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The Role of Mutations on Gene IRF6 in IRF6 Related Syndrome

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1. Abstract

IRF6-related syndrome is a group of cleft lip and palate disorders including Van der Wood Syndrome (VWS) and Popliteal Pterygium Syndrome (PPS). People with VWS are at the lowest end of the spectrum. They can have cleft lip or palate or cleft palate or a combination of these abnormalities. People with PPS usually have cleft lip, cleft lip, or cleft palate, with additional skin and limb abnormalities, including dark skin on the back of both feet (papillary) and between the legs (between the veins), deformity, or abnormalities of the device. Mutations in the interferon-6 regulatory factor (IRF6) gene, located on the long arm of chromosome 1 at 1q32.2, have been linked to IRF6 syndrome.

2. Generalities of IRF6 Related Syndrome

IRF6-related syndrome is a group of cleft lip and palate disorders including Van der Wood Syndrome (VWS) and Popliteal Pterygium Syndrome (PPS). People with VWS are at the lowest end of the spectrum. They can have cleft lip or palate or cleft palate or a combination of these abnormalities. People with PPS usually have cleft lip, cleft lip, or cleft palate, with additional skin and limb abnormalities, including dark skin on the back of both feet (papillary) and between the legs (between the veins), deformity, or abnormalities of the device. Genital warts are swollen or swollen fingers or toes (syndactyly), maxillary and mandibular adhesions (intraoral adhesions), and upper and lower eyelids (ankylobulpharon). The conical crease of the skin on the thumb nail is one of the definite findings in PPS [1, 2] Figure 1.

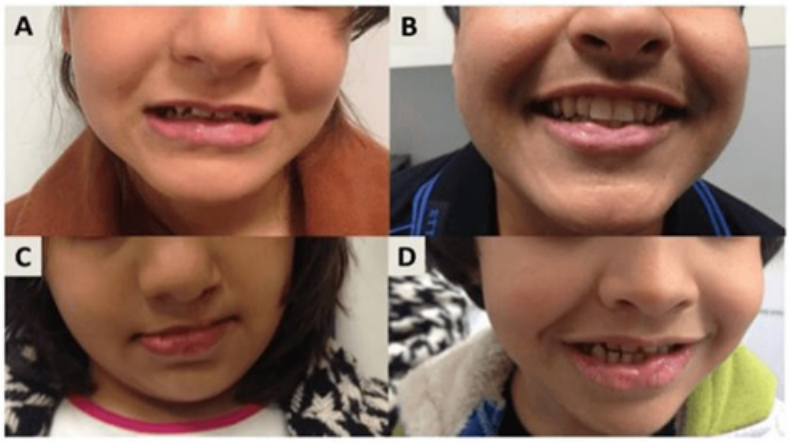

Figure 1: Images of patients with IRF6-related syndrome.

3. Clinical Signs and Symptoms of IRF6 Related Syndrome

The symptoms of IRF6 syndrome vary greatly from person to person. Some people with the disease may have mild clinical symptoms, while others may have a more severe form of the disease (variable expression) [1, 3].

People with VWS can have lip sores, cleft lip or cleft palate alone, or a combination of these abnormalities. Lip sores are usually formed as a pair of dimples on the lower lip. In less common cases in VWS, a person may develop lip cone, lip pit, partial missing teeth, incomplete cleft palate, and limited tongue movement (angioglossia) [1, 3].

People with PPS typically have a thick network of skin on the back of both feet that extends from the hip (isial tuberosity) to the heel. In some patients, this abnormal thick skin network may be present on one foot (unilateral). Because full leg stretching may be limited or the legs may rotate abnormally (in or out), this may make it difficult to walk [1, 3].

In most patients, dark skin may also be present between the legs in the upper thigh area (intermittent fingernail). Some joints may become permanently bent (joint contraction), especially the knees. Babies with PPS may also have swelling or swelling of one or more toes and / or toes (syndactyly), and some children may have a triangular (pyramidal) crease in the toenails, especially the big toe. To cover. There may also be dimples on the skin of the elbows and knees [1, 4].

