, one in the USA and one in the Netherlands. It is not yet possible to determine the prevalence of hearing loss due to COL11A2, although it seems to be rare. It is not clear whether any ethnic group is particularly affected. The condition is autosomal dominant which normally is inherited from at least one affected parent.

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Non-syndromic Hearing Loss and Deafness (GJB2) related (connexin 26) nonsyndromic deafness

Non-syndromic hearing loss can be caused by mutations in a number of genes, including the GJB2 gene, which causes what is known as DFNB1 deafness. The GJB2 gene encodes for a protein called connexin 26 (also known as gap junction beta 2), which is involved in producing gap junctions for the transport of ions, nutrients, and other important functions. Faulty connexin 26 in the inner ear can lead to hearing loss or deafness. The degree of hearing loss can vary widely between affected individuals. The disease is not progressive. The faulty GBJ2 gene is autosomal recessive, which typically requires both parents to be carriers of the faulty gene, usually occurring asymptomatically. DFNB1 deafness (i.e. deafness from the GJB2 gene, in around 98% of cases) is estimated to affect around 42,000 people in the USA/ Western Europe. Some ethnic groups, such as Palestinians, Iran Kurds, and Siberian Altaians have particularly high levels of the faulty gene.

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Non-syndromic Deafness (GJB3) (Connexin 31)

Non-syndromic hearing loss can be caused by mutations in a number of genes, including the GJB3 gene, which causes what is known as DFNA2B deafness. The GJB3 gene encodes for a protein called connexin 31 (also known as gap junction beta 3), which is involved in producing gap junctions for the transport of ions, nutrients, etc. Faulty connexin 31 in the inner ear can lead to hearing loss or deafness. Hearing loss is particularly marked in the higher frequencies. No reliable data on prevalence are available. The genetic defect and associated hearing loss were found in two Chinese families. There have been no subsequent reports on any such association, suggesting that it may be very rare. The faulty gene is autosomal dominant, which typically requires at least one affected parent.

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Non-syndromic Deafness (KCNQ4)

Non-syndromic hearing loss can be caused by mutations in a number of genes, including the KCNQ4 gene, which causes what is known as DFNA2 deafness. The KCNQ4 gene encodes for a protein called potassium voltage-gated channel KQTlike protein 4, which is involved in potassium ion channel formation, particularly in the inner ear and auditory nerve. Hearing is particularly poor for high frequencies, but better for lower frequencies. The condition is progressive, and most patients will have to start wearing a hearing aid between the ages of 10 and 40. No reliable data on prevalence are available. There is no evidence that mutations in KCNQ4 are prevalent in any one ethnic group. The condition is autosomal dominant, which typically requires at least one affected parent.

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Pendred syndrome (SLC26A4)

Pendred syndrome is a syndromic condition that involves deafness and the formation of a goiter on the thyroid gland. The gene SLC26A4 encodes a protein called pendrin, which is involved in anion transport. It is found in the thyroid (where it is believed to be involved in iodide ion transport), kidney, and inner ear. Those born with Pendred syndrome are normally deaf at birth, although in some cases deafness arrives during early childhood. A goiter is normally seen during adolescence or early adulthood. In some cases SLC26A4 defects cause deafness without any other symptoms, known as non-syndromic hearing loss, or DFNB4 deafness. The exact occurrence of Pendred syndrome is not known, although one estimate calculated that 7.5% of all congenital deafness are due to the syndrome. It is not clear whether some ethnic groups are more affected than others. The condition is autosomal recessive, which typically occurs when both parents of an affected child are asymptomatic carriers.

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USHER SYNDROME

Usher Syndrome Type 1B (MYO7A)

Usher syndrome is a condition that involves various degrees of deafness and gradual impairment of vision. Those with Usher syndrome type 1 are usually born deaf, and begin to lose vision while still children. A number of different genetic mutations can cause Usher syndrome type 1, including mutations in the MYO7A gene (Usher syndrome type 1B). MYO7A encodes for the protein myosin VIIA, which is involved in molecular transport. MYO7A is produced in the retina and inner ear, and is important for proper functioning. In the inner ear, it is involved in the production and maintenance of the hair-like stereocilia, which are essential for hearing. The vision loss from Usher's syndrome is due to the condition retinitis pigmentosa, which involves the gradual deterioration of retinal rod photoreceptor cells (leading to night blindness), followed by cone receptor cells (leading eventually to complete blindness). In addition to deafness, Usher syndrome type 1 affects the ability to balance. Children with the condition are typically slow to stand up and walk. Usher syndrome type 1 affects overly 12,000 people in the USA alone. Roughly half of these are due to MYO7A mutations. Usher syndrome type 1 is more common in certain ethnic groups such as Ashkenazi Jews and the Acadians (Cajuns) of Louisiana. The condition is autosomal recessive, which typically requires both parents to be carriers, and usually are asymptomatic.

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Usher Syndrome Type 1F (PCDH15)

Usher syndrome is a condition that involves various degrees of deafness and gradual impairment of vision. Those with Usher syndrome type 1 are usually born deaf, and begin to lose vision while still children. A number of different genetic mutations can cause Usher syndrome type 1, including mutations in the PCDH15 gene (Usher syndrome type 1F). PCDH15 encodes for the protein protocadherin 15, which is produced in the retina and inner ear, and is involved with cell adhesion. The vision loss from Usher's syndrome is due to the condition retinitis pigmentosa, which involves the gradual deterioration of retinal rod receptor cells (leading to night blindness), followed by cone receptor cells (leading eventually to complete blindness). In addition to deafness, Usher syndrome type 1 affects the ability to balance. Children with the condition are typically slow to stand up and walk. The prevalence of Usher syndrome type 1 in the USA is over 4 in 100,000. Out of 34 families with Usher syndrome type 1, 6 were found to have defects in the PCDH15 gene. Usher syndrome type 1 is more common in certain ethnic groups, such as Ashkenazi Jews (where PCDH15 defects are believed to be particularly important) and the Acadians (Cajuns) of Louisiana. The condition is autosomal recessive, which typically requires an affected child to have two asymptomatic carrier parents.

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Usher Syndrome Type 1C (USH1C)

Usher syndrome is a condition that involves various degrees of deafness and gradual impairment of vision. Those with Usher syndrome type 1 are usually born deaf, and begin to lose vision while still children. A number of different genetic mutations can cause Usher syndrome type 1, including mutations in the USH1C gene (Usher syndrome type 1C). USH1C encodes for the scaffold protein harmonin, which is produced in the retina and inner ear. It has a vital role in the stereocilia, the hair-like structures in the inner ear which are essential for stimulating neural pathways responsible for hearing. The vision loss from Usher's syndrome is due to the condition retinitis pigmentosa, which involves the gradual deterioration of retinal rod photoreceptor cells (leading to night blindness), followed by cone receptor cells (leading eventually to complete blindness). In addition to deafness, Usher syndrome type 1 affects the ability to balance. Children with the condition are typically slow to stand up and walk. The prevalence of Usher syndrome type 1 in the USA is over 4 in 100,000. Out of 34 families with Usher syndrome type 1, only 2 were found to have defects in the USH1C gene. Usher syndrome type 1 is more common in certain ethnic groups, such as Ashkenazi Jews and the Acadians (Cajuns) of Louisiana. In the latter group, mutations of the USH1C gene are the main cause of the disease, although the gene is a minor cause for other populations. The condition is autosomal recessive, so typically an affected child will have two asymptomatic carrier parents.

