# Freeman-Sheldon Syndrome

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Freeman-Sheldon syndrome is a condition that primarily affects the face, hands, and feet. People with this disorder have a distinctive facial appearance including a small mouth (microstomia) with pursed lips, giving the appearance of a "whistling face." For this reason, the condition is sometimes called "whistling face syndrome."

genetic conditions

## 1. Introduction

People with Freeman-Sheldon syndrome may also have a prominent forehead and brow ridges, a sunken appearance of the middle of the face (midface hypoplasia), a short nose, a long area between the nose and mouth (philtrum), deep folds in the skin between the nose and lips (nasolabial folds), full cheeks, and a chin dimple shaped like an "H" or "V".

Affected individuals may have a number of abnormalities that affect the eyes. These may include widely spaced eyes (hypertelorism), deep-set eyes, outside corners of the eyes that point downward (down-slanting palpebral fissures), a narrowing of the eye opening (blepharophimosis), droopy eyelids (ptosis), and eyes that do not look in the same direction (strabismus).

Other facial features that may occur in Freeman-Sheldon syndrome include an unusually small tongue (microglossia) and jaw (micrognathia) and a high arch in the roof of the mouth (high-arched palate). People with this disorder may have difficulty swallowing (dysphagia), a failure to gain weight and grow at the expected rate (failure to thrive), and respiratory complications that may be life-threatening. Speech problems are also common in this disorder. Some affected individuals have hearing loss.

Freeman-Sheldon syndrome is also characterized by joint deformities (contractures) that restrict movement. People with this disorder typically have multiple contractures in the hands and feet at birth (distal arthrogryposis). These contractures lead to permanently bent fingers and toes (camptodactyly), a hand deformity in which all of the fingers are angled outward toward the fifth finger (ulnar deviation, also called "windmill vane hand"), and inward- and downward-turning feet (clubfoot). Affected individuals may also have a spine that curves to the side (scoliosis).

People with Freeman-Sheldon syndrome also have an increased risk of developing a severe reaction to certain drugs used during surgery and other invasive procedures. This reaction is called malignant hyperthermia. Malignant hyperthermia occurs in response to some anesthetic gases, which are used to block the sensation of

pain. A particular type of muscle relaxant may also trigger the reaction. If given these drugs, people at risk for malignant hyperthermia may experience muscle rigidity, breakdown of muscle fibers (rhabdomyolysis), a high fever, increased acid levels in the blood and other tissues (acidosis), and a rapid heart rate. The complications of malignant hyperthermia can be life-threatening unless they are treated promptly.

Intelligence is unaffected in most people with Freeman-Sheldon syndrome, but approximately one-third have some degree of intellectual disability.

## 2. Frequency

Freeman-Sheldon syndrome is a rare disorder; its exact prevalence is unknown.

## 3. Causes

Freeman-Sheldon syndrome may be caused by mutations in the *MYH3* gene. The *MYH3* gene provides instructions for making a protein called embryonic skeletal muscle myosin heavy chain 3. This protein belongs to a group of proteins called myosins, which are involved in cell movement and transport of materials within and between cells. Myosin and another protein called actin are the primary components of muscle fibers and are important for the tensing of muscles (muscle contraction). Embryonic skeletal muscle myosin heavy chain 3 forms part of a myosin protein complex that is active before birth and is important for normal development of the muscles.

*MYH3* gene mutations that cause Freeman-Sheldon syndrome likely disrupt the function of the embryonic skeletal muscle myosin heavy chain 3 protein, reducing the ability of fetal muscle cells to contract. This impairment of muscle contraction may interfere with muscle development in the fetus, resulting in the contractures and other muscle and skeletal abnormalities associated with Freeman-Sheldon syndrome. It is unclear how *MYH3* gene mutations may cause other features of this disorder.

Some people with Freeman-Sheldon syndrome do not have mutations in the *MYH3* gene. In these individuals, the cause of the disorder is unknown.

### 3.1. The Gene Associated with Freeman-Sheldon Syndrome

- MYH3

## 4. Inheritance

Freeman-Sheldon syndrome can have different inheritance patterns. In some cases, the condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. The condition can also have an autosomal recessive inheritance pattern, which means both copies of the

gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

In some cases, the inheritance pattern is unknown.

## 5. Other Names for This Condition

- craniocarpotarsal dysplasia
- craniocarpotarsal dystrophy
- DA2A
- distal arthrogryposis, type 2A
- FSS
- whistling face syndrome
- whistling face-windmill vane hand syndrome

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