17/MHS01/302

NEUROANATOMY

MEDICINE AND SURGERY

MEDICINE AND HEALTH SCIENCE

QUESTION: Write a concise review of the developmental genetics of the cerebellum and highlight the genetic basis of known cerebellar disorders

ANSWER:

ABSTRACT

The cerebellum is a pre-eminent model for the study of neurogenesis and circuit assembly. Increasing interest in the cerebellum as a participant in higher cognitive processes and as a locus for a range of disorders and diseases makes this simple yet elusive structure an important model in a number of fields. The cerebellum ('little brain') resides at the anterior end of the hindbrain and is classically defined by its role in sensory-motor processing. In amniotes, it represents one of the most architecturally elaborate regions of the central nervous system (CNS), and in humans it contains over half of the mature neurons in the adult brain. Although it is easiest to consider how developmental phases fit together in the mammal, it is important to recognize that, beyond the stereotyped neuronal Purkinje-granule cell circuit, evolutionary variability in cerebellum form reflects variability in how these phases are deployed in the embryo. Thus, the territory that will generate the cerebellum – its 'anlage'–is allocated during the early embryonic segmental phase of hind brain development close to the boundary (the 'isthmus') between the hindbrain and the midbrain. However, as we will describe, regulation of patterning in this earliest phase seems particularly important for the development of the uniquely mammalian midline expanded region of the cerebellum known as the 'vermis'.

INTRODUCTION

Although the cerebellum is crucial for controlling movement, it is also implicated in higher order function such as cognition. Accordingly, its contribution to disease likely extends beyond the ataxias to include autism spectrum disorders and schizophrenia. Its potential involvement in developmental and adult onset diseases and its well-understood circuitry makes the cerebellum an attractive model for investigating the mechanistic underpinnings and embryonic origins of brain circuit malformation. Soon after the cerebellar primordium is formed at the midbrain/hindbrain boundary, two primary germinal zones, the ventricular zone and the rhombic lip, sequentially generate various inhibitory and excitatory neurons, respectively.

OVERVIEW OF HUMAN CEREBELLAR DEVELOPMENT

The cerebellum develops from the dorsal region of the posterior neural tube. The embryonic cerebellum begins as little more than symmetric bulges into the early fourth ventricle: cerebellar

hemispheres arise as mere buds from laminae on either side of the rhombencephalic midline, and the most rostral segment of the metencephalon produces outgrowths that form the first elements of the cerebellum. These lateral elements develop towards the midline and fuse in a rostral-to caudal direction. As the primitive hemispheres come into contact with each other, they form first the superior and then the inferior vermis. The lateral elements from this fusion develop into the cerebellar hemispheres. Cells in the cerebellum arise from two different germinal matrices. From the ventricular zone (also known as the ventricular germinal matrix), cells radiate laterally and evolve into the deep cerebellar nuclei and Purkinje cells of the cerebellar cortex. The first cells to be born become the deep cerebellar nuclei at about week eight in human embryogenesis. At week nine, the ventricular zone begins to produce cells that will eventually form the Purkinje neurons. By 24 weeks, these proto-Purkinje cells send dendrites to the PARALLEL FIBRES of the granule neurons. The full number of Purkinje cells is present early on, but their mature monolayer forms sometime between 16 and 28 weeks postnatally. Purkinje cells continue their maturation after birth, projecting to the deep cerebellar nuclei and refining the input they receive from the CLIMBING FIBRES of inferior olivary neurons. From the ventricular zone, a third population of neurons is born after the formation of Purkinje cells. These neurons include the stellate, basket and Golgi interneurons that can be found in the molecular layer. These three kinds of neurons have a modulatory action on the Purkinje cells and granule neurons. Unlike most of the cell types of the cerebellum, which are born at the ventricular zone, cerebellar granule neurons come from a specialized germinal matrix called the rhombic lip. Migration of these primitive cells over the surface of the cerebellum starts as early as week 11 in humans; neuronal elements are present in the external granular layer (EGL) by week 27. From the EGL, a second zone of proliferation, the granule neuron precursors, migrate deeper into the cortex. This inward migration continues after birth, with the EGL disappearing within the first year of life in humans. In the past decade, genetic studies of various mouse mutants became the primary source of information about cerebellar development. The rest of the review will focus on what is known about the development of the mouse cerebellum, highlighting some of the important genes and signaling pathways involved.

