

Varadi-Papp Syndrome

(Oral-facial-digital Syndrome, type VI or OFD, type VI)

Varadi-Papp syndrome refers to one type of oral-facial-digital (OFD) disorder. This particular OFD syndrome occurs as part of a group of genetic conditions that result from an abnormality in the part of the brain called the cerebellar vermis. The disorders that share this cerebellar malformation are known as Joubert syndrome and related disorders (JSRD). These conditions have some characteristics in common, but there is a spectrum of symptoms and abilities in affected individuals. For additional information regarding this family of conditions, please refer to the Joubert Syndrome Foundation & Related Cerebellar Disorders website at www.jsfrcd.org.

Individuals diagnosed with Varadi-Papp syndrome traditionally exhibit the following features:

- Cleft lip or palate
- Anomalies of the tongue such as nodules or benign tumors
- Extra strands of tissue between the gums, tongue, and mouth (oral frenulae)
- Abnormalities in teeth, particularly tooth shape and/or tooth enamel hypoplasia
- Facial abnormalities, including abnormalities in the region of the eyes, which can include a prominent fold of skin over the central corners of the eye (epicanthal folds), squinting or paralysis of the ocular muscles (strabismus), or widely-spaced eyes (hypertelorism)
- Extra fingers and/or toes (polydactyly), especially of central digits (with a Y-shaped metacarpal bone of the hands) and duplicated great toes. Extra digits on the pinkie side of the hand or foot can also occur.
- A variety of brain malformations, such as an underdeveloped cerebellar vermis (hypoplasia) or complete lack of the cerebellar vermis (aplasia/agenesis), that may be indicated by the “Molar Tooth” sign found on axial views on an MRI scan.
- Developmental delays/mental retardation—variable severity
- Short stature/poor growth

While less common, the following features may also be present in some individuals:

- Abnormalities of the forebrain (holoprosencephaly), corpus callosum, hypothalamus, pituitary gland, or occipital lobes (encephaloceles) can be seen
- Heart defects, such as holes in the heart or malformations of the aorta
- Abnormalities of the genitalia, such as a undescended testicles or small penis in males
- Decreased muscle tone (hypotonia)
- Difficulty coordinating voluntary muscle movements; uncoordinated movements (ataxia)
- Retinal dystrophy, particularly increased pigmentation of the retinal or flattened electroretinogram (ERG) traces.
- Renal insufficiency, typically polycystic or cystic dysplastic kidneys
- Abnormal breathing pattern with periods of rapid breathing or panting (episodic hyperpnea), which may be followed by pauses in breathing (apnea)
- Difficulty processing and reacting to information received through any of their five senses
- Abnormalities of the liver, including hepatic fibrosis
- Oculomotor apraxia (OMA), which is a specific eye movement abnormality in which it is difficult for children to track objects smoothly. Rapid, involuntary movements of the eyes (nystagmus) can also occur
- Other conditions not listed here may also be observed

Explanation of features:

Varadi-Papp syndrome is distinguished from other oral-facial-digital syndromes due to an abnormality consisting of an extra digit coming off of the second, third, or fourth finger (or toe) with x-rays showing a Y-shaped metacarpal bone (central polydactyly). Also associated with Varadi-Papp are cerebellar abnormalities, in which there is an absence or underdevelopment of part of the brain called the cerebellum vermis which controls balance and coordination. In addition, the brainstem may be malformed, which may cause an abnormal breathing pattern called episodic

hyperpnea, in which babies pant, that may be followed by apnea (cessation of breathing). The severity of both the ataxia (uncoordinated movements) and the abnormal breathing patterns varies from person to person. A child with severe episodes of apnea should be monitored regularly and be under the care of a pulmonologist. Children affected with this disorder may be severely impaired and in some cases, may have a shortened life span.

Decreased muscle tone is common in children with Varadi-Papp. As a result of the poor muscle tone, developmental delay (usually in gross motor, fine motor and speech areas) is common. Many children have also been noted to have abnormal eye and tongue movements. Developmental delays are usually treated through physical therapy, occupational therapy, speech therapy, and infant stimulation. Feeding issues that may arise as a result of cleft palates, other oral malformations and low muscle tone can be addressed with the help of specially trained therapists.

Some individuals experience difficulties resulting from an inability to appropriately process information received through the five senses - hearing, seeing, tasting, touching, and smelling - as well as from their poor sense of balance and muscle movement. Some families have found that sensory integration therapy can help to minimize these sensory issues.

Management and treatment:

Presently, there is no cure for Varadi-Papp syndrome. It is recommended that individuals diagnosed with Varadi-Papp syndrome regularly see the appropriate specialists necessary to help monitor their various clinical features. Suggested specialists include an ophthalmologist (eye doctor), geneticist and neurologist, as well as any others recommended by your doctor. Oral clefts require surgical closure, generally within the first year of life. Surgical removal of extra fingers and toes may be recommended. Oral frenulae can also be removed if they impair oral function.

Monitoring for some of the complications associated with Varadi-Papp syndrome, such as vision loss or kidney or liver involvement that may become progressive over time, is recommended on an annual basis. Please refer to the Joubert Syndrome Foundation & Related Cerebellar Disorders website's "Evaluation Recommendations" link for a complete listing of recommended annual tests.

Inheritance and recurrence:

Varadi-Papp syndrome is passed from parent to offspring as an autosomal recessive trait, which means that both parents have at least one altered copy of the gene responsible for this disorder in their DNA. (In order for a child to be born with Varadi-Papp, both the egg and the sperm must contain the same altered gene in question). The odds of having a child born with this condition to parents who carry the gene involved are 1 in 4 births, or 25%, in each pregnancy that they share.

Genetic cause:

To date, no genes known to be responsible specifically for Varadi-Papp syndrome have been identified. Although three genes are known to cause JSRD, none of these has been associated with the features of Varadi-Papp syndrome.

Research is currently underway to assist medical professionals in developing a greater understanding about this disease. For more information about genetic research, please contact the Joubert Syndrome Foundation and Related Cerebellar Disorders.

Additional resources for families:

- The Joubert Syndrome Foundation and Related Cerebellar Disorders: www.jsfrcd.org
- Children's Craniofacial Association: www.ccakids.com
- FACES: The National Craniofacial Association: www.faces-cranio.org

Resources used in the creation of this document:

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- Munke, M, et al. (1990). Oral-Facial-Digital Syndrome Type VI (Varadi Syndrome): Further Clinical Delineation. *American Journal of Medical Genetics*, 35, 360-369.
- ORPHA.NET database on rare diseases and orphan drugs www.orphanet.net
- Parisi, M.A. and Glass, I. A. "Joubert Syndrome" GeneReviews, Online publication of expert-authored disease reviews: www.genereviews.org

The information presented is intended to summarize this condition as it is presently understood by medical professionals. The statements included in this document are for information only and should not be considered as medical advice. Please always consult your physician for medical advice.