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Usher Syndrome Type 2A (USH2A)

Usher syndrome is a condition that involves various degrees of deafness and gradual impairment of vision. Those with Usher syndrome type 2 are usually born with some hearing impairment: typically they cannot hear higher frequencies. Progressive vision loss occurs slowly from the teenage years onwards, although some vision may be retained for many decades. A number of different genetic mutations can cause Usher syndrome type 2, including those of the USH2A gene (Usher syndrome type 2A). USH2A encodes for the protein usherin, which forms basement membranes in the inner ear and retina. The vision loss from Usher's syndrome is due to the condition retinitis pigmentosa, which involves the gradual deterioration of retinal rod photoreceptor cells (leading to night blindness), followed by cone receptor cells (affecting day time vision as well). Unlike Usher syndrome type 1, Usher syndrome type 2 does not affect a child's balance or their ability to stand up and walk. The prevalence of Usher syndrome type 2 in the USA is unknown, but it is believed to be more common than type 1, which occurs in over 4 in 100,000 people. The large number of relatively mild cases of type 2 mean that it is difficult to obtain accurate figures. It is estimated that 57-79% of Usher syndrome type 2 cases are caused by mutations in the USH2A gene. The condition is autosomal recessive, so typically an affected child will have two asymptomatic carrier parents.

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Usher Syndrome Type 1D (CDH23)

Usher syndrome is a condition that involves various degrees of deafness and gradual impairment of vision. Those with Usher syndrome type 1 are usually born deaf, and begin to lose vision while still children. A number of different genetic mutations can cause Usher syndrome type 1, including mutations in the CDH23 gene (Usher syndrome type 1D). CDH23 encodes for the protein cadherin 23, which is involved in cell aggregation, including aggregation in the retina and ear. The vision loss from Usher's syndrome is due to the condition retinitis pigmentosa, which involves the gradual deterioration of retinal rod photoreceptor cells (leading to night blindness), followed by cone receptor cells (leading eventually to complete blindness). In addition to deafness, Usher syndrome type 1 affects the ability to balance. Children with the condition are typically slow to stand up and walk. The prevalence of Usher syndrome type 1 in the USA is over 4 in 100,000. The number due to CDH23 mutations is relatively low. In a survey of 34 families with members affected by Usher syndrome type 1, only 6 were affected by defects in the CDH23 gene. Usher syndrome type 1 is more common in certain ethnic groups, such as Ashkenazi Jews and the Acadians (Cajuns) of Louisiana. The condition is autosomal recessive, so typically an affected child will have two asymptomatic carrier parents.

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SPINAL MUSCULAR ATROPHY

Spinal Muscular Atrophy (SMN1 Linked) (Werdnig-Hoffman)

Spinal muscular atrophy (SMA) can be caused by mutations in a number of genes. One of these is the SMN1 gene, which encodes for the spinal motor neuron protein. This protein is required for the maintenance of motor neurons in the spinal cord and brainstem. SMA is divided into different types: types 1-4 of SMA are all caused by mutations of the SMN1 gene, and all involve muscle weakness. Type 1 SMA first occurs before 6 months. Affected babies are unable to hold their heads up or sit up; they typically have difficulty swallowing and breathing, so they tend not to survive beyond the age of two. Type 2 SMA first occurs between 6 months and a year. Babies can sit up, but do not go on to stand or walk unaided in the usual manner. Type 3 SMA first occurs in older children. They can normally walk unaided, but may find climbing stairs or other similar tasks difficult. They may need to use a wheelchair by mid-life. Type 4 SMA first occurs in adulthood. Sufferers have some muscle weakness, tremors, and mild breathing problems. The incidence of all types of spinal muscular atrophy is around 1 in 6,000 to 1 in 10,000 births. It is estimated that around 1 in 40 to 1 in 50 people is a carrier. Although the incidence varies somewhat from country to country, it does not seem to be highly present in any ethnic group. The faulty gene is transmitted in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Modification of the Severity of Spinal Muscular Atrophy (SMN2)

Spinal muscular atrophy (SMA) can be caused by mutations in a number of genes. One of these is the SMN1 gene, which encodes for the spinal motor neuron protein. This protein is required for the maintenance of motor neurons in the spinal cord and brainstem. The SMN2 gene is also capable, to some extent, of producing spinal neuron protein. Most people have two or fewer copies of the SMN2 gene. However, some have three or more copies. In this latter group, the extra copies of the SMN2 gene can moderate the effects of mutations in the SMN1 gene, making any resulting SMA disease less severe than it would otherwise have been. SMA is divided into different types: types 1-4 of SMA are all caused by mutations of the SMN1 gene, and all involve muscle weakness. Type 1 SMA first occurs before 6 months. Affected babies are unable to hold their heads up or sit up. They typically have difficulty swallowing and breathing, and tend not to survive beyond the age of two. Type 2 SMA first occurs between 6 months and a year. Babies can sit up, but do not go on to stand or walk unaided in the usual manner. Type 3 SMA first occurs in older children. They can normally walk unaided, but may find climbing stairs or other similar tasks difficult. They may need to use a wheelchair by mid-life. It has been shown that patients from type 3 SMA are much more likely to have 3 or more copies of the SMN2 gene than patients from type 1 or the general population. Type 4 SMA first occurs in adulthood. Sufferers have some muscle weakness, tremors, and mild breathing problems. The incidence of all types of spinal muscular atrophy is around 1 in 6,000 to 1 in 10,000 births. It is estimated that around 1 in 40 to 1 in 50 people is a carrier. Although the incidence varies somewhat from country to country, it does not seem to be highly present in any ethnic group. The faulty SMN1 gene is transmitted in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Spinal Muscular Atrophy (UBA1)

