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The role of mutations on gene SLITRK1, in Tourette's Syndrome

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ABSTRACT

Tourette's syndrome is a problem with the nervous system that causes people to make sudden movements or sounds, called tics, that they can't control. For example, someone with Tourette's might blink or clear their throat over and over again. Some people may blurt out words they don't intend to say.
Keywords: Tourette's Syndrome, Nervous Disorder, Genetic Mutation, SLITRK1 Gene.

Generalities of Tourette Syndrome

Tourette's syndrome is a complex genetic disorder characterized by repetitive, sudden, or tic-like movements. Tics usually appear in childhood and their severity changes over time. In most cases, tics are less common in the last years of adolescence and adulthood [1].

Clinical Signs and Symptoms of Tourette's Syndrome

People with Tourette's syndrome perform repetitive, involuntary movements known as tics. In addition, people with Tourette's syndrome make sounds that are incomprehensible. Some tics involve only one muscle group, such as the occasional blinking or contact of the chin with the shoulder, or the shaking of the nostrils, which are usually the first signs of Tourette's syndrome. Multiple tics that affect multiple muscles include kicking in doors and walls, jumping, dancing, or spinning [1][2].

Vocal tics, which usually appear after movement tics, can be simple or complex. Simple vocal sounds include moaning, wheezing, and sore throat. Complex vocal sounds include: repeating the words of others or repeating one's own words. In addition to frequent tics, people with Tourette's syndrome are at risk for attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, depression, and sleep problems [1][3].

Etiology of Tourette Syndrome

Various genetic and environmental factors may play a role in the development of Tourette's syndrome. Many of these factors are unknown, and researchers are studying prenatal and postnatal risk factors that may contribute to this complex disorder. Scientists believe that Tourette's syndrome tics may be caused by changes in brain chemicals (neurotransmitters) that are responsible for producing and controlling voluntary movement [1][4].

A mutation in the SLITRK1 gene, located on the long arm of chromosome 13 as 13q31.1, has been identified in a small number of people with Tourette's syndrome. This gene provides the instructions for the synthesis of a protein that is active in the brain. This gene encodes a member of the SLITRK protein family. Members of this family are integral membrane proteins that are characterized by two N-terminal leucine-rich repeat (LRR) domains and a C-terminal region that shares homology with trk neurotrophin receptors. However, the protein encoded by this gene lacks the region of homology to neurotrophin receptors. This protein is thought to be involved in neurite outgrowth. Mutations in this gene may be associated with Tourette syndrome. Alternative splicing results in multiple transcript variants. The SLITRK1 protein probably plays an important role in the development of neurons, including the growth of axons and dendrites that allow each neuron to communicate with adjacent cells. It is not yet clear how mutations in the SLITRK1 gene can lead to Tourette's syndrome [1][5].

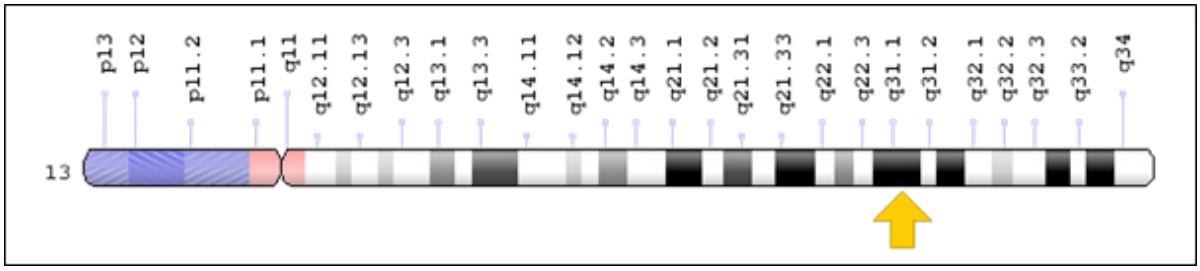

Figure 1: Schematic of chromosome 13 where the SLITRK1 gene is located in the long arm of this chromosome as 13q31.1. [1]

Most people with Tourette's syndrome do not have a mutation in the SLITRK1 gene. Because mutations have been reported in very few individuals with this syndrome, the association of the SLITRK1 gene with Tourette's syndrome has not been confirmed. Researchers believe that changes in other genes that have not yet been identified may be linked to Tourette's Syndrome [1][6].

The hereditary pattern of Tourette's syndrome is unknown. Tourette's syndrome was previously thought to follow an autosomal dominant inheritance pattern. But research has shown that this inherited pattern is not correct for Tourette's syndrome. Almost all cases of Tourette's syndrome are probably caused by various genetic and environmental factors, not a change in a particular gene [1][7].

