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The Role of the Genetic Mutation on COPA Gene in COPA Syndrome

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Abstract

COPA syndrome is a rare genetic autoimmune disorder that can affect various body systems, especially the lungs, kidneys, and joints. Symptoms usually appear in childhood in the first or second decade of life. The signs and symptoms and severity of the disorder can vary greatly from one person to another. An autoimmune disorder is a disorder in which the body's adaptive immune system, which protects the body from infectious agents or other foreign substances, mistakenly attacks healthy tissue. COPA is caused by a mutation in the coatomer complex protein alpha subunit (COPA) gene. The COPA gene is located on the long arm of chromosome 1 at 1q23.2. Genes provide instructions for making proteins that play an important role in many body functions.

Keywords: COPA Syndrome, Rare Genetic Autoimmune Disorder, COPA Gene

COPA Syndrome Overview

COPA syndrome is a rare genetic autoimmune disorder that can affect various body systems, especially the lungs, kidneys, and joints. Symptoms usually appear in childhood in the first or second decade of life. The signs and symptoms and severity of the disorder can vary greatly from one person to another. This is true even for members of the same family. COPA syndrome is an immune-mediated disorder, meaning that the characteristic inflammation is caused by abnormal functioning (dysregulation) of the immune system and the presence of specific autoantibodies. The disorder is caused by changes (mutations) in the COPA gene and can occur spontaneously as a new change or be inherited in an autosomal dominant pattern [1].

COPA syndrome has been described as having features of both autoimmune disorders and autoinflammatory disorders. An autoimmune disorder is a disorder in which the body's adaptive immune system, which protects the body from infectious agents or other foreign substances, mistakenly attacks healthy tissue. Autoinflammatory syndromes are a group of disorders characterized by recurrent episodes of inflammation due to abnormalities in the innate immune system [1].

Clinical Signs and Symptoms of COPA Syndrome

Although researchers have been able to establish a clear syndrome with characteristic or "core" symptoms, much of the disorder is not fully understood. Several factors, including the small number of patients identified, the lack of large clinical studies, and the possibility that genes or other factors (such as environmental factors) influence the disorder, prevent doctors from developing a complete picture of the associated symptoms and prognosis. Therefore, it is important to note that affected individuals may not have all of the symptoms listed below. Individuals and parents should talk to their doctor and medical team about their specific case, associated symptoms, and overall prognosis [1, 2].

The lung disease associated with COPA syndrome can be classified as interstitial lung disease (ILD), a general term for disorders that cause progressive scarring of the lungs. The lung disease

may occur before the development of joint disease. Common symptoms associated with lung disease include a chronic or persistent cough, shortness of breath, and abnormally rapid breathing (tachypnea). Affected individuals may also develop inflammation of the airways of the lungs (bronchitis) and lung cysts. Chronic wheezing and chest pain may also occur. There may be a slow, gradual decline in lung function [1, 2].