PPS may also be associated with facial abnormalities, including incomplete closure of the roof of the mouth (cleft palate) or upper lip (cleft lip) in most infants. Children with cleft palate may also be prone to recurrent middle ear infections (otitis media). Children with PPS may have abnormal bands of fibrous tissue on the gums (gums) or between the upper (maxillary) and lower (mandible) bones of the jaws (syngenatia), which can cause problems with opening the mouth. In addition, some people with the disease may have abnormal fibrous tissue that connects the edges of the eyelids (filiform ankylosing spondylitis) and may show limited tongue movement (angioglossia). Many of these facial abnormalities, especially cleft palate, can contribute to eating problems, breathing problems, or speech disorders. [1, 4] Figure 2.

People with PPS may also have genital abnormalities. In some women, two long folds of skin on either side of the vaginal opening (large lips) or uterus may not have grown (hypoplastic). In some patients, the clitoris may not grow enough. In some men with this disorder, the scrotum may split abnormally (bifid). In rare cases, the scrotum may be small (hypoplastic) or absent, leaving the testicles in the abdomen (undescended testicles). In approximately 40% of men with testicular disorder, the testicles may also not be able to descend from the abdomen to the scrotum (cryptorchidism) [1, 5].

In severe cases of PPS, abnormalities of the hands and feet (limbs) may be present, including the absence (agenesis) or insufficient growth (hypoplasia) of the fingers or toes, abnormal bending of the outside (valgus), or Bending inside (varus) of the foot, or deformity (dysplasia) of the nails. It is worth noting that growth and intelligence are usually normal in IRF6 syndrome [1, 5].

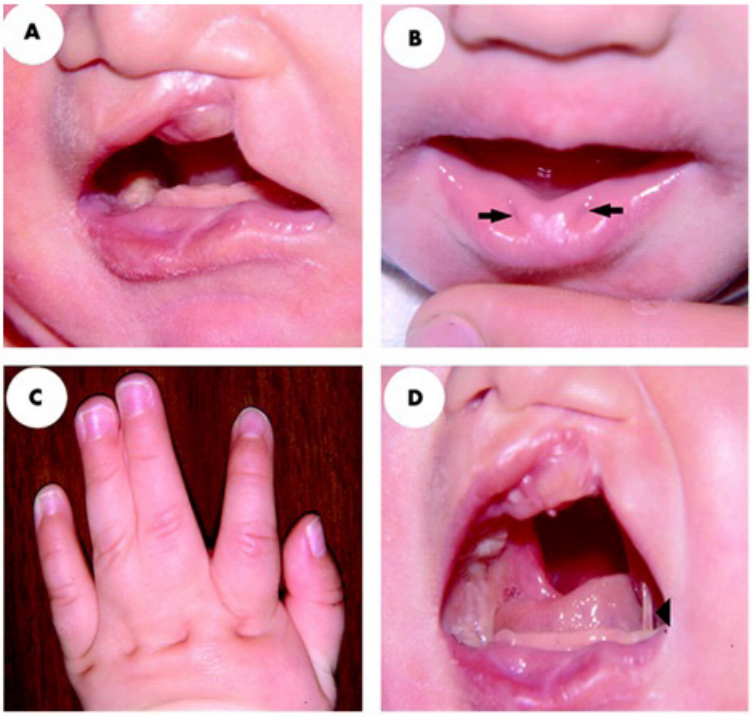

Figure 2: Images of disorders associated with IRF6-related syndrome.

4. Etiology of IRF6-Related Syndrome

Mutations in the interferon-6 regulatory factor (IRF6) gene, located on the long arm of chromosome 1 at 1q32.2, have been linked to IRF6 syndrome [1, 6].