Spinal muscular atrophy (SMA) can be caused by mutations in a number of genes, most commonly the SMN1 gene. However, it can also be caused by the UBA1 gene, which encodes for the ubiquitin-activating enzyme E1. SMA from UBA1 is referred to as X-linked SMA, as the gene resides on the X chromosome. This ubiquitin-activating enzyme breaks down unwanted proteins which can damage motor neurons responsible for muscle movement. Babies usually exhibit muscle weakness from birth, and are prone to lung disease and bone fractures. Typically, breathing becomes progressively more difficult, and very few survive childhood. Other types of SMA are the result of SMN1 mutations. Type 1 SMA first occurs before 6 months. Affected babies are unable to hold their heads up or sit up. They typically have difficulty swallowing and breathing, so tend not to survive beyond the age of two. Type 2 SMA first occurs between 6 months and a year. Babies can sit up, but do not go on to stand or walk unaided in the usual manner. Type 3 SMA first occurs in older children. They can normally walk unaided, but may find climbing stairs or other similar tasks difficult. They may need to use a wheelchair by mid-life. Type 4 SMA first occurs in adulthood. Sufferers have some muscle weakness, tremors, and mild breathing problems. The incidence of spinal muscular atrophy (all types) is around 1 in 6,000 to 1 in 10,000 births. However, SMA caused by the UBA1 gene is very rare. Less than 20 families with this condition have been found by researchers. The gene is on the Xchromosome, which affects males far more than females, as males only have one Xchromosome, and are affected by the disease if the chromosome carries a mutated UBA1 gene. For females, both X-chromosomes need to have a mutated UBA1 gene for the disease to occur, which is very unlikely. A woman with a mutated UBA1 gene on one X-chromosome can act as a carrier without showing symptoms.

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Spinal Muscular Atrophy (VAPB)

Spinal muscular atrophy (SMA) can be caused by mutations in a number of genes, usually the SMN1 gene. However, a few cases of adult-onset SMA have been linked to mutations in the VAPB gene, which produces the protein named "VAMP-associated protein B and C." Those with SMA from VAPB mutations begin to suffer from progressive muscle weakness, and may have cramps, tremors, and swallowing or breathing difficulties. Symptoms can begin at any age between 20 and 60. SMA from SMN1 defects is divided into different types, types 1-4: all involve muscle weakness. Type 1 SMA first occurs before 6 months. Affected babies are unable to hold their heads up or sit up. They typically have difficulty swallowing and breathing, so tend not to survive beyond the age of two. Type 2 SMA first occurs between 6 months and a year. Babies can sit up, but do not go on to stand or walk unaided in the usual manner. Type 3 SMA first occurs in older children. They can normally walk unaided, but may find climbing stairs or other similar tasks difficult. They may need to use a wheelchair by mid-life. Type 4 SMA first occurs in adulthood. Sufferers have some muscle weakness, tremors, and mild breathing problems. The incidence of spinal muscular atrophy (all types) is around 1 in 6,000 to 1 in 10,000 births. However, the adult-onset form related to the VAPB gene is much rarer, having only been found in a small number of families. The faulty gene is transmitted in an autosomal dominant manner, typically requiring at least one affected parent. If an asymptomatic parent died at a relatively young age, it is possible that the disease did not have time to present itself. The faulty gene is also associated with some cases of ALS (amyotrophic lateral sclerosis), also known as Lou Gehrig's disease.

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Spinal Muscular Atrophy (DYNC1H1)

Spinal muscular atrophy (SMA) can be caused by mutations in a number of genes, usually the SMN1 gene. However, in a few cases SMA is caused by mutations in the DYNC1H1 gene. This gene encodes for a protein that is part of a motor protein complex called dynein. If dynein is ineffective in moving proteins and other materials around cells, the motor neurons in the spinal cord may not function properly. The SMA caused by the DYNC1H1 gene causes muscle weakness only in the lower limbs, particularly the thigh muscles, so is referred to as spinal muscular atrophy, lower extremity, dominant (SMA-LED). Sufferers find it difficult to climb stairs, get up from a chair, or walk long distances. The disease normally first occurs in childhood, but is not life-threatening. SMA caused by SMN1 defects is divided into different types; types 1-4 of SMA all involve muscle weakness. Type 1 SMA first occurs before 6 months. Affected babies are unable to hold their heads up or sit up. They typically have difficulty swallowing and breathing, and tend not to survive beyond the age of two. Type 2 SMA first occurs between 6 months and a year. Babies can sit up, but do not go on to stand or walk unaided in the usual manner. Type 3 SMA first occurs in older children. They can normally walk unaided, but may find climbing stairs or other similar tasks difficult. They may need to use a wheelchair by mid-life. Type 4 SMA first occurs in adulthood. Sufferers have some muscle weakness, tremors, and mild breathing problems. The incidence of spinal muscular atrophy (all types) is around 1 in 6,000 to 1 in 10,000 births. However, SMA from DYNC1H1 mutations only affects a small number of families. Unlike SMN1 defects, which are autosomal recessive, the mutations in DYNC1H1 are autosomal dominant. Typically, autosomal dominant inheritance require at least one affected parent.

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MAPLE SYRUP DISEASE

Maple Syrup Urine Disease Type 1A (BCKDHA)

Maple syrup urine disease (MSUD) can be caused by mutations in a number of different genes, such as the BCKDHA gene. The BCKDHA gene encodes for the alpha subunit of the enzyme complex known as branched-chain alpha-keto acid dehydrogenase (BCKD), which is essential for the breakdown of branched chain amino-acids (leucine, isoleucine, and valine). Maple syrup urine disease is named due the sweet "maple syrup" smell from the urine of those with the disease. In the most common form of MSUD, untreated babies suffer from poor feeding and vomiting, followed by poor breathing, lethargy, and seizures. Death normally occurs within a few weeks of birth. Treatment is possible using special formula milk, followed by a special diet as an infant becomes older. However, it is difficult to always balance the amount of branched chain amino acids in the diet, since a small amounts must be supplied to maintain health. As they grow up, those with the condition tend to suffer from movement disorders, such as tremors, and various mental problems such as ADHD, low intelligence, autism, depression, and anxiety. In a minority of cases, the disease first shows itself later in infancy or during childhood, rather than immediately after birth. Some children suffer from an intermittent form of MSUD, where they appear normal most of the time, but attacks of the disease can be triggered by infections, stress, etc. Both the common form of the disease and the less severe forms can occur with defects in the BCKDA (Type 1A), BCKDB (Type 1B), and DBT (Type 2) genes; there is not a simple relation between severity and which gene is the cause. All types of Maple syrup urine disease occurs in about 1 in 185,000 live births worldwide. However, it is much more prevalent in old order Amish (BCKDHA defects) and Ashkenazi Jewish families (BCKDHB defects). The frequency of the disease reaches 1 in 380 live births in some old order Amish communities. The faulty gene is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Maple Syrup Urine Disease Type 1B (BCKDHB)