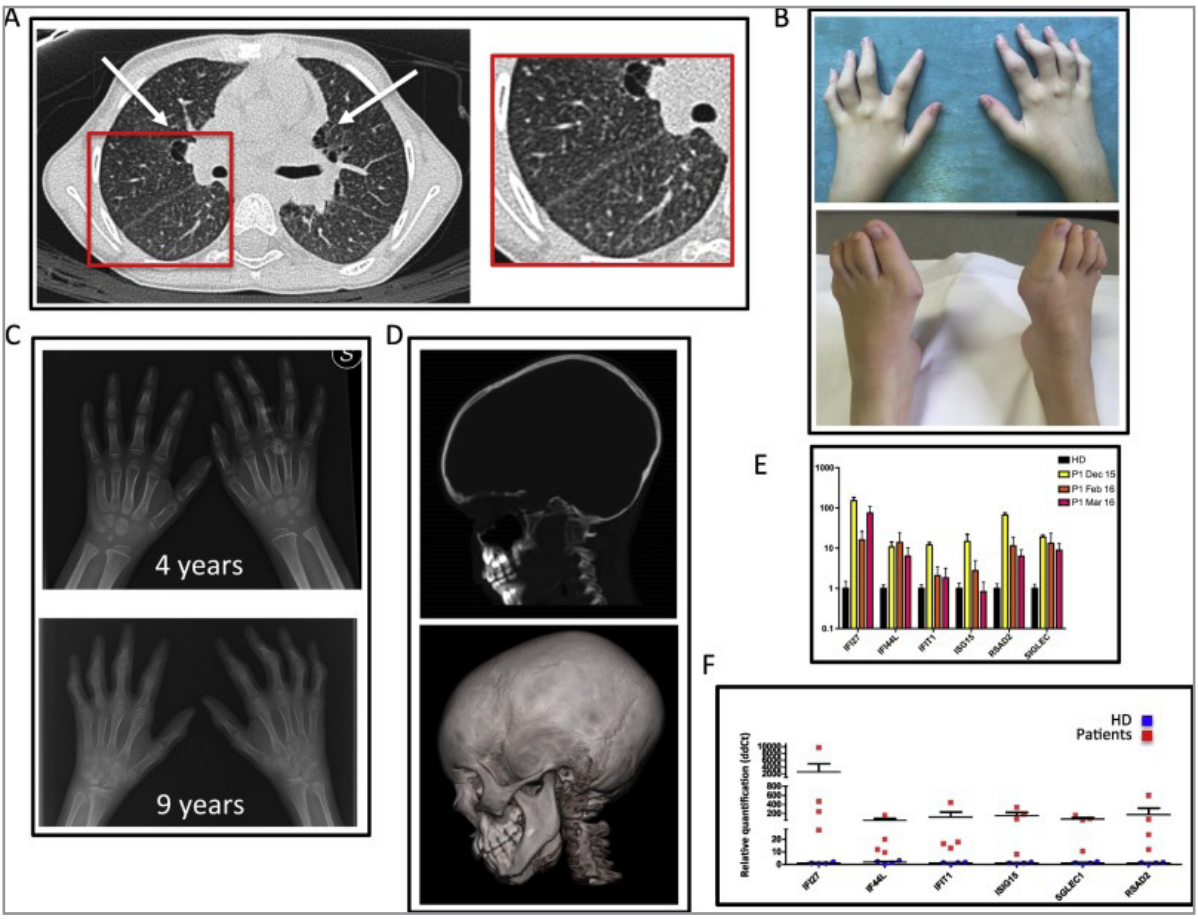

Figure 1: Images of disorders associated with COPA syndrome [1].

About half of people with COPA syndrome experience bleeding from the alveoli (alveolar hemorrhage). The lungs contain millions of tiny air sacs called alveoli. When a person breathes in air, oxygen moves into the lungs and alveoli. It passes through the walls of the alveoli into small blood vessels called capillaries and then into the bloodstream to be carried throughout the body. Alveolar hemorrhage is a serious condition that can cause coughing up blood (hemoptysis) and low levels of red blood cells in the bloodstream (anemia). Anemia can cause fatigue, lightheadedness, pale skin color, dizziness, rapid heartbeat, and shortness of breath. Alveolar hemorrhage is a potentially life-threatening condition that can lead to blood leaking through the lungs (diffuse pulmonary infiltrates) and rapid inability to breathe (acute respiratory failure). Many people with the condition develop inflammation of the joints (arthritis). Affected joints include large joints such as the shoulders and knees and smaller joints such as those in the fingers. Affected people experience pain, swelling, and stiffness in the affected joints. Joint pain can be potentially severe and disabling. Symptoms may be worse upon waking. Children may also experience severe arthritis. Arthritis can sometimes develop before symptoms of lung disease [1-3].

Affected people may also develop inflammation of the kidneys (nephritis). Progressive damage to the kidneys can lead to blood in the urine (hematuria), abnormal levels of protein in the urine (proteinuria), and decreased urine output. Eventually, swelling occurs due to fluid buildup (edema) and decreased kidney function. Some people develop scarring (fibrosis) of the kidneys [1-3].