GENES INVOLVED IN VARIOUS STAGES OF CEREBLLAR DEVELOPMENT.

S/N	STAGES/AREAS OF DEVELOPMENT	GENES, PROTEINS AND MOLECULES
1	Cerebellar primordium	Otx2, Gbx2, Fgf8, Wnt1, En1/2, Pax2/5, Bmps, Shh, Hoxa2
2	Granule cell generation	Math1, RU49/Zipro1, Zic1,2,3, Shh pathway, Ccnd2, p27, Neurod1, NSCL1
3	Granule cell migration	Tag1, Tuj1, Pax6, Dcc/netrin pathway, Unc5h2,3 GIRK2, astrotactin, thrombospondin, tenascin, neuregulin
4	Purkinje cell maintenance	Ngf, BDNF, ciliary neurotrophic factor, acetylcholine, Nt4/5, Rorα

5	Purkinje cell migration	Reelin pathway

Genes in the developing cerebellar primordium: The neural tube can be thought of as comprising four different regions during early development. The most anterior portion of the neural tube, the prosencephalon, gives rise to the forebrain. The mesencephalon, just caudal to the prosencephalon, gives rise to the midbrain, whereas hindbrain regions evolve from the metencephalon and myelencephalon. The proper patterning of the mesencephalon and the metencephalon is dependent on molecular signals released from the ISTHMUS organizer (IO), which is located just caudal to the junction of these two regions. Morphologically, this region is marked by a sharp bend of the neural tube. It has been shown in various mouse mutants, as well as in transplant experiments, that the IO is necessary and sufficient for patterning the mid-/ hindbrain region from the neural tube. The IO is, in turn, set up by the expression of a complex array of genes. Two, in particular, are central to its development: Otx2, one of the mouse homologues of the Drosophila gene orthodenticle, and Gbx2, a homologue of the Drosophila gene unplugged. At embryonic day, Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon, whereas Gbx2 expression in the metencephalon is bounded anteriorly by the caudal mesencephalon. The sharp boundary between the expression domains of these two genes reflects their reciprocal repression. In addition to helping form the IO molecularly, Gbx2 and Otx2 also regulate the expression of Fgf8 (fibroblast growth factor 8); Otx2 negatively regulates Fgf8 expression, whereas Gbx2 maintains its. Fgf8 is involved in regulating the various genes expressed in the mid- and hindbrain regions. Mutant mice with a reduced level of Fgf8 expression have a severe patterning defect of the mid-/hindbrain region, which usually affects the cerebellum. Fgf8 is a diffusable factor that exerts its action partially by inducing the expression of wingless homologue 1 (Wnt1) through Lim homeobox 1b (Lmx1b). Wnt1, in turn, maintains the expression of Engrailed (En1), which then positively regulates Fgf8 expression, completing the feedback regulatory loop. Mutants of Wnt1, En1 and Lmx1b all show patterning defects in the mid-/hindbrain region. Wnt1 and Lmx1b probably exert their influence through the action of En1. En2, a paralogue of En1, might also function in mid-/hindbrain patterning. En2 is expressed shortly after En1. Deletion of En2 against a haplo insufficient En1 mutant background was accompanied by a patterning defect in the mid-/hindbrain region more severe than that seen in a single mutant of En1; similarly, deletion of En1 against a haplo insufficient En2 mutant background also leads to an exaggerated phenotype21. Although the cross-regulation between Wnt1, En1 and Fgf8is beginning to be understood, several other genes that are not part of this pathway are also important in patterning of the mid-/hindbrain region. The paired box genes Pax2 and Pax5 are expressed in the mid-/hindbrain region. Pax2-null mice never develop a cerebellum or posterior mesencephalon. Although Pax5 mutants have only a mild phenotype in the mid-/hindbrain region, mice with a Pax5 mutation against a Pax2 sensitized background lack a cerebellum and posterior midbrain. Pax2 and Pax5 might also be involved in the regulation of En1, Wnt1 and other patterning genes, and together constitute another positive regulatory loop. The Hox gene family, which has an active role in patterning the hindbrain, seems

