Van der Woude syndrome

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Abstract. Orofacial clefts (OFCs) are the most common craniofacial birth defect in all populations worldwide and include cleft lip with or without cleft palate (CL/P) and cleft palate alone (CP). Approximately 70% of OFC are non-syndromic while 30% are syndromic. Syndromic OFCs are often caused by structural chromosomal anomalies or by coding mutations in a single gene. The most common OFC syndrome is Van der Woude syndrome (VWS, MIM #119300) which has 2% of all OFCs with an overall prevalence of 1/35,000-1/100,000 live births. The characteristic features of Van der Woude syndrome are orofacial clefts and congenital lower lip pits. IRF6 or GRHL3 plays an important role in VWS mutations. Van der Woude syndrome is inherited in an autosomal dominant pattern, mostly an affected person has one parent with the condition. Patients with Van der Woude Syndrome who has OFCs increased the risk of delayed language development, learning disabilities, or other mild cognitive problems. The average IQ of individuals with van der Woude syndrome is not significantly different. IRF6 or GRHL3 plays an important role in VWS mutations. The IRF6 protein is active in cells that give rise to tissues in the head and face. A shortage of the IRF6 protein affects the development and maturation of tissues in the face, resulting in the signs and symptoms of van der Woude syndrome such as OFCs. GRHL3 was shown to be required for the development of the periderm, and an important player in the IRF6 dependent pathway of periderm development. In this review, author will explain further about Van der Woude Syndrome and review the literature available on recent studies toward the caused of Van der Woude Syndrome whether it is developed from IRF6 genes.

1. Introduction
Orofacial cleft (OFC) is the most famous congenital craniofacial disorder among all people in the world, including only cleft palate (CP), cleft lips or no cleft palate (CL/P) [1,2]. In a larger proportion, about 70% OFC are non-syndromic, while the other 30% are syndromic due to mixing with other structural or cognitive disorders. Non-syndromic OFCs etiology are complex and are causally impacted by genetic risk factor, measurements of genetic susceptibility and comprehensive environmental exposure, or other unidentified events. At the same time, syndromic OFC is usually carried by structural chromosomal abnormalities or code mutations in a single gene. The most widely known OFC syndrome is Van der Woude condition (VWS, MIM #119300), which constitutes 2% of all OFC, with a total prevalence of 1/35,000-1/100,000 live births [4,6]. VWS features can be seen in the gap of the congenital upper jaw (orofacial clefts) and the opening of the lower lip (congenital lower lip pits). Although the VWS is very sharp, it has an extraordinary expression factor. People converting VWS can display CL, CLP (built-in gap with built-in gaps), CP, or no OFC at all [4].

This study was conducted in order to provide more information about Van der Woude syndrome and to review existing literature on recent research on the causes of Van der Woude syndrome,
regardless of whether the syndrome is caused by the IRF6 gene. All recognized VWS causalities are located in IRF6 or GRHL3, which play an important role in early development. Van der Woude's condition is obtained in autosomal dominant mode, which means that one copy of the modified mass in each cell is enough to cause syndrome. In most cases, the affected person has an elderly person who has the syndrome. Sometimes people with altered copies of genes show no signs or symptoms of the disorder [4].

2. Orofacial development

2.1 Lip formation

At the beginning of the sixth week of prenatal growth, the upper jaw lip begins to form, this is because each process of the upper jaw merges with each intranasal process on both sides of the airway, thus approaching the proliferation of mesenkim derived from the Neural Crest Cell. Therefore, the process of the upper jaw works on the sides of the upper lip, while the two medial nasal processes work on the philtrum. At the end of the seventh week of prenatal development, when the gap between the processes is cleared, the process of formation of the upper lip is completed combined. The process of the upper jaw on each side of the developmental surface fuses with the mandible arch on each side to form each labial lip, and the mandibular arch has formed the lower lip [18].

At the beginning of the 6th week of prenatal growth, each process of the upper jaw merges with each process of the nasal cavity on both sides of the airway, the upper lip begins to form, and the proliferation of Neural Crest cells derived from mesenkim makes it close. Therefore, the process of the upper jaw begins to merge with the sides of the upper lip, and the two medial nasal process add to the philtrum. At the end of the 7th week the growth of the upper bead lip, when the groove between the processes is destroyed, the process of forming the upper lip is finished mixed. The protrusions of the upper jaws on each side fuse with the mandible arches on each side forming each lip, the curvature of the lower jaw forming the lower lip [18].