Other conditions reported in a few people with COPA syndrome include inflammation of the spinal cord and optic nerve (neuromyelitis optica) and bone loss near the junction of the long leg bone with the pelvis (avascular necrosis). However, it is not known whether these are potential complications of the disorder or incidental findings [1-3].

Etiology of COPA Syndrome

COPA is caused by a mutation in the coatomer complex protein alpha subunit (COPA) gene. The COPA gene is located on the long arm of chromosome 1 at 1q23.2. Genes provide instructions for making proteins that play an important role in many body functions. When a mutation occurs in a gene, the protein product may be defective, ineffective, absent, or overproduced.

Depending on the function of the specific protein, this can affect many organs in the body [1-4].

The COPA gene makes (encodes) a protein complex that is involved in transporting other proteins from the Golgi apparatus to the endoplasmic reticulum. The Golgi complex (or apparatus) is a structure found in most cells that modifies, sorts, packages, and transports proteins. The endoplasmic reticulum is an extensive membrane network of a cell where proteins are processed. The exact way in which disease-causing changes in the COPA gene contribute to or cause the specific signs and symptoms of COPA syndrome is not fully understood [1-4].

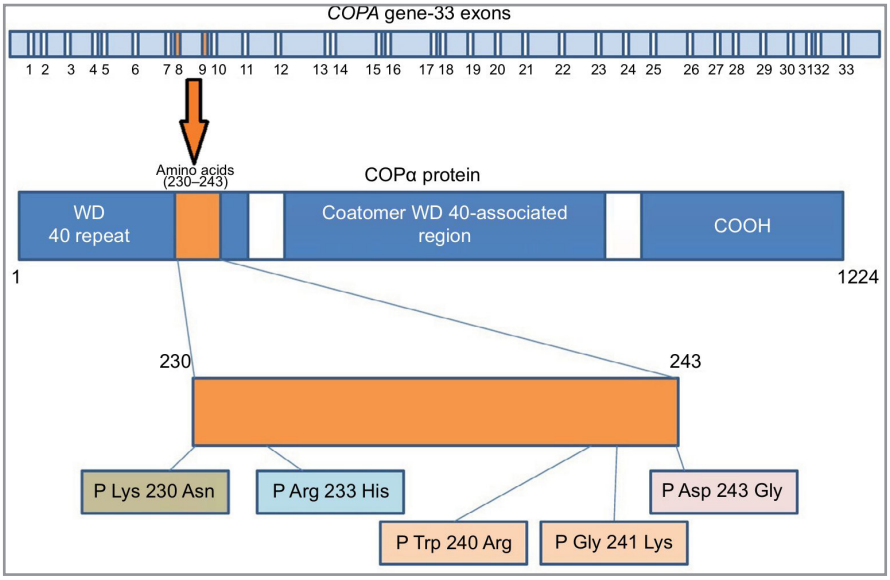

Figure 2: Schematic of the COPA gene structure [1].

COPA syndrome is an immune-mediated disorder, meaning that the characteristic inflammation is caused by abnormal functioning (dysregulation) of the immune system and the presence of specific autoantibodies. Antibodies are part of the immune system. They are specialized proteins that target foreign or invading organisms. Autoantibodies are antibodies that mistakenly attack healthy tissues. Affected individuals often develop antineutrophil cytoplasmic antibodies and antinuclear antibodies. Some individuals may be positive for rheumatoid factor. The exact role of these autoantibodies in causing COPA syndrome is not fully understood. COPA syndrome can be inherited from a parent or can occur as a new (sporadic or de novo) change, meaning that the gene change occurred only when an egg or sperm was formed for that child. One family member will be affected. Affected individuals can then pass on the altered gene in an autosomal dominant pattern [1-5].