IRF6-related syndrome follows an autosomal dominant inheritance pattern. Therefore, a copy of the IRF6 mutant gene (either parent) is required to cause the syndrome, and the chance of having a child with the autosomal dominant syndrome is 50% for each possible pregnancy [1, 6] Figure 3.

Figure 3: Schematic of chromosome 1 where the IRF6 gene is located in the long arm of this chromosome as 1q32.2.

5. Frequency of IRF6-Related Syndrome

VWS is the most common cause of a single cleft lip and palate gene. The prevalence of this syndrome in Europe and Asia is estimated at 1 in 35,000 to 1 in 100,000. The prevalence of PPS is approximately 1 in 300,000 [1, 7].

6. IRF6-Related Syndrome Disorders

The symptoms of the following disorders may be similar to those of IRF6 syndrome. A comparison may be useful for the differential diagnosis of this syndrome:

Van der Woude 2 Syndrome (VWS2) is an autosomal dominant cleft palate disorder that is almost identical to VWS. They differ in two ways. First, the phenotypic spectrum of VWS2 is the same as VWS. Therefore, it is impossible to distinguish an individual case of VWS from VWS2 based on clinical criteria alone. However, people with VWS2 are more prone to cleft palate and less likely to develop cleft lip and palate. Second, VWS2 is a GRHL3-related disorder because it is caused by a mutation in the gene encoding the GRHL3 transcription factor. While 70% of VWS cases are due to mutations in IRF6, 5% of VWS cases are due to mutations in GRHL3 [1, 8] Figure 4.

Kabuki Syndrome, also known as Nikawa-Kuruki Syndrome, is a rare genetic disorder characterized by mental retardation, short stature, unusual facial features (reminiscent of Kabuki makeup in Japanese theater), skeletal abnormalities, and prominent skin patterns on the fingers. Hands, toes, and palms are marked. Disorders of the palms of the hands and soles of the feet, cleft lip and palate are relatively common findings in Kabuki syndrome. In addition, cases of Kabuki syndrome, cleft palate, and cleft lip have been reported, as seen in IRF6 syndrome [1, 8].

Hirschsprung's Disease (HSCR) is characterized by aganglonic megacolon. However, it has been reported that the cases include cleft palate and in one case, cleft palate and lip cavity [1, 9].

Oro-Facio-Digital syndrome (OFD) is a predominantly X-related disorder that is fatal in men. Affected women have a highly variable phenotype characterized by abnormalities of the mouth, face, and fingers, and can include kidney and brain abnormalities. Oral abnormalities include an arched palate or cleft palate or cleft lip. In one reported case, an infected person had an internal pit in the lower lip [1, 9].

Branchio-Oculo-Facial Syndrome (BOFS) is a very rare genetic disease that is evident from birth (congenital). This disorder may be characterized by low birth weight. An abnormal pit, seen as a cleft lip, or a tumor-like skin abnormality (hemangiomatous or atrophic skin lesion) occur behind both ears (postauricular area) in this syndrome. Specific abnormalities in the head and face (skull and face); Eye abnormalities; Premature graying of the scalp during adolescence or other abnormalities also occur in this syndrome. Some people with BOFS have cleft lip or cleft palate, while others may have unusually wide, prominent upper lip protrusion (filtrum) that resembles surgery-repaired cleft lip. Additional skull and facial abnormalities may include a large, dysplastic nose and defective ears. In people with this disorder, characteristic eye abnormalities may include abnormally small eyes (microphthalmia). Blurring of the lenses of the eyes (cataracts); Congenital ocular stenosis (congenital strabismus); Wide distance of eyes from each other (hyperthermia); Or the absence of tissue (coloboma) from the colored part of the eye (iris), gives the iris an appearance like a "keyhole". BOFS is inherited as an autosomal dominant genetic trait [1, 10].

