The Role of Genetic Mutations in Gene Mapt in Richardson Syndrome

Shahin Asadi* and Hossein Amjadi
Division of Medical Genetics and Molecular Pathology Research, Harvard University, Boston Children’s Hospital, USA

Abstract
Richardson syndrome is an uncommon degenerative neurological disorder that causes progressive impairment of balance and walking; impaired eye movement, especially in the downward direction; abnormal muscle tone (rigidity); speech difficulties (Dysarthria); and problems related to swallowing and eating (Dysphagia). Affected individuals frequently experience personality changes and cognitive impairment. Symptoms typically begin after age 60 but can begin earlier. The exact cause of Progressive Supranuclear Palsy (PSP) is unknown. PSP is often misdiagnosed as Parkinson disease, Alzheimer disease, corticobasal degeneration and other neurodegenerative disorders. In most cases the genetic cause of Richardson syndrome is unknown, but in some cases it is caused by a MAPT gene mutation located on the long arm of chromosome 17 at 17q21.31. This gene provides instructions for the synthesis of a protein called tau.

Keywords: Richardson syndrome; Genetics mutation; MAPT gene; Progressive supranuclear palsy

Introduction
Overview of Richardson syndrome
Richardson syndrome, also known as advanced paralytic syndrome, is a genetic disorder of the brain structure that affects motility, vision, speech and thinking ability. Signs and symptoms of this syndrome usually appear in the mid-to late adulthood, and most often at age 60. Most people with Richardson Syndrome die about five to nine years after the symptoms of the disease, although some sufferers have survived more than 10 years after the onset of symptoms [1].

Clinical signs and symptoms of Richardson syndrome
Balance loss and frequent falls are the most common early symptoms of Richardson syndrome. People with this syndrome have difficulty walking and often fall to the ground. Other motor disorders in this syndrome include unusual slow movements (Brady Keynesia) and muscle stiffness. These problems worsen over time and most people with Richardson syndrome need wheelchairs to move around [2].

Richardson syndrome is also known as abnormal eye movements, which include forward and downward eye movements (Vertical Eye Paralysis). Other eye disorders in Richardson’s syndrome include: difficulty opening and closing the eyelids and repeated blinking of the eyelids. These abnormalities can lead to blurred vision and increased sensitivity to light (photophobia) [2].

Additional features of Richardson’s syndrome include: slow and unpleasant speech (Dysarthria) and Dysphagia. In addition, most people affected by Richardson’s syndrome also experience changes in personality and behavior, such as loss of interest and enthusiasm (numbness or numbness). These problems worsen over time and injured people need personal care in their daily activities [1].

Etiology of Richardson syndrome
In most cases the genetic cause of Richardson syndrome is unknown, but in some cases it is caused by a MAPT gene mutation located on the long arm of chromosome 17 at 17q21.31. This gene provides instructions for the synthesis of a protein called tau. It is found throughout the nervous system, including neurons in the brain. The tau protein is involved in the assembly and stabilization of microtubules that form the cellular structural framework (cytoskeleton). Microtubules help cells maintain their shape and are also involved in the cell division process and are essential for the transport of substances within cells. Variants of least three other genes (STX6, EIF2AK3, and MOBP) are associated with an increased risk of developing PSP. The study of genetic mechanisms should eventually lead to effective medical therapies [1-3].

The signs and symptoms of Richardson syndrome appear to be related to tau protein deficiency. Mutation in the MAPT gene disrupts the structure and function of the tau protein. However, abnormal tau protein has also been found in people with Richardson syndrome lacking the MAPT gene mutation. Defective tau protein accumulates abnormally in neurons and other brain cells, although it is unclear what effect it has on the function and survival of these cells. Thus, impairment of tau protein results in the gradual death of brain cells, especially cells that are essential for coordinating movements. As a result, brain cell loss causes motor disorders and other features of Richardson syndrome [1-4].

Researchers believe that additional genetic factors may also be linked to Richardson syndrome. For example, genetic alterations in chromosomes 1 and 11 may be related to Richardson syndrome. However, the specific genes that cause Richardson syndrome have not yet been identified on these chromosomes [1-5].

Most cases of Richardson syndrome are caused by new mutations with no family history. When this syndrome is caused by the MAPT gene mutation, it follows the dominant autosomal inherited pattern.
Therefore, a copy of the MAPT (Parent or mother) mutant gene is required to cause this syndrome, and the chance of having a child with Richardson syndrome in autosomal dominant state is 50% for each possible pregnancy [1-6].

**Frequency of Richardson syndrome**

Richardson’s syndrome is a rare genetic disorder whose frequency is unknown in the world. The syndrome may affect about 6 in 100,000 people worldwide. The onset of this disorder occurs between 45 and 75 years of age, with the average age of onset at about 63 years. Males are affected more often than females [1-7].

**Diagnosis of Richardson syndrome**

Richardson syndrome is diagnosed on the basis of clinical and physical findings of patients and some pathological tests. The most accurate method for detecting this syndrome is molecular genetic testing of the MAPT gene to detect possible mutations [1-8].

**Richardson syndrome treatment pathways**

Treatment of progressive supranuclear palsy is symptomatic and supportive. There is no cure at the present time. In some cases, drugs used to treat Parkinson disease (Anti-parkinsonian Agents), such as levodopa, may be of some benefit in relieving symptoms of slowness, but the effect is usually limited and temporary. Antidepressant medications are of some benefit in some cases. The use of these drugs should be monitored carefully by a neurologist experienced in their administration. There is no cure for Richardson’s syndrome, and unfortunately most people with this syndrome die several years after the onset of symptoms (Figures 1-5) [1-9].

**Figure 1**: Schematic of the brain with Richardson syndrome with related disorders.

**Figure 2**: Schematic overview of chromosome 17 where the MAPT gene is located on the long arm of chromosome 17q21.31.
Discussion and Conclusion

The most common presentation is the Richardson syndrome, consisting of gait and balance impairment, a wide-eyed staring facial expression, abnormal speech, memory and cognitive impairment and a slowing or loss of voluntary eye movement, particularly in the downward direction (Supranuclear ophthalmoplegia). Cognitive symptoms include forgetfulness and personality changes, such as loss of interest in formerly pleasurable activities (apathy), impaired attention and concentration, depression, and increased irritability. Muscles of the body may contract involuntarily, causing the affect body part (e.g., the upper or lower limbs) to assume bizarre postures. This is called dystonia. Blepharospasm is a form of dystonia affecting the muscles around the eyes.

References