to help to restrict the development of metencephalon structures into the myelencephalon. For example, Hoxa2 (homeobox A2), the most anteriorly expressed Hox gene, probably marks the caudal limit of the cerebellar anlage at rhombomere. Mice without Hoxa2 develop enlarged cerebellum. Less is known about the dorsoventral patterning in this region. Bone morphogenetic proteins (Bmps) and sonic hedgehog (Shh) govern neuronal fates in the spinal cord; they have also been implicated in dorsoventral patterning of the mid-/hindbrain region. Bmps can induce the cerebellar granule neuron marker mouse atonal homologue (Math1) when expressed in the ventral neural tube of the region, and ectopic expression of SHH in the chick dorsal neural tube leads to ventralization of the neural tube and disruption of the mid-/hindbrain region. Cerebellar development is also affected by ectopic expression of Shh, which leads to defects of the midline of the neural tube. In summary, the reciprocal repression of Otx2 and Gbx2 forms the IO, which in turn uses Fgf8 and En1 to pattern the prospective mid-/hindbrain region. Cells from both the mesencephalon and the metencephalon give rise to cerebellar tissues.

Development of Purkinje cells The Purkinje, Golgi, stellate and basket cells all arise from the ventricular neuroepithelium. Purkinje cells are born around E13, at which time they exit the cell cycle and migrate along the radial glial fibre system into the cerebellar anlage. Relatively little is known about the specific factors that govern Purkinje cell differentiation. Shortly after their final mitosis at E14, Purkinje cells begin to express the calcium-binding protein calbindin. Calbindin positive cells migrate from E14–E17 in a radial direction over the already formed deep cerebellar nuclei. These Purkinje cells then settle and become suspended beneath the EGL, awaiting the inward migration of granule neurons. The timely arrest of migration is dependent on the reelin pathway. Mutations in the Reelin gene or in components of its signaling pathway lead to various cerebellar defects. Although Purkinje cells depend on signals from the granule neuron precursors to migrate, their differentiation programme seems to be independent of granule neurons. Mutants that lack granule neuron precursors, such as weaver or Math1-null mice, seem to have differentiating Purkinje cells at this stage. In late embryogenesis, climbing fibres from the inferior olivary nucleus start to innervate Purkinje cells. Extensive interactions occur between the climbing fibres and the Purkinje cells, and these interactions are believed to influence Purkinje cell development. Different markers, such as NST-1 (Hsp70-4, heat-shock protein), are expressed at the time of contact. At the same time, Purkinje cells are eliminating supernumerary climbing fibre synapses in several phases, at least one of which (during postnatal days 15–16) is activity- and NMDA (N-methyl-D-aspartate)-receptor-dependent. During their final maturation phase, Purkinje cells develop extensive dendritic arbors and synapse onto granule neurons. As might be expected, this phase of development depends on granule neuron signals. In mutants such as weaver, which do not have granule neurons, dendritic trees of Purkinje cells are altered. Furthermore, culturing of Purkinje cells in vitro requires co-culturing with granule neurons for proper dendritic arborizations. Given the known role of some of the Wnt genes in axon and dendrite development, Wnt3 is a good candidate for influencing this phase of development. Wnt3 is expressed in Purkinje cells during this period, and its expression is dependent on granule neurons. Throughout the course of development, various growth factors are important for Purkinje cell survival. Nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived