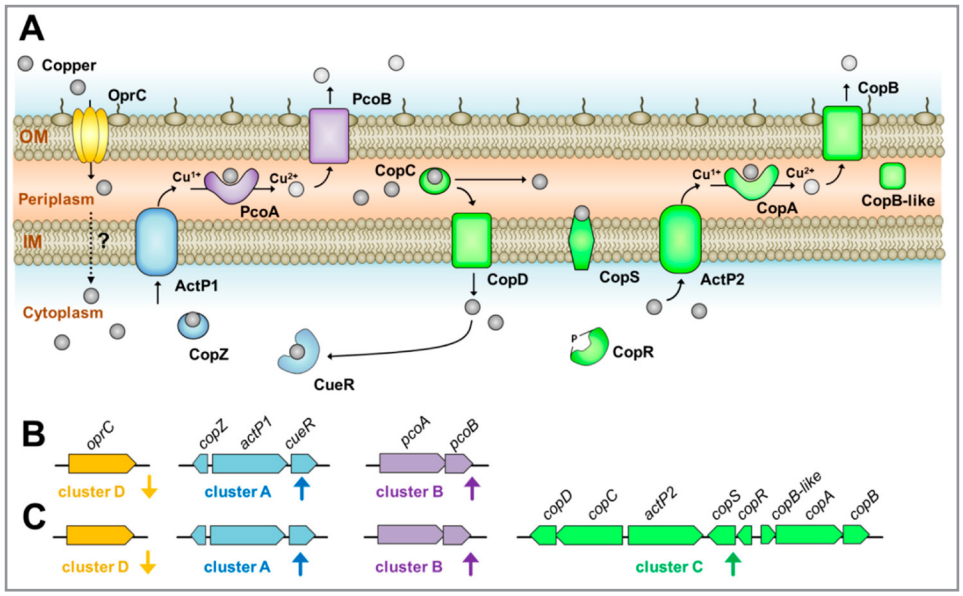

Figure 3: Schematic of the biochemical mechanism of the COPA gene [1].

Dominant genetic disorders occur when only one copy of an inactive gene is needed to cause a particular condition. The inactive gene can be inherited from either parent or can be the result of a mutated (changed) gene in the affected person. The risk of passing the inactive gene from an affected parent to their child is 50% for each pregnancy. This risk is the same for men and women [1-5].

COPA syndrome is described as having incomplete or reduced penetrance and variable expression. These are genetic terms. Incomplete penetrance means that some people who inherit the gene for a dominant disorder will not be affected by the disorder. Variable expression in a dominant disorder means that very different signs and symptoms can occur among affected people [1-5].

Frequency of COPA Syndrome

Early reports suggest that women are more affected than men. Larger groups of patients need to be identified to confirm whether women are more affected than men. Fewer than 100 families with the disorder have been identified in the medical literature, but the exact number of people affected is unknown. The low number of people identified with the disorder is because COPA syndrome was first defined as a disorder in 2015 and genetic testing has only recently become available. In general, rare disorders are often misdiagnosed or underdiagnosed, making it difficult to determine their true frequency in the general population. COPA syndrome is likely underdiagnosed and underdiagnosed [1-6].

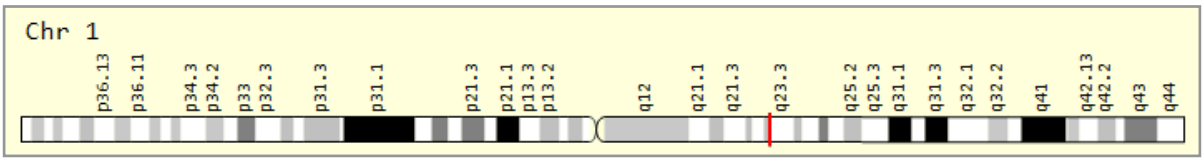

Figure 4: Schematic of the physical map of chromosome number 1, where the COPA gene is located on the long arm of this chromosome as 1q23.2 [1].

Disorders Associated with COPA Syndrome

The following disorders can present with similar symptoms to those of COPA syndrome. Comparison may be helpful for differential diagnosis .A variety of disorders or conditions can present with signs and symptoms similar to those of COPA syndrome. These include autoimmune pulmonary hemorrhage, granulomatosis with polyangiitis, systemic lupus erythematosus, and STING-associated vasculopathy of infancy (SAVI). Interstitial pneumonia can be seen in several disorders, including common variable immunodeficiency, LRBA deficiency, Churg-Strauss syndrome, and Goodpasture syndrome [1-7].