Maple syrup urine disease (MSUD) can be caused by mutations in a number of different genes, such as the BCKDHB gene. The BCKDHB gene encodes for the beta subunit of the enzyme complex known as branched-chain alpha-keto acid dehydrogenase (BCKD), which is essential for the breakdown of branched chain amino-acids (leucine, isoleucine, and valine). Maple syrup urine disease is named due the sweet "maple syrup" smell from the urine of those with the disease. In the most common form of MSUD, untreated babies suffer from poor feeding and vomiting, followed by poor breathing, lethargy, and seizures. Death normally occurs within a few weeks of birth. Treatment is possible using special formula milk, followed by a special diet as an infant becomes older. However, it is difficult to always balance the amount of branched chain amino acids in the diet, since a small amounts must be supplied to maintain health. As they grow up, those with the condition tend to suffer from movement disorders, such as tremors, and various mental problems, such as ADHD, low intelligence, autism, depression, and anxiety. In a minority of cases, the disease first shows itself later in infancy or during childhood, rather than immediately after birth. Some children suffer from an intermittent form of MSUD, where they appear normal most of the time, but attacks of the disease can be triggered by infections, stress, etc. Both the common form of the disease and the less severe forms can occur with defects in the BCKDA (Type 1A), BCKDB (Type 1B), and DBT (Type 2) genes; there is not a simple relation between severity and which gene is the cause. Maple syrup urine disease (all types) occurs in about 1 in 185,000 live births worldwide. However, it is much more prevalent in old order Amish (BCKDHA defects) and those of Ashkenazi Jewish descent (BCKDHB defects). The faulty gene is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Maple Syrup Urine Disease Type II (DBT)

Maple syrup urine disease (MSUD) can be caused by mutations in a number of different genes, such as the DBT gene. The DBT gene encodes for the E2 component of the enzyme complex known as branched-chain alpha-keto acid dehydrogenase (BCKD), which is essential for the breakdown of branched chain amino-acids (leucine, isoleucine, and valine). Maple syrup urine disease is named due the sweet "maple syrup" smell from the urine of those with the disease. In the most common form of MSUD, untreated babies suffer from poor feeding and vomiting, followed by poor breathing, lethargy, and seizures. Death normally occurs within a few weeks of birth. Treatment is possible using special formula milk, followed by a special diet as an infant becomes older. However, it is difficult to always balance the amount of branched chain amino acids in the diet, since a small amounts must be supplied to maintain health. As they grow up, those with the condition tend to suffer from movement disorders, such as tremors, and various mental problems such as ADHD, low intelligence, autism, depression, and anxiety. In a minority of cases, the disease first shows itself later in infancy or during childhood, rather than immediately after birth. Some children suffer from an intermittent form of MSUD, where they appear normal most of the time, but attacks of the disease can be triggered by infections, stress, etc. Both the most common form of the disease and the less severe forms can occur with defects in the BCKDA (Type 1A), BCKDB (Type 1B), and DBT (Type 2) genes; there is not a simple relation between severity and which gene is the cause. All types of Maple syrup urine disease occur in about 1 in 185,000 live births worldwide. However, it is much more prevalent in old order Amish (BCKDHA defects) and those of Ashkenazi Jewish descent (BCKDHB defects). The faulty gene is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Maple Syrup Urine Disease Type 3 (Dihydrolipoamide dehydrogenase deficiency) (DLD)

Maple syrup urine disease (MSUD) can be caused by mutations in a number of different genes, including the DLD gene. The DLD gene encodes for the enzyme dihydrolipoamide dehydrogenase. This enzyme is involved in a number of different enzyme complexes, including branched-chain alpha-keto acid dehydrogenase (BCKD), which is essential for the breakdown of branched chain amino-acids (leucine, isoleucine, and valine). Maple syrup urine disease is named due the sweet "maple syrup" smell from the urine of those with the disease, although the odor is seldom present in the type 3 disease. In the more common form of MSUD, untreated babies suffer from poor feeding and vomiting, followed by poor breathing, lethargy, and seizures. Death normally occurs within a few weeks of birth, but can be avoided by special formula milk, etc. As they grow up, those with the condition tend to suffer from movement disorders, such as tremors, and various mental problems, such as ADHD, low intelligence, autism, depression, and anxiety. However, in type 3 of maple syrup disease, many other symptoms can be present, since the dihydrolipoamide dehydrogenase enzyme is a component of other enzyme complexes, such as the pyruvate dehydrogenase complex. Lactic acidosis is common in infants with the type 3 disease, giving rise to muscle weakness and lethargy. Type 3 MSUD is vary variable, and in some cases the symptoms of the most common form of MSUD are absent, or their onset delayed. The disease is often episodic, worsening when the body is stressed by an infection, etc. Adult-onset liver disease can occur, which is not a normal symptom of MSUD. All types of Maple syrup urine disease occur in about 1 in 185,000 live births worldwide. Type 3 MSUD is extremely rare, but is most commonly seen in those of Ashkenazi Jewish descent, where it affects about 1 in 40,000 individuals. The faulty gene is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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FANCONI ANEMIA

Fanconi Anemia: Type A (FANCA)

Fanconi Anemia can be caused by defects in a number of genes, one of which is FANCA. This gene is involved in producing a protein involved in DNA repair, which it carries out via the so-called Fanconi anemia pathway. If the protein fails to function, DNA repair will not be carried out as normal, which can lead to many abnormalities, particularly affecting the bone marrow and blood cells. Patients have anemia and tend to suffer from infections. They are much more at risk of leukemia and other cancers than the general population. The majority of patients have one or more physical abnormalities, although a large minority are physically normal. A wide range of physical problems are possible. Common issues include short statue, unusual skin pigmentation, misshapen thumbs, microcephaly, eye defects, and deformed kidneys or genitals. The majority of those with the disease die before the age of 30. The overall incidence of Fanconi anemia is roughly 1 in 160,000, of which about 60- 70% are due to defects in the FANCA gene. Some populations, such as Spanish Roma, black South Africans, and Ashkenazi Jews, are at greater risk of the disease. Fanconi anemia type A is inherited in an autosomal recessive manner, typically requiring both parents to carry a faulty gene asymptomatically.

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Recombine Website: Fanconi Anemia Type A.
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Fanconi Anemia: Type C (FANCC)

Fanconi Anemia can be caused by defects in a number of genes, one of which is FANCC. This gene is involved in producing a protein involved in DNA repair, which it carries out via the so-called Fanconi anemia pathway. If the protein fails to function, DNA repair will not be carried out as normal, which can lead to many abnormalities, particularly affecting the bone marrow and blood cells. Sufferers have anemia and tend to suffer from infections. They are much more at risk of leukemia and other cancers than the general population. The majority of sufferers have one or more physical abnormalities, although a large minority are physically normal. A wide range of physical problems are possible. Common issues include short statue, unusual skin pigmentation, misshapen thumbs, microcephaly, eye defects, and deformed kidneys or genitals. The majority of those with the disease die before the age of 30. The overall incidence of Fanconi anemia is roughly 1 in 160,000, of which about 14% are due to defects in the FANCC gene. Some populations, such as Spanish Roma, black South Africans, and Ashkenazi Jews, are at greater risk of the disease. There is high incidence of Fanconi anemia type C in the latter community, the carrier rate being about 1 in 100. Fanconi anemia type C is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Fanconi Anemia: Type F (FANCF)