Bartsocas-Papas syndrome is a disorder that can include cleft lip or palate and dark skin similar to that seen in PPS. This is a more severe phenotype and in some cases, but not all, is fatal. This is an autosomal recessive inherited pattern and has been shown to have mutations in the RIPK4 gene, at least in some cases. In addition, a recent molecular study showed that RIPK4 activates IRF6 function [1, 11].

Isolated cleft lip and palate (iCLP), also called non-syndromic cleft lip and palate, is a disorder that involves only the cleft lip and palate and has no other abnormal features of a syndrome. Isolated CLP is special because it is related to IRF6 syndrome in two phenotypic and genotypic ways. This is phenotypically related because up to 15% of people with VWS do not have dimples. Because these people with VWS only have an oral-facial cleft, their phenotype is the same as that of people with iCLP. In most cases, they were diagnosed with VWS because another affected family member had a lip sore with a cleft lip. Therefore, physicians can diagnose these two disorders only by careful analysis of the family tree. Isolated CLP is genotypically related to IRF6 syndrome because common types of DNA in IRF6, although not

causing IRF6-related syndrome, can increase the risk of cleft lip and palate. The role of IRF6 mutations in iCLP is less clear due to the phenotypic overlap between iCLP and IRF6-related syndrome. Data from 2472 families identified rare IRF6 mutations in 0.24-0.44% of apparently iCLP families. The ability to distinguish between autosomal dominant disorders associated with IRF6 and iCLP is significant because the risk of recurrence for an individual with iCLP (3%) while much higher than the general population risk (0.1%) is much lower than the risk of recurrence [1, 12].

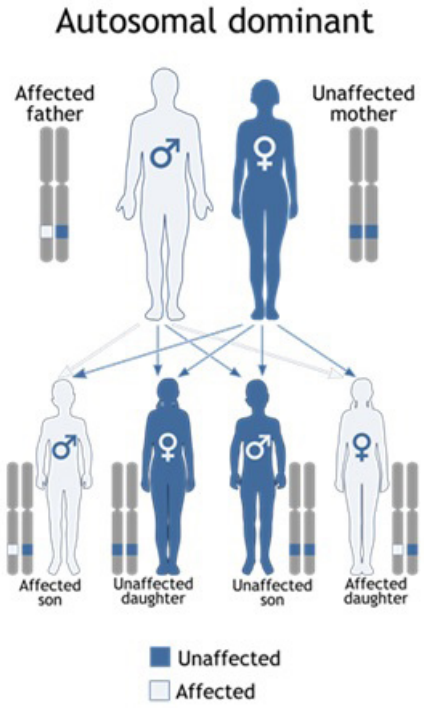

Figure 4: Schematic of the dominant autosomal inherited pattern that IRF6-related syndrome follows.

7. Diagnosis of IRF6-Related Syndrome

The diagnosis of IRF6 syndrome is based on physical characteristics confirmed by molecular genetic testing. If a baby is born with cleft lip or palate, a diagnosis of VWS should be considered, even if there are no cleft lip and palate. However, the current method does not include the IRF6 sequence for such individuals because the cost is very high and the performance is very low (<0.5). Molecular genetic testing can be used to confirm a diagnosis based on physical characteristics. Traditionally, molecular genetic testing of the Sanger method has been used to sequence each of the 9 IRF6 exons. For VWS, more mutations were detected in exons 3, 4, 7 and 9, suggesting a two-tier method for optimal screening. For PPS, almost all mutations were detected in exons 3, 4, and 9, and a rationale for a two-tier screening method is provided. In addition, mutations in MCS9.7 were observed in a family with VWS. MCS9.7 is a 600 bp sequence that is 9.7 KB upstream of the IRF6 gene. Studies have shown that MCS9.7 is an amplifying element, a DNA sequence that acts as a regulatory key to the production of IRF6 gene products. Mutations detected in this VWS family reduce MCS9.7 enhancer activity, suggesting that it may be the cause of the phenotype in infected individuals. Thus, recent molecular genetic testing protocols include the MCS9.7 region. To date, approximately 70% of people with VWS have detectable mutations in the IRF6 gene. Approximately 97% of people with PPS have detectable mutations in the IRF6 gene [1, 13].