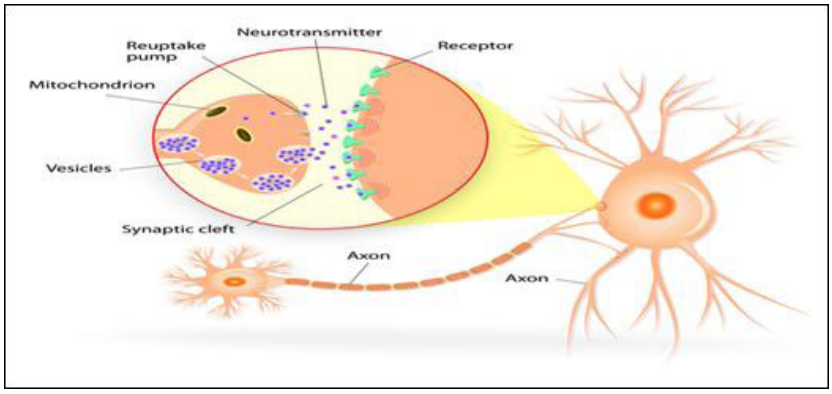

Figure 2: Schematic of the structure of the nerve fiber and the biochemical mechanism of the nerve fiber [1].

Frequency of Tourette Syndrome

Tourette's syndrome is a genetic and epigenetic disorder whose exact frequency of occurrence in the world is unknown. Tourette's syndrome is estimated to affect between 1 and 10 per 1,000 children. This syndrome occurs in different populations and ethnic groups around the world and is more common in men than women [1][8].

Diagnosis of Tourette's Syndrome

Tourette's syndrome is diagnosed based on the patient's clinical and physical findings and some pathological tests. Doctors diagnose Tourette's syndrome after confirming that the patient has had both motor and vocal tics for at least 1 year. Other neurological or psychiatric conditions can also help doctors make a diagnosis. Common tics are often misdiagnosed by specialist doctors. However, unusual symptoms or presentation (for example, the onset of symptoms in adulthood) may require a specialist to diagnose.

No laboratory, blood or imaging tests are required for diagnosis. In rare cases, Tourette's syndrome may be accompanied by other disorders that appear to be suspected in a person's history or clinical examination. These studies include:

i. MRI magnetic resonance imaging
ii. CT computed tomography
iii. Electroencephalogram (EEG) studies

The above tests are used to rule out other disorders that may be associated with Tourette's syndrome.

It is not uncommon for a patient to have a definitive diagnosis of Tourette's syndrome only when symptoms are present in some cases. The reasons for this diagnosis are many. For families and physicians unfamiliar with Tourette's syndrome, mild to moderate symptoms may be a minor issue, part of a developmental period, or the result of another illness. For example- Parents may think that blinking is related to vision problems or that snoring is related to seasonal allergies.

Many patients diagnose the disease themselves after their parents, other relatives or friends have read or heard about Tourette's Syndrome! (This reminds us all of the importance of studying health.) The most accurate way to diagnose Tourette's syndrome is to have a molecular genetic test, at least for the SLITRK1 gene, to check for possible mutations. Prenatal diagnosis of this syndrome is difficult [1][9].

Therapeutic Routes of Tourette's Syndrome

The treatment and management strategy of Tourette's syndrome is symptomatic and supportive. Treatment may be done with the efforts and coordination of a team of specialists including a pediatrician, a neurologist, a psychiatrist, speech therapists and motion therapists, and other health care professionals. The use of neuroleptic drugs can also be somewhat helpful. Neuroleptics (drugs that may be used to treat psychotic and non-psychotic disorders) are drugs that are consistently useful in suppressing tics. Some are available, but some are more effective than others (such as haloperidol and pimozide). Many neuroleptic side effects can be controlled by starting treatment slowly and reducing the dose if side effects occur. The most common side effects of neuroleptics include numbness and drowsiness, weight gain, and slowness of cognition. Neurological side effects such as tremor, dystonic reactions (movement of the body), Parkinson-like symptoms, and other (involuntary) movement disorders are less common and are easily treated by reducing the dose [1][9].