Fanconi Anemia can be caused by defects in a number of genes, one of which is FANCF. This gene is involved in producing a protein involved in DNA repair, which it carries out via the so-called Fanconi anemia pathway. If the protein fails to function, DNA repair will not be carried out as normal, which can lead to many abnormalities, particularly affecting the bone marrow and blood cells. Patients have anemia and tend to suffer from infections. They are much more at risk of leukemia and other cancers than the general population. The majority of sufferers have one or more physical abnormalities, although a large minority are physically normal. A wide range of physical problems are possible. Common issues include short statue, unusual skin pigmentation, misshapen thumbs, microcephaly, eye defects, and deformed kidneys or genitals. The majority of those with the disease die before the age of 30. The overall incidence of Fanconi anemia is roughly 1 in 160,000, of which about 2% are due to defects in the FANCF gene. Some populations, such as Spanish Roma, black South Africans, and Ashkenazi Jews, are at greater risk of the disease. Fanconi anemia type F is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Fanconi Anemia: Type G (FANCG)

Fanconi Anemia can be caused by defects in a number of genes, one of which is FANCG. This gene is involved in producing a protein involved in DNA repair, which it carries out via the so-called Fanconi anemia pathway. If the protein fails to function, DNA repair will not be carried out as normal, which can lead to many abnormalities, particularly affecting the bone marrow and blood cells. Sufferers have anemia and tend to suffer from infections. They are much more at risk of leukemia and other cancers than the general population. The majority of patients have one or more physical abnormalities, although a large minority are physically normal. A wide range of physical problems are possible. Common ones include short statue, unusual skin pigmentation, misshapen thumbs, microcephaly, eye defects, and deformed kidneys or genitals. The majority of those with the disease die before the age of 30. The various types of the disease produce similar symptoms, although there is some evidence that leukemia is more likely to develop with Type G. The overall incidence of Fanconi anemia is roughly 1 in 160,000, of which about 10% are due to defects in the FANCG gene. Some populations, such as Spanish Roma, black South Africans, and Ashkenazi Jews, are at greater risk of the disease. Fanconi anemia type G is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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LONG Q-T SYNDROME

Long QT Syndrome 5 (KCNE1)

Long QT Syndrome 5 (KCNE1) Long QT syndrome 5 (LQT5) is a heart condition caused by defects in the KCNE1 gene, which encodes for a protein involved in potassium channel regulation. Potassium channels in the heart muscles are important for maintaining a consistent heartbeat Long QT refers to the elongation of the heartbeat, depicting an abnormal wave pattern on an electrocardiogram (ECG) seen with LQT patients. Such patients are at risk of episodes of increased heart rate, known as torsades de point, which may result in fainting or cardiac arrest. Death can sometimes occur, even in young people, so it is important that any fainting episodes are properly investigated. Treatments are by means of beta-blockers or implantable cardioverter-defibrillators (ICDs). Long QT syndrome types such as this, which only affect the heart, are also known as Romano-Ward syndrome.

Overall, it's estimated that about 1 in 2,000 people, suffer from LQT, some without knowing it. The condition does not seem to be more prevalent in any ethnic group. LQT5 (KCNE1 gene) only makes up <1% of the total cases of LQT, leading to less than 1 in 200,000 having the condition. The affected gene is inherited in an autosomal dominant manner, which normally is inherited from one parent who also has the condition.

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Long QT Syndrome 6 (KCNE2)

Long QT syndrome 6 (LQT6) is a heart condition caused by defects in the KCNE2 gene, which encodes for a protein involved in potassium channel regulation. Potassium channels in the heart muscles are important for maintaining a consistent heartbeat. Long QT refers to the elongation of the heartbeat, depicting an abnormal wave pattern on an electrocardiogram (ECG) seen with LQT patients. Such patients are at risk of episodes of increased heart rate, known as torsades de point, which can result in fainting or cardiac arrest. Death can sometimes occur, even in young people, so it's important that any fainting episodes are properly investigated. Treatment is by means of beta-blockers or implantable cardioverter-defibrillators (ICDs). Long QT syndromes, which only affect the heart, are also known as Romano-Ward syndrome. Overall, it's estimated that about 150,000 people suffer from LQT, some without knowing it. The condition does not seem to be more prevalent in any ethnic group. LQT6 (KCNE2 gene) only makes up <1% of the total cases of LQT, so less than 1 in 200,000, or 1,500 people, have the condition. The affected gene is inherited in an autosomal dominant manner, which normally is inherited from one parent who also has the condition.

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Long QT Syndrome 1 (KCNQ1)

Long QT syndrome 1 (LQT1) is a heart condition caused by defects in the KCNQ1 gene, which encodes for a protein involved with potassium channels, which are fundamental for maintaining a consistent heartbeat. Long QT refers to the elongation of the heartbeat, depicting an abnormal wave pattern on an electrocardiogram (ECG) seen with LQT patients. Such patients are at risk of episodes of increased heart rate, known as torsades de point, which can result in fainting or cardiac arrest. Death can sometimes occur, even in young people, so it's important that any fainting episodes are properly investigated. Treatment is by means of beta-blockers or implantable cardioverter-defibrillators (ICDs). Long QT syndrome types such as this, which only affect the heart, are also known as Romano-Ward syndrome. Overall, it's estimated that about 1 in 2,000 people suffer from LQT, translating to approximately 150,000 cases. The condition does not seem to be more prevalent in any ethnic group. LQT1 makes up 30 to 35% of the total cases of LQT, so roughly 1 in 6,000, or 50,000 cases, have the condition caused by the KCNQ1 gene. The affected gene is inherited in an autosomal dominant manner, which normally is inherited from one parent who also has the condition.

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Long QT Syndrome 3 (SCN5A)

Long QT syndrome 3 (LQT3), is a heart condition caused by defects in the SCN5A gene, which encodes for a protein, sodium channel voltage gated type V alpha subunit, that makes up sodium channels. Such channels in the heart muscles are important for maintaining a regular heartbeat. Long QT refers to the elongation of the heartbeat, depicting an abnormal wave pattern on an electrocardiogram (ECG) seen with LQT patients. Such patients are at risk of episodes of increased heart rate, known as torsades de point, which can result in fainting or cardiac arrest. Death can sometimes occur, even in young people, so it's important that any fainting episodes are properly investigated. Treatment is by means of beta-blockers or implantable cardioverter-defibrillators (ICDs). Long QT syndrome types such as this, which only affect the heart, are also known as Romano-Ward syndrome. Overall, it's estimated that about 1 in 2,000, or 150,000 people, suffer from LQT, some without knowing it. The condition does not seem to be more prevalent in any ethnic group. LQT3 makes up 5 to 10% of the total cases of LQT, roughly 1 in 20,000 to 1 in 40,000 have the condition caused by the SCN5A gene. The affected gene is inherited in an autosomal dominant manner, which normally is inherited from one parent who also has the condition.