If the suspected diagnosis of IRF6-related disorder is not molecularly confirmed, there are at least two hypotheses for the inability to detect all mutations. First, traditional methods for molecular genetic testing do not screen the entire IRF6 and surrounding region for mutations in potential regulatory sequences. In support of this hypothesis, a highly penetrating mutation in the MCS9.7 amplifier of IRF6 was detected in a family with VWS. Second, mutations in other genes may be IRF6-related phenotypes in some families. This includes 5% of VWS families that have mutations in the VWS2 locus in GRHL3 and 2-3% of PPS cases with mutations in RIPK4 or other genes associated with this syndrome (e.g., SFN and IKKA). Over time, molecular genetic plates are becoming next-generation sequencing platforms that allow the sequencing of whole organisms (all exons in the genome) and whole genomes. These platforms provide a more complete evaluation of the IRF6 gene and regulatory elements in order to detect any mutations in the IRF6 syndrome [1, 14].

If the diagnosis of IRF6 syndrome is confirmed, the affected person should have a thorough physical examination to determine if they have any symptoms of the disorder. For example, the presence of an abnormality in the lower lip or the presence of a pyramidal skin fold on the toenail [1, 15].

If an IRF6 gene mutation is detected, prenatal diagnosis and preimplantation genetic diagnosis are available for IRF6 syndrome. Molecular genetic testing for IRF6 gene mutations can be performed on amniocentesis-induced embryonic cells at 18-16 weeks of gestation or placental aberrations at 12-12 weeks of gestation. Pre-implantation genetic diagnosis involves in vitro fertilization and testing for gene mutations in blastocyst-derived cells. Only embryos that do not have mutations are implanted [1, 16].

8. Treatment Routes for IRF6-Related Syndrome

Genetic counseling is an important intervention for sufferers and their families. The risk of recurrence for IRF6-related disorders is up to 50%, as expected for autosomal dominant inheritance with high permeability. In addition, a specific set of mutations in the IRF6 gene (unpleasant mutations that alter amino acids predicted to interact directly with DNA) are associated with PPS, but are not identified. In other words, people with VWS who have one of these PPS-related mutations are potentially at risk of having a child with a more severe PPS phenotype. Conversely, people with PPS can have a child with a low-intensity VWS phenotype. At this time, the factors that modify the phenotype in both directions are

unknown. Thus, while the risk of having a child with IRF6 syndrome is predictable, the severity of the phenotype for children at risk is unpredictable [1, 17].

Cleft lip and palate are treated with surgery and orthodontics. People with cleft palate usually need speech therapy and hearing tests. Lip pits can be surgically cut for cosmetic or lip function reasons [1, 17].

Treatment for PPS is specific to the symptoms that are specific to each individual. Treatment may require the coordinated efforts of a team of specialists, including pediatricians; Plastic, orthopedic and maxillofacial surgeons, speech pathologists; And specialists who treat the ear, nose and throat (ENT specialists) may need regular and comprehensive planning to diagnose and treat the affected child [1, 18].

Dark skin on the back of the legs (papillary) may be removed surgically. Corrective surgery should be performed as soon as possible because the skin networks may limit the injured person's ability to stretch their legs and inhibit normal gait. In many cases, however, surgery can be complicated because it can block nerves (for example, the sciatic nerve and its branches) and blood vessels that run down through the legs (vascular bundles). Is located in the skin tissue. In these cases, surgeons must remove the nerves and blood vessels from the extra skin and try to place them in their natural place inside the legs [1, 19].

The extra skin network between the legs may also be surgically removed, as it may limit a person's ability to open and close the legs and move the legs independently, interfering with normal walking. Swelling or fusion of one or more fingers or toes (syndactyly) may also be corrected with surgery [1, 19].