neurotrophic factor (BDNF) and ciliary neurotrophic factor have all been shown to have a positive effect on Purkinje cell number in vitro. Similarly, the Ror α (RAR-related orphan receptor α) gene, which is mutated in staggerer mice, is also important for the survival of Purkinje cells. In staggerer mice, although Purkinje cell genesis is normal, these neurons degenerate after E17. Apoptosis also controls Purkinje cell number; for example, transgenic mice overexpressing Bcl2 (B-cell leukemia/lymphoma 2), a protector against apoptosis, have more Purkinje cells than do wild-type mice.

Development of rhombic lip and granule neurons unlike all other cerebellar cells, which derive from the ventricular zone, the granule neurons derive from a separate germinal epithelium known as the rhombic lip. The rhombic lip is located between the fourth ventricle and the ROOF PLATE in the metencephalon. Along the anteroposterior axis, the rhombic lip extends from the first rhombomere to the eighth. A source of dividing progenitors, the rhombic lip might also be able to induce other cells to adopt its fate through some diffusable signal. For example, cells from the ventral neural tube can adopt the fate of granule neurons when they are interspersed with rhombic lip cells. Expression of the Math1 gene governs the germinal epithelium of the rhombic lip. Math1 is expressed in the mid-/hindbrain region as early as E9.5, and persists in the rhombic lip and many of its derivatives. Math1-null mice lack several rhombic lip derivatives, including the granule neurons of the cerebellum and the pontine nucleus of the pre cerebellar system. The defect can be traced back to as early as E10.5, with a marked reduction in the proliferating cell population in the rhombic lip region. Inside the rhombic lip, granule neuron precursors proliferate and then assume a unipolar morphology, with a single process that projects away from the rhombic lip. They begin to migrate out from the rhombic lip at E13, and spread over the roof of the cerebellar anlage to populate the EGL. At this point, the granule neuron precursors are still expressing Math1 and nestin, which labels undifferentiated precursors, but they also begin to express several other markers, including RU49/Zipro1 (zinc finger proliferation 1), Zic1and Zic3 (zinc finger proteins of the cerebellum). These precursors will become granule neurons when placed into the postnatal EGL. This indicates that, fairly early on in development, rhombic lip cells are specified to become granule neurons, and are competent to respond to proper signals for differentiating into granule neurons. It is unclear, however, exactly what the roles of these transcription factors (Math1, RU49/Zipro1, Zic1 and Zic3) are during the migration of rhombic lip cells. Rhombic lip cells continue to migrate to the cerebellar anlage and settle on its periphery to become the EGL. The outer EGL is another zone of proliferation. Granule neuron precursors in the outer EGL express several markers, including Math1, RU49/Zipro1 and Zic1. Although the role of Math1 at this outer EGL stage of development is not known, both RU49/Zipro1 and Zic1 are thought to participate in cell proliferation. Although RU49/Zipro1-null mice do not have obvious defects of cerebellar granule neurons, the over expression of RU49/Zipro1 leads to an increase in the number of granule neurons and an increase in proliferation in the outer EGL.