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Long QT Syndrome 11 (AKAP9)

Long QT syndrome 11 (LQT11) is a heart condition caused by defects in the "A kinase anchor protein 9," or AKAP9 gene, which encodes for protein AKAP9. It is involved in the anchoring of the protein kinase A enzyme complex in the cell and other cellular functions. In the heart, protein kinase A is involved in the activation of various ion channel proteins through phosphorylation, which are important for maintaining a regular heartbeat. Long QT refers to the abnormal signal on an electrocardiogram (ECG) seen with LQT patients. Such patients are at risk of episodes of increased heart rate, known as torsades de point, which may result in fainting or cardiac arrest. Death can sometimes occur, even in young people, so it is important that any fainting episodes are properly investigated. Treatment is by means of beta-blockers or implantable cardioverter-defibrillators (ICDs). Long QT syndrome types such as this, which only affect the heart, are also known as Romano-Ward syndrome. Overall, it's estimated that about 1 in 2000 people, or 150,000 cases, suffer from LQT, some without knowing it. The condition does not seem to be more prevalent in any ethnic group. The affected gene is inherited in an autosomal dominant manner, which normally is inherited from one parent who also has the condition.

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NIEMANN PICK DISEASE

Niemann-pick Disease Type C1 (NPC1)

Niemann-Pick Disease Type C1 is caused by mutations in the NPC1 gene. This gene is involved in producing a protein involved in the transportation of lipids, including cholesterol. Mutations in the NPC2 gene cause similar effects (Type C2). Symptoms of Niemann Pick C1 typically develop in early childhood, but can first appear in adults. Muscle weakness and ataxia (poor control of movements, etc.) become gradually apparent, along with liver disease, seizures (in some cases), and progressive mental deterioration. Patients are often unable to move their eyes vertically (vertical supranuclear gaze palsy). Swallowing and speech deteriorate progressively, leading to a complete inability to ingest food. Respiratory failure may also occur. Most patients die in their 20's or 30's. When the disease first appears in adulthood, psychiatric symptoms tend to predominate. The total incidence of Niemann-Pick disease Type C is around 1 in 120,000 births. About 90% are due to the NPC1 gene. The disease is more common in some ethnic groups, such as Hispanics whose ancestors lived in the upper Rio Grande valley. The defective genes are inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers.

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Niemann Pick Disease: Type C2 (NPC2)

Niemann-Pick Disease Type C2 is caused by mutations in the NPC2 gene. This gene is involved in producing a protein involved in the transportation of lipids, including cholesterol. Mutations in the NPC1 gene cause similar effects (Type C1, which is much more common). Symptoms of Niemann Pick C2 typically develop in early childhood, but can first appear in adults. Muscle weakness and ataxia (poor control of movements, etc.) become gradually apparent, along with liver disease, seizures (in some cases), and progressive mental deterioration. Sufferers are often unable to move their eyes vertically (vertical supranuclear gaze palsy). Swallowing and speech deteriorate progressively, leading to a complete inability to ingest food. Respiratory failure can also occur. Early death is likely, although some sufferers live for many decades. When the disease first appears in adulthood, psychiatric symptoms tend to predominate. The total incidence of Niemann-Pick disease Type C is around 1 in 120,000 births, translating to 2,500 occurrences in the USA. About 4-5% are due to the NPC2 gene. The defective genes are inherited in an autosomal recessive manner, typically requiring both parents to carry the faulty gene asymptomatically.

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Tay-Sachs (HEXA)

Tay-Sachs disease is caused by mutations in the HEXA gene, which encodes for one subunit of the enzyme beta-hexosaminidase A. The enzyme breaks down the toxic substance GM2 ganglioside in the brain and spinal cord. Symptoms usually develop from three months onwards, including loss of motor skills, increasing weakness, and strong startle response. Loss of vision and hearing, seizures, and paralysis normally follow. Life expectancy is 2 to 4 years. Very rare related diseases, which begin later in childhood, adolescence, or early adulthood are also known, but the symptoms are usually much milder. Tay-Sachs is rare in the general population, but tends to be concentrated in various ethnic groups. Among those of Ashkenazi Jewish descent, about 1 in 30 are carriers for the disease. There is also a high level of carriers in the Acadian (Cajun) population of Louisiana, and among French Canadians. However, extensive genetic counseling has led to a large reduction in the number of live births over recent decades. The faulty gene is autosomal recessive, typically requiring both parents to be asymptomatic carriers of the faulty gene copy.

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Canavan Disease (ASPA)

Canavan disease is a disease affecting the brain, caused by defects in the ASPA gene. The gene encodes for the enzyme aspartoacylase, whose function is to decompose excess N-acetyl-L-aspartic acid (NAA) in the brain. If the enzyme fails to function, excess NAA interferes with the development of the myelin sheath, the insulating covering around axons which functions to increase speed of neural transmission. The most common form of Canavan Disease, the neonatal or infantile form, causes a failure to develop normal motor skills. They suffer from macrocephaly, hypotonia, and often irritability. Seizures and difficulty swallowing may occur. Children rarely survive beyond their teens, and many die earlier. A milder form of the disease, the juvenile form, sometimes occurs. This is associated with slower than normal development of speech and motor skills, but does not normally lead to severe symptoms or a shortened lifespan. Canavan disease is most common in those of Ashkenazi Jewish descent, where it is estimated to occur in 1 in 6,400 to 1 in 13,500 births. The incidence in the general population is much lower, but accurate estimates are not available. The disease is inherited as autosomal recessive, which typically requires both parents to be carriers of the faulty gene, most likely asymptomatically.

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Sickle Cell Disease (HBB)

Sickle cell disease is caused by mutations in the HBB gene, which encodes for the protein beta-globin, a component of hemoglobin. The main form of the disease is sickle cell anemia, where the red blood cells are bent into a sickle shape. Sickle cells break down more quickly than normal cells, often resulting in anemia. The irregular cell shape tends to block blood vessels, which can lead to pain and ischemia of organs, including strokes. Jaundice and damage to the spleen often occur. In some cases, pulmonary hypertension can occur and lead to heart failure. Other than sickle cell formation, other abnormal forms of hemoglobin can form. The various symptoms of sickle cell anemia shorten live expectancy to about 40 to 60 years. Sickle cell disease tends to be concentrated in particular ethnic groups. About 1 in 500 African Americans have sickle cell disease, while the figure is about 1 in 1,000 to 1 in 1,400 for Hispanic Americans. In all about 100,000 Americans suffer from sickle cell disease. As the population of the USA is around 321 million, this means that about 1 in 3210 Americans has the disease, making it the most common inherited blood disease. The faulty gene is autosomal recessive, typically requiring both parents to be asymptomatic carriers of the faulty gene copy.