Abnormal fibrous fibers of the mouth (oral syncytia), such as those that connect the jaws (syngathia) or the gums (synechiae gums) and abnormal fibrous tissue that connects the edges of the eyelids (ankyloblepharon phylliform) It may also be corrected with surgery [1, 20].

Surgery may also be performed to correct genital abnormalities that may be associated with PPS but lead to infertility. In women, plastic surgery may help regenerate the vagina and related structures (big lip, clitoris). In men, surgery can be performed to transfer the undescended testicles to the scrotum and attach them to prevent them from contracting (archipexia). Plastic surgery may also be performed to correct the abnormal division of the scrotum. Treatment with an endocrinologist may be necessary to remove any small penis (micropenis) that may be present [1, 21].

Movement support (dynamic splint) or surgery may be used to treat joint contractions. Physiotherapy is also useful for children with joint contractions [1, 22].

A team approach for infants with the disorder may be helpful and may include special social support, speech therapy, physiotherapy and other medical services. Other treatments are symptomatic and supportive. All babies born with cleft lip and palate are best monitored by a cleft or skull and face medical team [1, 22].

9. Discussion and Conclusion

People with VWS are at the lowest end of the spectrum. They can have cleft lip or palate or cleft palate or a combination of these abnormalities. People with PPS usually have cleft lip, cleft lip, or cleft palate, with additional skin and limb abnormalities, including dark skin on the back of both feet (papillary) and between the legs (between the veins), deformity, or abnormalities of the device. Genital warts are swollen or swollen fingers or toes (syndactyly), maxillary and mandibular adhesions (intraoral adhesions), and upper and lower eyelids (ankylobulpharon). Van der Woude 2 Syndrome (VWS2) is an autosomal dominant cleft palate disorder that is almost identical to VWS. They differ in two ways. First, the phenotypic spectrum of VWS2 is the same as VWS. Therefore, it is impossible to distinguish an individual case of VWS from VWS2 based on clinical criteria alone. However, people with VWS2 are more prone to cleft palate and less likely to develop cleft lip and palate. Genetic counseling is an important intervention for sufferers and their families. The risk of recurrence for IRF6-related disorders is up to 50%, as expected for autosomal dominant inheritance with high permeability. Treatment may require the coordinated efforts of a team of specialists, including pediatricians; Plastic, orthopedic and maxillofacial surgeons, speech pathologists; And specialists who treat the ear, nose and throat (ENT specialists) may need regular and comprehensive planning to diagnose and treat the affected child. Surgery may also be performed to correct genital abnormalities that may be associated with PPS but lead to infertility. In women, plastic surgery may help regenerate the vagina and related structures (big lip, clitoris). In men, surgery can be performed to transfer the undescended testicles to the scrotum and attach them to prevent them from contracting (archipexia) [1-22].

References

1. Asadi S. Pathology in Medical Genetics Book, Vol 18, Amidi Publications Iran 2021.
2. Rincic M, Rados M, Krsnik Z, et al. Complex intrachromosomal rearrangement in 1q leading to 1q32.2 microdeletion: a potential role of SRGAP2 in the gyrification of cerebral cortex. Mol Cytogenet. 2016; 9: 19.
3. Mangold E, Bohmer AC, Ishorst N, et al. Sequencing the GRHL3 Coding Region Reveals Rare Truncating Mutations and a Common Susceptibility Variant for Nonsyndromic Cleft. Am J Hum Genet. 2016; 98: 755-62.
4. Ikwa MQ, Huynh J, Reynolds EC, Hamilton JA, Scholz GM. Disease-associated mutations in IRF6 and RIPK4 dysregulate their signalling functions. Cell Signal. 2015; 27(7): 1509-16.
5. Leslie EJ1, O'Sullivan J, Cunningham ML, Singh A, Goudy SL, Ababneh F, et al. Expanding the genetic and phenotypic spectrum of popliteal pterygium disorders. Am J Med Genet A. 2015; 167A(4): 545-52.