CEREBELLAR DISORDERS AND THEIR GENETIC BASIS

1. **PROGRESSIVE MYOCLONUS EPILEPSY**: Lafora progressive myoclonus epilepsy is a brain disorder characterized by recurrent seizures (epilepsy) and a decline in intellectual function. The signs and symptoms of the disorder usually appear in late childhood or adolescence and worsen with time. Myoclonus is a term used to describe episodes of sudden, involuntary muscle jerking or twitching that can affect part of the body or the entire body. Myoclonus can occur when an affected person is at rest, and it is made worse by motion, excitement, or Bashing light (photic stimulation). In the later stages of Lafora progressive myoclonus epilepsy, myoclonus often occurs continuously and affects the entire body. Several types of seizures commonly occur in people with Lafora progressive myoclonus epilepsy. Generalized tonic-clonic seizures (also known as grand mal seizures) affect the entire body, causing muscle rigidity, convulsions, and loss of consciousness. Affected individuals may also experience occipital seizures, which can cause temporary blindness and visual hallucinations. Over time, the seizures worsen and become more difficult to treat. A life-threatening seizure condition called status epilepticus may also develop. Status epilepticus is a continuous state of seizure activity lasting longer than several minutes. About the same time seizures begin, intellectual function starts to decline. Behavioral changes, depression, confusion, and speech difficulties (dysarthria) are among the early signs and symptoms of this disorder. As the condition worsens, a continued loss of intellectual function (dementia) impairs memory, judgment, and thought. Affected people lose the ability to perform the activities of daily living by their mid-twenties, and they ultimately require comprehensive care. People with Lafora progressive myoclonus epilepsy generally survive up to 10 years after symptoms first appear.

CAUSES: Lafora progressive myoclonus epilepsy can be caused by mutations in either the EPM2A gene or the NHLRC1 gene. These genes provide instructions for making proteins called laforin and malin, respectively. Laforin and malin play a critical role in the survival of nerve cells (neurons) in the brain.

2. **NIEMANN-PICK DISEASE:** Niemann-Pick disease is a condition that affects many body systems. It has a wide range of symptoms that vary in severity. Niemann-Pick disease is divided into four main types: type A, type B, type C1, and type C2. These types are classified on the basis of genetic cause and the signs and symptoms of the condition. Infants with Niemann-Pick disease type A usually develop an enlarged liver and spleen (hepatosplenomegaly) by age 3 months and fail to gain weight and grow at the expected rate (failure to thrive). The affected children develop normally until around age 1 year when they experience a progressive loss of mental abilities and movement (psychomotor regression). Children with Niemann-Pick disease type A also develop widespread lung damage (interstitial lung disease) that can cause recurrent lung infections and eventually lead to respiratory failure. All affected children have an eye abnormality called a cherry-red spot, which can be identified with an eye examination. Children with Niemann-Pick disease type A generally do not survive past early childhood. Niemann-Pick disease type B usually presents in mid-childhood. The signs and symptoms of this type are similar to type A, but

not as severe. People with Niemann-Pick disease type B often have hepatosplenomegaly, recurrent lung infections, and a low number of platelets in the blood (thrombocytopenia). They also have short stature and slowed mineralization of bone (delayed bone age). About one-third of affected individuals have the cherry-red spot eye abnormality or neurological impairment. People with Niemann-Pick disease type B usually survive into adulthood. The signs and symptoms of Niemann-Pick disease types C1 and C2 are very similar; these types differ only in their genetic cause. Niemann-Pick disease types C1 and C2 usually become apparent in childhood, although signs and symptoms can develop at any time. People with these types usually develop difficulty coordinating movements (ataxia), an inability to move the eyes vertically (vertical supranuclear gaze palsy), poor muscle tone (dystonia), severe liver disease, and interstitial lung disease. Individuals with Niemann-Pick disease types C1 and C2 have problems with speech and swallowing that worsen over time, eventually interfering with feeding. Affected individuals often experience progressive decline in intellectual function and about one-third have seizures. People with these types may survive into adulthood.