Diagnosis of COPA Syndrome

The diagnosis of COPA syndrome is based on the identification of characteristic symptoms, a detailed patient and family history, a thorough clinical evaluation, and a variety of specialized tests. Molecular genetic testing can confirm the diagnosis. Two findings that are suggestive of COPA syndrome are diffuse alveolar hemorrhage and follicular bronchiolitis. Follicular bronchiolitis is when there is an overgrowth (hyperplasia) of lymphoid tissue in the small airways (bronchioles) of the lungs, causing inflammation of those airways. Lymphoid tissue is a tissue in the body that produces white blood cells and antibodies [1-7].

Molecular genetic testing can identify changes in the COPA gene that cause the disorder. Doctors take a blood sample from people suspected of having COPA syndrome, and the sample is subjected to targeted sequencing of a region of the COPA gene known to cause the disease to evaluate for the presence of known disease-causing changes [1-7].

Additional tests may be done before or after molecular genetic testing to determine the extent of the disease or to rule out other conditions. Such tests may include a chest X-ray (radiography) or a specialized imaging technique such as a computed tomography (CT) scan of the lungs. During a CT scan, a computer and X-rays are used to create a film that shows cross-sectional images of specific tissue structures. People with lung cancer have specific changes in their lung tissue that can be seen on an X-ray. For example, a CT scan can show dark areas that look like small bumps (nodules) in the lungs [1-7].

Pulmonary function tests may be done to determine how well or poorly the lungs are working. This may involve having the person breathe into a machine called a spirometer to measure the amount of air they can breathe out or in, and can show a decrease in airflow and a decrease in air volume. Doctors may also measure a person's forced vital capacity, which is the amount of air that can be forcibly exhaled after a deep breath. A similar test called forced expiratory volume may also be recommended. This test measures the amount of air a person can exhale during a forced breath [1-7].

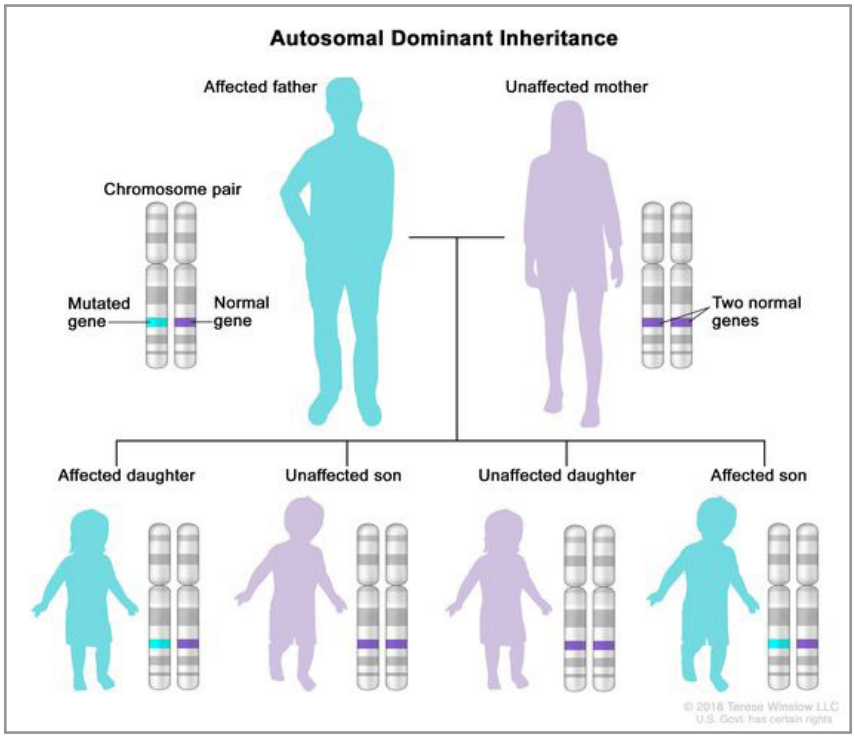

Figure 5: Schematic of the autosomal dominant inheritance pattern that COPA syndrome follows.1 [1].