6. Fakhouri, W, Rahimov F, Attanasio C, et al. An etiologic regulatory mutation in IRF6 with loss- and gain-of-function effects. Hum Mol Genet. 2014; 23: 2711-20.
7. Peyrard-Janvid, M, Leslie EJ, Kousa YA, et al. Dominant mutations in GRHL3 cause Van der Woude syndrome and disrupt periderm development. Am J Hum Genet. 2014; 94: 23-32.
8. Leslie EJ, Mancuso JL, Schutte BC, et al. Search for genetic modifiers of IRF6 and genotype-phenotype correlations in Van der Woude and popliteal pterygium syndromes. Am J Med Genet. 2013; 161A(10): 2535-44.
9. Tan E-C, Lim ECP, Lee S-T. De novo 2.3 Mb microdeletion of 1q32.2 involving the Van der Woude Syndrome locus. Mol Cytogenet. 2013; 6: 31-36.
10. Mitchell K, O'Sullivan J, Missero C, et al. Exome sequence identifies RIPK4 as the Bartsocas-Papas syndrome locus. Am J Hum Genet. 2012; 90(1): 69-75.
11. Kalay E, Sezgin O, Chellappa V, dt al. Mutations in RIPK4 cause the autosomal-recessive form of popliteal pterygium syndrome. Am J Hum Genet. 2012; 90(1): 76-85.
12. Salahshourifar I, Halim AS, Sulaiman WA, Zilfalil BA. De novo interstitial deletion of 1q32.2-q32.3 including the entire IRF6 gene in a patient with oral cleft and other dysmorphic features. Cyogenet Genome Res. 2011; 134(2): 83-87.
13. Desmyter L, Ghassibe M, Revencu N, et al. IRF6 Screening of Syndromic and a priori Non-Syndromic Cleft Lip and Palate Patients: Identification of a New Type of Minor VWS Sign. Mol Syndromol. 2010; 1(2): 67-74.
14. Jones JLP, Canady JW, Brookes JT, et al. Wound Complications after cleft repair in children with Van der Woude syndrome. J Craniofac Surg. 2010; 21: 1350-3.
15. de Lima RL, Hoper SA, Ghassibe M, et al. Prevalence and nonrandom distribution of exonic mutations in interferon regulatory factor 6 in 307 families with Van der Woude syndrome and 37 families with popliteal pterygium syndrome. Genet Med. 2009; 11(4): 241-7.
16. Houweling AC, Gille JJP, Baart JA, van Hagen JM, Lachmeijer AM. Variable phenotypic manifestation of IRF6 mutations in the Van der Woude syndrome and popliteal pterygium syndrome: implications for genetic counseling. Clin Dysmorphol. 2009; 18: 225-7.
17. Yeetong P, Mahatumarat C, Siriwan P, Rojvachiranonda N, Suphapeetiporn K, Shotelersuk V. Three novel mutations of the IRF6 gene with one associated with an unusual feature in Van der Woude syndrome. Am J Med Genet A. 2009; 149A: 2489-92.
18. Rahimov F, Visel A, Pennacchio LA, et al. Disruption of a transcription factor AP-2a binding site in an IRF6 enhancer is commonly associated with nonsyndromic cleft lip and palate. Nat Genet. 2008; 40: 1341-7.
19. Schutte BC, Saal HM, Goudy S, et al. IRF6-Related Disorders. 2003.
20. Online Mendelian Inheritance in Man (OMIM). The Johns Hopkins University. Van Der Woude Syndrome 1; VWS1. Entry No: 119300. Last Update 2015.
21. Online Mendelian Inheritance in Man (OMIM). The Johns Hopkins University. Popliteal Pterygium Syndrome; PPS. Entry No: 119500.
22. Online Mendelian Inheritance in Man (OMIM). The Johns Hopkins University. Interferon Regulatory Factor 6; IRF6 . Entry No: 607199.