CAUSES: Niemann-Pick disease types A and B is caused by mutations in the SMPD1 gene. This gene provides instructions for producing an enzyme called acid sphingomyelinase. This enzyme is found in lysosomes, which are compartments within cells that break down and recycle different types of molecules. Acid sphingomyelinase is responsible for the conversion of a fat (lipid) called sphingomyelin into another type of lipid called ceramide. Mutations in SMPD1 lead to a shortage of acid sphingomyelinase, which results in reduced break down of sphingomyelin, causing this fat to accumulate in cells. This fat buildup causes cells to malfunction and eventually die. Over time, cell loss impairs function of tissues and organs including the brain, lungs, spleen, and liver in people with Niemann-Pick disease types A and B. Mutations in either the NPC1 or NPC2 gene cause Niemann-Pick disease type C. The proteins produced from these genes are involved in the movement of lipids within cells. Mutations in these genes lead to a shortage of functional protein, which prevents movement of cholesterol and other lipids, leading to their accumulation in cells. Because these lipids are not in their proper location in cells, many normal cell functions that require lipids (such as cell membrane formation) are impaired. The accumulation of lipids as well as the cell dysfunction eventually leads to cell death, causing the tissue and organ damage seen in Niemann Pick disease types C1 and C2.

3. **LEIGH SYNDROME:** Leigh syndrome is a severe neurological disorder that usually becomes apparent in the first year of life. This condition is characterized by progressive loss of mental and movement abilities (psychomotor regression) and typically results in death within two to three years, usually due to respiratory failure. A small number of individuals do not develop symptoms until adulthood or have symptoms that worsen more slowly. The first signs of Leigh syndrome seen in infancy are usually vomiting, diarrhea, and difficulty swallowing (dysphagia), which disrupts eating. These problems often result in an inability to grow and gain weight at the expected rate (failure to thrive). Severe muscle and movement problems are common in Leigh syndrome. Affected individuals may develop weak muscle

tone (hypotonia), involuntary muscle contractions (dystonia), and problems with movement and balance (ataxia). Loss of sensation and weakness in the limbs (peripheral neuropathy), common in people with Leigh syndrome, may also make movement difficult.

CAUSES: Leigh syndrome can be caused by mutations in one of more than 75 different genes. In humans, most genes are found in DNA in the cell's nucleus, called nuclear DNA. However, some genes are found in DNA in specialized structures in the cell called mitochondria. This type of DNA is known as mitochondrial DNA (mtDNA). While most people with Leigh syndrome have a mutation in nuclear DNA, about 20 percent have a mutation in mtDNA. Most genes associated with Leigh syndrome are involved in the process of energy production in mitochondria. Mitochondria use oxygen to convert the energy from food into a form cells can use through a process called oxidative phosphorylation. Five protein complexes, made up of several proteins each, are involved in this process. The complexes are named complex I, complex II, complex III, complex IV, and complex V. During oxidative phosphorylation, the protein complexes drive the production of adenosine triphosphate (ATP), the cell's main energy source, through a step-by-step transfer of negatively charged particles called electrons. Many of the gene mutations associated with Leigh syndrome affect proteins in these complexes or disrupt their assembly. These mutations reduce or eliminate the activity of one or more of these complexes, which can lead to Leigh syndrome. Disruption of complex I, also called NADH: ubiquinone oxidoreductase, is the most common cause of Leigh syndrome, accounting for nearly one third of cases of the condition. At least 25 genes involved in the formation of complex I, found in either nuclear or mitochondrial DNA, have been associated with Leigh syndrome.

4. **HUNTINGTON DISEASE**: Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin. A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington disease tends to progress more quickly than the adult onset form; affected individuals usually live 10 to 15 years after signs and symptoms appear.

CAUSES: Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain. The HTT mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

5. **ATAXIA-TELANGIECTASIA:** This is a rare inherited disorder that affects the nervous system, immune system, and other body systems. This disorder is characterized by progressive difficulty with coordinating movements (ataxia) beginning in early childhood, usually before age 5. Affected children typically develop difficulty walking, problems with balance and hand coordination, involuntary jerking movements (chorea), muscle twitches (myoclonus), and disturbances in nerve function (neuropathy). The movement problems typically cause people to require wheelchair assistance by adolescence. People with this disorder also have slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectases, which occur in the eyes and on the surface of the skin, are also characteristic of this condition. Affected individuals tend to have high amounts of a protein called alpha fetoprotein (AFP) in their blood. The level of this protein is normally increased in the bloodstream of pregnant women, but it is unknown why individuals with ataxia telangiectasia have elevated AFP or what effects it has in these individuals. People with ataxia-telangiectasia often have a weakened immune system, and many develop chronic lung infections. They also have an increased risk of developing cancer, particularly cancer of blood-forming cells (leukemia) and cancer of immune system cells (lymphoma). Affected individuals are very sensitive to the effects of radiation exposure, including medical x-rays. The life expectancy of people with ataxia telangiectasia varies greatly, but affected individuals typically live into early adulthood.