Another test called plethysmography measures the amount of air people can hold in their lungs, called total lung capacity. During this test, patients sit or stand in an air chamber that resembles a telephone booth. The nostrils are closed and the patient is asked to breathe into a mouthpiece. A sample of lung tissue taken through a surgical lung biopsy (sometimes called a video-assisted thoracoscopic surgery (VATS) lung biopsy) and studied under a microscope can show characteristic changes in the lung that indicate COPA syndrome. During this procedure, a small needle is passed through the skin into the lungs to obtain a small sample of tissue. The sample is looked at under a microscope by a specialized doctor called a pathologist, who studies the cells and specific features of the tissue sample to identify the disease. Follicular bronchiolitis can be confirmed by a lung biopsy [1-8].

A bronchoscopic examination may be needed during the procedure to evaluate for alveolar hemorrhage or other conditions that may be present, such as a lung infection. During a bronchoscopy, the doctor inserts a bronchoscope through the person's mouth and throat and takes a sample of tissue for analysis (biopsy). A bronchoscopic examination may also be used to allow doctors to see the airways and airways of the lungs. Blood tests can show the presence of autoantibodies, including antineutrophil cytoplasmic antibodies and antinuclear antibodies. Some people may test positive for rheumatoid factor [1-8].

Treatment Pathways for COPA Syndrome

Treatment for COPA syndrome is directed at the specific symptoms that are evident in each person. Treatment may require the coordinated efforts of a team of specialists. A pediatrician, general internist, lung disease specialist (pulmonologist), kidney disease specialist (nephrologist), rheumatologist, physical therapist, and other health care professionals may need to plan a systematic and comprehensive treatment plan. Genetic counseling is recommended for affected individuals and their families. Psychosocial support for the entire family is also essential. Several organizations listed in the Resources section provide support and information about COPA syndrome [1-9].

There is no standard treatment protocol or guideline for affected individuals. Because of the rarity of the condition, there are no clinical trials that have been tested on large groups of patients. Various treatments have been reported in the medical literature as part of single case reports or small series of patients. Clinical trials would be very useful to determine the long-term safety and effectiveness of specific medications and treatments for individuals with COPA syndrome [1-9].

There is no cure for COPA syndrome, but people with it can be treated with medications that suppress the immune system (immunosuppressants). COPA syndrome involves abnormal functioning (dysregulation) of the immune system. By suppressing the activity of the immune system, doctors can reduce damage to healthy organ systems (such as the lungs) affected by the disorder. Some people with this condition may also receive low doses of systemic corticosteroids, which are drugs that reduce inflammation in the body. People respond differently to these drugs [1-9].

During periods when symptoms get worse, called exacerbations, stronger immunosuppressive drugs may be used. Sometimes, high doses of systemic corticosteroids are used. Long-term use of high doses of systemic corticosteroids is often associated with

significant side effects. In most patients, the dose is slowly reduced after the exacerbation is over [1-10].

Some people with this condition needs supplemental oxygen at a young age. Supplemental oxygen, or oxygen therapy, is needed when the lungs are unable to get enough oxygen to deliver oxygen to the bloodstream. Supplemental oxygen can help with symptoms such as shortness of breath or fatigue. In severe disease, endotracheal intubation may be necessary. This involves placing a thin tube through the mouth or nostrils, down the windpipe, and into the lungs. This allows air to flow freely into the lungs. Several patients have received or are awaiting lung transplants due to progressive and severe disease [1-10].