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Gaucher Disease (GBA)

Gaucher Disease is caused by mutations in the GBA gene. This gene encodes for the enzyme beta-glucocerebrosidase, which breaks down the substance glucocerebroside. The buildup of glucocerebroside causes damage to various organs. There are various types of Gaucher disease. Type 1 is the most common, and involves anemia, lung disease, enlargement of the spleen and liver, easy bruising of the skin, and skeletal disorders such as arthritis and high risk of fractures. The nervous system is not affected in type 1 Gaucher disease. Types 2 and 3 involve serious damage to the nervous system, with type 2 being the more aggressive, leading normally to early mortality. A perinatal form of the disease is also known, leading to prompt death after birth. Finally, a cardiovascular form of the disease mainly involves damage to the heart valves. In the general population, Gaucher disease is found in 1 in 60,000 to 1 in 80,000 new births. It is much more prevalent in various ethnic groups. Among those of Ashkenazi Jewish descent, the disease is found in 1 in 855 people (nearly all Type 1), with around 1 in 18 people being carriers. The disease is autosomal recessive, typically requiring both parents to be asymptomatic carriers of the faulty gene copy.

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Phenylketonuria (PAH)

Phenylketonuria (PKU) is caused by mutations in the PAH gene. This gene encodes for the enzyme phenylalanine hydroxylase, which breaks down the amino acid phenylalanine. The buildup of phenylalanine causes damage to the body, affecting mainly the brain. If left untreated, those with phenylketonuria suffer from intellectual disability, seizures, delayed development, and psychiatric problems. A musty odor from phenylalanine may be evident. Treatment is by a special low phenylalanine diet, which can allow for normal development if strictly adhered to. There are rarer, less damaging forms of the disease, known as non-PKU hyperphenylalaninemia. Phenylketonuria is found in 1 in 10,000 to 1 in 15,000 new births. Since screening and prompt treatment are almost universal in the USA, the symptoms are very rarely seen. The disease is more common in some ethnic groups, such as Turks (1 in 2,600 births) and Irish (1 in 4,600 births). The condition follows an autosomal recessive pattern, typically requiring both parents to be carriers asymptomatically.

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Glycogen Storage Disease II (GAA)

Glycogen storage disease II, also known as Pompe disease, is caused by mutations in the GAA gene. This gene encodes for the enzyme alpha-glucosidase, which breaks down glycogen into glucose. Without this enzyme, glycogen can build up to toxic levels, damaging muscles, including the heart muscles, as well as an inability to maintain normal fasting glucose levels. The classic form of the disease emerges in the first few months of life. Babies exhibit muscle weakness, breathing difficulties, heart problems, and fail to thrive. Mortality rates are high, few surviving the first year without treatment. A "non-classic" infantile form appears in the first year of life. Symptoms are similar, but the heart tends to be less severely affected. Even so, breathing difficulties mean that few survive for more than a few years without treatment. A late-onset form of the disease is also known, in which symptoms first appear during late childhood, adolescence, or adulthood. Here muscle weakness and respiratory problems arise, but usually the heart is unaffected. Most sufferers from this form die within 30 years of diagnosis without treatment. Enzyme replacement therapy, along with treatment for the various symptoms, can extend survival to some extent. The incidence of glycogen storage disease type II is around 1 in 40,000 in the USA, rising to 1 in 14,000 among African Americans. The carrier rate reaches about 1 in 60 in the latter population. The defective genes are inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers for the faulty gene.

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Bloom Syndrome (BLM)

Bloom syndrome is caused by mutations in the BLM gene, which encodes for one of the RecQ helicase proteins. These proteins have an important role in preserving the integrity of DNA, as well as catalyzing key reactions that are crucial for DNA unwinding. Those with the disease have unusually short stature, and are very sensitive to sunlight, often having reddish marks on their faces. Men are sterile, while women have reduced fertility with an early onset of menopause. Most sufferers are of normal intellectual ability, although some suffer from learning difficulties. Cancer is much more likely in those with Bloom syndrome, often first appearing in their 20s or 30s. Early mortality from cancer is common, although sufferers often respond successfully to treatment. Bloom disease is an extremely rare condition, with about 300 cases known worldwide, about a quarter of which are among those Ashkenazi Jewish descent. The condition is autosomal recessive, which typically requires an affected child to have two asymptomatic carrier parents.

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Alpha Thalassemia (HBA1 / HBA2)

Alpha Thalassemia is caused by defects in the HBA1 or HBA2 genes. These genes encode for the protein alpha-globin, a component of hemoglobin. There are two forms of the disease: Hb Bart syndrome and HbH disease. The former is more severe, affecting unborn babies. They suffer from general edema (swelling from fluid buildup), anemia, heart defects, and enlargement of the liver and spleen. Most are stillborn, or die within a few days of birth. Carrying an Hb Bart fetus may be harmful to the mother. HbH disease involves moderate anemia, jaundice, and enlargement of the liver and spleen. Abnormal skeletal changes are sometimes seen. Symptoms may begin in either childhood or adulthood. Generally, those with HbH can live a near-normal lifespan, although some may need blood transfusions if anemia becomes severe. The inheritance of the faulty genes is complex, but involves a number of categories of both carriers and those with symptoms. The disease is relatively common, particularly in South-East Asia. Other regions badly affected include India, the Middle East, Africa, and Mediterranean countries. Worldwide, about 1 in 48 people are carriers for the condition.

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Beta Thalassemia (HBB)

Beta Thalassemia is caused by mutations in the HBB gene, which encodes for the protein beta-globin, a subunit of hemoglobin. There are two forms of the disease, beta thalassemia major and beta thalassemia intermedia, the latter being less severe. With beta thalassemia major, symptoms develop before the age of two. Severe anemia is common, necessitating frequent blood transfusions. Other symptoms include jaundice, skeletal defects, and enlargement of the heart, liver, and spleen. Delayed adolescence may occur. Over time, excess iron from transfusions builds up in the body, and needs to be removed by chelation drugs. Premature death from cardiac mortality is common, but decreasing as treatments improve. Thalassemia intermedia is associated with mild anemia, some skeletal abnormalities, and in some cases growth inhibition. The worldwide incidence of beta-thalassemia is 1 in 100,000 new births. Regions with high levels of the disease include Mediterranean countries, the Middle-East, Central Asia, Africa, and the Far East. In the USA, those whose ancestors came from these regions have a higher risk of the disease than other ethnic groups. The mutated gene is inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers of the faulty gene copy.