CAUSES: Mutations in the ATM gene cause ataxia telangiectasia. The ATM gene provides instructions for making a protein that helps control cell division and is involved in DNA repair. This protein plays an important role in the normal development and activity of several body systems, including the nervous system and immune system. The ATM protein assists cells in recognizing damaged or broken DNA strands and coordinates DNA repair by activating enzymes that fix the broken strands. Efficient repair of damaged DNA strands helps maintain the stability of the cell's genetic information. Mutations in the ATM gene reduce or eliminate the function of

the ATM protein. Without this protein, cells become unstable and die. Cells in the part of the brain involved in coordinating movements (the cerebellum) are particularly affected by loss of the ATM protein. The loss of these brain cells causes some of the movement problems characteristic of ataxia telangiectasia. Mutations in the ATM gene also prevent cells from responding correctly to DNA damage, which allows breaks in DNA strands to accumulate and can lead to the formation of cancerous tumors.

6. **FRIEDREICH ATAXIA**: Friedreich ataxia is a genetic condition that affects the nervous system and causes movement problems. People with this condition develop impaired muscle coordination (ataxia) that worsens over time. Other features of this condition include the gradual loss of strength and sensation in the arms and legs; muscle stiffness (spasticity); and impaired speech, hearing, and vision. Individuals with Friedreich ataxia often have a form of heart disease called hypertrophic cardiomyopathy, which enlarges and weakens the heart muscle and can be life threatening. Some affected individuals develop diabetes or an abnormal curvature of the spine (scoliosis). Most people with Friedreich ataxia begin to experience the signs and symptoms of the disorder between ages 5 and 15. Poor coordination and balance are often the first noticeable features. Affected individuals typically require the use of a wheelchair about 10 years after signs and symptoms appear. About 25 percent of people with Friedreich ataxia have an atypical form in which signs and symptoms begin after age 25. Affected individuals who develop Friedreich ataxia between ages 26 and 39 are considered to have late-onset Friedreich ataxia (LOFA). When the signs and symptoms begin after age 40 the condition is called very late-onset Friedreich ataxia (VLOFA). LOFA and VLOFA usually progress more slowly than typical Friedreich ataxia.

CAUSES: Mutations in the FXN gene cause Friedreich ataxia. This gene provides instructions for making a protein called frataxin. Although its role is not fully understood, frataxin is important for the normal function of mitochondria, the energy-producing centers within cells. One region of the FXN gene contains a segment of DNA known as a GAA trinucleotide repeat. This segment is made up of a series of three DNA building blocks (one guanine and two adenines) that appear multiple times in a row. Normally, this segment is repeated 5 to 33 times within the FXN gene. In people with Friedreich ataxia, the GAA segment is repeated 66 to more than 1,000 times. The length of the GAA trinucleotide repeat appears to be related to the age at which the symptoms of Friedreich ataxia appear, how severe they are, and how quickly they progress. People with GAA segments repeated fewer than 300 times tend to have a later appearance of symptoms (after age 25) than those with larger GAA trinucleotide repeats. The abnormally long GAA trinucleotide repeat disrupts the production of frataxin, which severely reduces the amount of this protein in cells. Certain nerve and muscle cells cannot function properly with a shortage of frataxin, leading to the characteristic signs and symptoms of Friedreich ataxia.

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