Discussion

COPA syndrome has been described as having features of both autoimmune disorders and autoinflammatory disorders. An autoimmune disorder is a disorder in which the body's adaptive immune system, which protects the body from infectious agents or other foreign substances, mistakenly attacks healthy tissue. The lung disease associated with COPA syndrome can be classified as interstitial lung disease (ILD), a general term for disorders that cause progressive scarring of the lungs. The lung disease may occur before the development of joint disease. Common symptoms associated with lung disease include a chronic or persistent cough, shortness of breath, and abnormally rapid breathing (tachypnea). Affected people may also develop inflammation of the kidneys (nephritis). Progressive damage to the kidneys can lead to blood in the urine (hematuria), abnormal levels of protein in the urine (proteinuria), and decreased urine output. Eventually, swelling occurs due to fluid buildup (edema) and decreased kidney function. Some people develop scarring (fibrosis) of the kidneys. COPA is caused by a mutation in the coatomer complex protein alpha subunit (COPA) gene. The COPA gene is located on the long arm of chromosome 1 at 1q23.2. Genes provide instructions for making proteins that play an important role in many body functions. The Golgi complex (or apparatus) is a structure found in most cells that modifies, sorts, packages, and transports proteins. The endoplasmic reticulum is an extensive membrane network of a cell where proteins are processed. The diagnosis of COPA syndrome is based on the identification of characteristic symptoms, a detailed patient and family history, a thorough clinical evaluation, and a variety of specialized tests. Molecular genetic testing can confirm the diagnosis. Molecular genetic testing can identify changes in the COPA gene that cause the disorder. Doctors take a blood sample from people suspected of having COPA syndrome, and the sample is subjected to targeted sequencing of a region of the COPA gene known to cause the disease to evaluate for the presence of known disease-causing changes. Treatment for COPA syndrome is directed at the specific symptoms that are evident in each person. Treatment may require the coordinated efforts of a team of specialists. A pediatrician, general internist, lung disease specialist (pulmonologist), kidney disease specialist (nephrologist), rheumatologist, physical therapist, and other health care professionals may need to plan a systematic and comprehensive treatment plan. There is no standard treatment protocol or guideline for affected individuals. Because of the rarity of the condition, there are no clinical trials that have been tested on large groups of patients. Various treatments have been reported in the medical literature as part of single case reports or small series of patients [1-10].

References

1. Asadi, S. (2025). Pathology in medical genetics. Amidi Publications. https://www.rcpa.edu.au/A-career-in-pathology/Genetic-pathology
2. Tsui, J. L., Estrada, O. A., Deng, Z., (2018). Analysis of pulmonary features and treatment approaches in the COPA syndrome. ERJ Open Research, 4(2), 00017.
3. Taveira-DaSilva, A. M., Markello, T. C., Kleiner, D. E. (2018). Expanding the phenotype of COPA syndrome: A kindred with typical and atypical features. Journal of Medical Genetics. Advance online publication. 56(11), 778-782.
4. Volpi, S., Tsui, J., Mariani, M., (2018). Type I interferon pathway activation in COPA syndrome. Clinical Immunology, 187, 33-36.
5. Brennan, M., McDougall, C., Walsh, J., Crow, Y. J., Davidson, J. (2017). COPA syndrome – A new condition to consider when features of polyarthritis and interstitial lung diseases are present. Rheumatology, 56(6). https://academic.oup.com/rheumatology/article-abstract/56/suppl_6/kex356.059/4331610
6. Vece, T. J., Watkin, L. B., Nicholas, S., et al. (2016). COPA syndrome: A novel autosomal dominant immune dysregulatory disease. Journal of Clinical Immunology, 36, 377-387.
7. de Jesus, A. A., Goldbach-Mansky, R. (2015). Newly recognized Mendelian disorders with rheumatic manifestations. Current Opinion in Rheumatology, 27(5), 511-519.
8. Watkin, L. B., Jessen, B., Wiszniewski, W., (2015). COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. Nature Genetics, 47(6), 654-660.
9. Park, M. S. (2013). Diffuse alveolar hemorrhage. Tuberculosis and Respiratory Diseases (Seoul), 74(4), 151-162.
10. McKusick, V. A. (Ed.). (2015). Online Mendelian Inheritance in Man (OMIM) (Entry No. 616414; Last update: August 21, 2015). The Johns Hopkins University. Retrieved November 27, 2018, from https://omim.org/entry/616414