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Mucolipidosis IV (MCOLN1)

Mucolipidosis type IV is a disease caused by defects in the MCOLN1 gene, which encodes for the protein mucolipin 1. This protein is found in the membranes of lysosomes and endosomes, and is involved in the transport of various molecules. Mucolipin 1 is essential for the development and maintenance of the brain and retina. Infants with the disease typically develop poor motor skills, being slow to crawl, and rarely learning to walk or speak properly. Sufferers may have muscle weakness and difficulties swallowing. Visual impairment gradually advances, usually leading to complete blindness before the age of 10. Iron deficiency may occur as well. A small number of sufferers, about 5% of the total, develop a milder form of the disease, where they may be able to walk and talk. People with mucolipidosis type IV may live for many decades, although they tend to have a shortened lifespan. Overall, it's estimated that about 1 in 625,000 people suffer from mucolipidosis type IV, although the figure rises to 1 in 37,000 among those of Ashkenazi Jewish descent, where about 1 in 100 may be carriers. The faulty gene is inherited in an autosomal recessive manner, which typically requires both parents to be asymptomatic carriers of the faulty gene copy.

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Familial Dysautonomia (IKBKAP)

Familial dysautonomia is caused by defects in the IKBKAP gene. This gene encodes for a protein called IKK complex-associated protein, which plays a role in protein transcription. Nerve cells are adversely affected when the protein fails to function. Children with the disease typically suffer from gastrointestinal problems (such as vomiting), feeding difficulties, somewhat stunted growth, muscle weakness, and a lack of sensitivity to pain or temperature. Sufferers are liable to suffer from lung infections far more than normal. Curvature of the spine and deterioration in vision often occur. Walking becomes increasingly difficult as adulthood is reached, and many patients reach the point where they are no longer able to walk unaided. Kidney damage is also common during adulthood. Early death is likely, often due to lung infections, although improvements to treatment mean that around half of all patients now survive to age 40. Familial Dysautonomia is normally found in those of Ashkenazi Jewish descent, where about 1 in 3,700 are affected; approximately 1 in 36 are carriers. The mutated gene is inherited in an autosomal recessive manner, which typically requires both parents to be asymptomatic carriers of the faulty gene copy. However, there have been cases of both male and female sufferers having children, although pregnancy is high risk for those with the condition. The offspring between affected patients and non-carriers will normally be asymptomatic carriers.

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Glycogen Storage Disease II (GAA)

Glycogen storage disease II, also known as Pompe disease, is caused by mutations in the GAA gene. This gene encodes for the enzyme alpha-glucosidase, which breaks down glycogen into glucose. Without this enzyme, glycogen can build up to toxic levels, damaging muscles, including the heart muscles, as well as an inability to maintain normal fasting glucose levels. The classic form of the disease emerges in the first few months of life. Babies exhibit muscle weakness, breathing difficulties, heart problems, and fail to thrive. Mortality rates are high, few surviving the first year without treatment. A "non-classic" infantile form appears in the first year of life. Symptoms are similar, but the heart tends to be less severely affected. Even so, breathing difficulties mean that few survive for more than a few years without treatment. A late-onset form of the disease is also known, in which symptoms first appear during late childhood, adolescence, or adulthood. Here muscle weakness and respiratory problems arise, but usually the heart is unaffected. Most sufferers from this form die within 30 years of diagnosis without treatment. Enzyme replacement therapy, along with treatment for the various symptoms, can extend survival to some extent. The incidence of glycogen storage disease type II is around 1 in 40,000 in the USA, rising to 1 in 14,000 among African Americans. The carrier rate reaches about 1 in 60 in the latter population. The defective genes are inherited in an autosomal recessive manner, typically requiring both parents to be asymptomatic carriers for the faulty gene.

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Recombine Website: Glycogen Storage Disease, Type 2.
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Classical Galactosemia (GALT)

Classical galactosemia is caused by mutations in the GALT gene. This gene encodes for the enzyme galactose-1-phosphate uridyltransferase, which is one of the enzymes that break down galactose. If the enzyme fails to function, increasing amounts of galactose-1-phosphate build up in the body, causing damage to tissues. The symptoms usually appear in the first few days of life. Babies suffer from vomiting, diarrhea, liver damage, jaundice, and fail to thrive. They are more susceptible to infection from bacteria such as E. coli than normal. Untreated babies usually die, or have severe brain damage. Feeding babies from birth on lactose-free formula milk is necessary. As they get older, a special diet absent of galactose and lactose is necessary. Even so, treated children are still at risk of poor growth, eye and speech problems, and mild intellectual disability. Women tend to suffer from premature ovarian insufficiency, so may not be able to have children. A "clinical variant" galactosemia, with slightly milder symptoms and without the increased risk of bacterial infection, has been described. This is also caused by defects in the GALT gene. Other types of galactosemia are caused by defects in other genes. The incidence of classical galactosemia has been estimated as 1 in 10,000 to 1 in 48,000 in the general population. The disease is particularly common among Irish travelers and their descendants, where up to 1 in 14 may be carriers, compared to about 1 in 125 in the general population. The "clinical variant" form is mainly found in African Americans. The disease is autosomal recessive, typically requiring both parents to be asymptomatic carriers of the faulty gene. If a sufferer has children with a partner who is not a carrier for the disease, the children will be asymptomatic carriers.

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Ornithine Transcarbamylase Deficiency (OTC)

Ornithine transcarbamylase deficiency is caused by mutations in the OTC gene. This gene encodes for the enzyme ornithine transcarbamylase, which carries out a key step in the urea cycle. The liver alters toxic ammonia and converts it to urea, a much safer is converted into urea, a much more neutral compound. If the enzyme is partially or wholly inactivated, damaging levels of ammonia will tend to build up in the body. The condition is much more common in males than females. Symptoms often occur within the first few days of life. They include poor feeding, muscle weakness, lethargy, seizures, and hyperventilation. Severe hypothermia and brain damage result if prompt treatment is not started. Dialysis and nitrogen scavenger compounds, such as sodium benzoate, can be used to remove ammonia from the body. Even when ammonia levels appear to be under control, a crisis can appear in which they become elevated again. Low protein diets are needed throughout life. Infants may even require a liver transplant. A late-onset form of the disease can commence later in life, sometimes triggered by injuries, operations, or starting a high protein diet. Typical symptoms include mental problems, headaches, and vomiting. The incidence of the disease is roughly 1 in 70,000 births, occurring in roughly 4,300 patients in the USA. There does not seem to be huge differences in its occurrence among different ethnic groups. The faulty gene resides on the X chromosome, also known as an X-linked disease. Unlike females, any male with the faulty gene will have the disease since males only have a single X chromosome. The severe version of the disease is very rare in females, since they would need two faulty genes, which is highly unlikely. Females with one faulty gene normally act as carriers with no symptoms, however 15% of them will show some symptoms during their lifetime. As the disease is linked to the X chromosome, affected fathers cannot pass it on to their sons. Their daughters of affected fathers will normally receive the faulty gene.. Mothers with the faulty gene, whether they are asymptomatic or not, have a 50% chance of passing it on to each child.

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