Discontinuation of neuroleptics after prolonged use should be done slowly to prevent recurrence of tics and recurrence of dyskinesia. A type of dyskinesia called chronic dyskinesia is a movement disorder distinct from Tourette's syndrome that may be due to chronic use of neuroleptics. The risk of these side effects can be reduced by using lower doses of neuroleptics for shorter periods. Other medications may also be helpful in reducing the severity of the tic, but they have often not been extensively studied or are consistently useful as neuroleptics. Additional drugs with relatively good efficacy include alpha-adrenergic agonists such as clonidine and guanfacine [1][10]. These drugs were used primarily for high blood pressure, but are also used to treat tics. The most common side effect of these drugs that prevents them from taking is drowsiness and confusion. However, due to the low side effects of these drugs, they are often used as first-line agents before starting neuroleptic therapy [1][10]. There are also effective drugs to treat some of the neurobehavioral disorders associated with Tourette's syndrome. Recent research shows that stimulant drugs such

as methylphenidate and dextroamphetamine can reduce the symptoms of ADHD in people with Tourette's syndrome without causing severe tics [1][10]. However, the use of these drugs is currently prohibited in children with Tourette's / Tics syndrome and those with a family history of tics. Scientists hope future studies, including a full discussion of the risks and benefits of using these brain stimulants will shed light on this issue [1][10]. Serotonin reuptake inhibitors (clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline) have been shown to be effective for symptoms of obsessive-compulsive disorder that significantly impair daily functioning [1][10]. There is no definitive treatment for this syndrome and patients should adapt to this disorder. Behavioral therapies such as awareness training and competitive response training can also be used to reduce tics. A new NIH-based controlled trial called Cognitive-Behavioral Intervention (or CBIT) for tics has shown that training voluntarily moves toward the predictive response to arousal to reduce tic symptoms [1][10]. Other behavioral therapies, such as biofeedback or supportive therapy, have been shown to reduce tic symptoms. However, supportive therapy can help a person with Tourette's syndrome cope better with the disorder and with the secondary social and emotional problems that sometimes occur. The psychological support of parents and relatives will also be effective in regulating the situation of these patients. Genetic counseling is also necessary for all families who want a healthy child [1][10].

History of Tourette Syndrome

Tourette's syndrome was first reported in 1885 by Dr. Georges Gilles de la Tourette, a French neurologist [1][11].

Figure 3: Picture of Dr. Georges Gilles de la Tourette, discoverer of Tourette's Syndrome in 1885.[1]

Discussion and Conclusion

Tourette's Syndrome has been linked to different parts of the brain, including an area called the basal ganglia, which helps control body movements. Differences there may affect nerve cells and the chemicals that carry messages between them. Researchers think the trouble in this brain network may play a role in Tourette's Syndrome. Treatments can control tics, but some people don't need any unless their symptoms really bother them. There is no definitive treatment for this syndrome and patients should adapt to this disorder. The psychological support of parents and relatives will also be effective in regulating the situation of these patients. Nerve tics appear after formation over time with different types, frequencies, locations and intensities.

The first symptoms usually occur in the head and neck area and may reach the muscles of the trunk and limbs. Motion tics generally precede vocal tics, and simple ticks often precede complex tics. Most patients recover before the mid-adolescence with the peak severity and in the late stages of adolescence. Approximately 10 to 15 percent of those affected by the disease have progressive or inactive periods that last into adulthood.

Although the symptoms of Tourette's syndrome are involuntary, some people can sometimes suppress, camouflage, or otherwise control their ticks in an attempt to minimize the effect of ticks on their performance [1][11]. However, people with Tourette's syndrome say they often put more pressure on their tics to suppress them to the point where they feel the tics should occur (against their will).

Tics in response to an environmental stimulus can appear intentionally or deliberately, but they do not! (So, the important thing to note is that these tics are involuntary! So, if one of the people around us had this syndrome, instead of doubling the pressure, we should understand him a little more...)

Many people with Tourette's syndrome experience additional neurobehavioral problems that often cause harm (even more than their own tics). These include:
i. Lack of attention
ii. Attention Deficit Hyperactivity Disorder (ADHD)
iii. Reading, writing and math problems
iv. Obsessive-compulsive symptoms such as repetitive thoughts / worries and behaviors

For example- Worries about dirt and germs may be associated with repeated hand washing, and worries about bad events may be accompanied by emotional behaviors such as counting, repeating, sorting, and picking items.

People with Tourette's Syndrome have also reported problems with depression or anxiety disorders, as well as other life problems that may or may not be directly related to Tourette's Syndrome. In addition, although many people with Tourette's Syndrome show a significant reduction in motor and vocal tics in late adolescence and early adolescence, they may still have disorders related to neurological problems.

Due to the wide range of potential complications, people with the syndrome will be greatly improved by receiving medical care that offers a comprehensive treatment plan. Although there is no definitive cure for Tourette's syndrome, it improves in many people in their late teens and early 20s. As a result, some people may actually be asymptomatic or may not need medication to suppress tics. Although this disorder is generally lifelong and chronic, it is not a destructive condition.

Tourette's syndrome does not destroy information. Although the symptoms of tics decrease with age, neurobehavioral disorders such as attention deficit / hyperactivity disorder (ADHD), obsessive-compulsive disorder, depression, general anxiety, panic attacks, and mood swings may persist into adult life [1][11].

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