Figure 1. Embryo at 6th weeks. A. Upper and lower lip formation. B and C. Sagittal sections of the head showing the development of the intermaxillary segment from the fusion of medial nasal processes on the inside of the stomadeum [18]
Maxillary and medial nasal processes that failed to fuse produces the common congenital malformation of cleft lip, which might be unilateral or bilateral. The medial nasal processes failure to merge produce the formation of median cleft lip. Most clefts of the lip have a multifactorial etiology, being related with both hereditary and ecological aggravations. The basic time frame for such interference is during the 6th and 7th long stretches of intrauterine life [19].

2.2 Palatum formation
By the 5th week of prenatal growth and still in the embryonic stage, the intermaxillary segment is already formed. The intermaxillary segment is produced due to the melting of two nasal cavities inside the embryo. The intermaxillary segment is the mass that forms an in-out slice that extends down and deep into the nostrils of the mouth. The lower part initially fills the nasal cavity and septum [18].

In the week 6th of prenatal growth, the bilateral process of the upper jaw will form two palate frames (or lateral palatine processes). This frame is along the sides of the formed tongue, low and deep in the stomodeum. Since the power to lift the rack is not yet clear, the shelf rack will then develop vertically, flipping in a column that dominates within a few hours of tongue movement. As a result, the frame moves to a horizontal position, which is currently better than the tongue being opened. Next, the two palate frames stretch and approach each other in, join together, then combine to form a second palate [18].

The secondary palate eventually produces two-thirds of the posterior of the hard palate, which contains certain anterior teeth of the upper jaw (canines) and posterior teeth, all of which are located behind the incision. Secondary palate rises to uvula and soft palate. The middle palatine raphe inside the mucosa lining and the more profound middle palatine suturee on the grown-up maxillary bone indicate the line of combination of the palatal shelves [18].

![Figure 2. The formation protrudes towards the coronal through the head of development. A, a skeleton formed by the Palatal bone in the process of the deep upper jaw. The palatal develops](image-url)
vertically (arrows), and the position of the developing tongue is between the frames. B, After turning up (arrows), the bone frame grows horizontally with each other forming a second ceiling. C, a combination of three processes (arrows) to complement the final palate of the fetus: the primary frame and the two palatals form a secondary palatal [18].

3. Van der woude syndrome

3.1 Definition and prevalence
The lower lip pits was first discovered by Dermaquay in 1845 and explored extensively by Van der Woude in 1954. Van der Woude pioneered the use of a mixture of lower lip pits with congenital fissure (CL) and congenital fissure (CP), presenting new clinical methods, and he described it as a hereditary method. Van der Woude's syndrome (VWS) is the most common form of asymptomatic fiss, accounting for about 2% of all OFCs, with a general gain of 1/35,000-1/100,000 live births [4,5].

VWS is a rare formative congenital syndrome with high penetrance and variable expression ability. Clinical qualities of VWS are lower lip, CL with or without CP, and isolated CP. Other phenotypic expressions differ from incomplete unilateral CL <CP submucosal, double uvula, and complete bilateral CLP [5]. Most of the affected individuals have a depression (pits) near the midpoint of the lower lip, which may appear wet due to the presence of saliva and mucus organs in the hole. Small tissues will also appear on the lower lip. In some cases, patients with Van der Woude syndrome lose their teeth [15]. Individuals with Van der Woude syndrome who have cleft lip and/or palate, as others with these facial conditions, have an expanded risk of postponed language advancement, learning disabilities, or other mild cognitive issues. The normal level of IQ of people with van der Woude disorder didn’t have much difference from the general population [15].

![Figure 3. Affected female with characteristic bilateral lower lip sinuses and a bilateral cleft lip and palate [7]](image)

3.2 Etiology
Studies have known that VWS mutations are located in IRF6 or GRHL3. Mutation of loss of function in IRF6 account for approximately 70% VWS (VWS1, MIM # 119300), transformation of job gain in GRHL3 account by 5% (VWS2, MIM # 606713), and only 25% of VWS cases without known cause mutation and unknown genes [2,15]. The IRF6 gives directions to making a protein that assumes a significant function in early development. Then, GRHL3 were demonstrated to be required for the improvement of the periderm [8, 91,10].

3.3 Inheritance pattern
Van der Woude syndrome is a congenital malformation with autosomal dominant inheritance, which implies one duplicate of the adjusted quality in every cell is adequate to cause the disorder. For most
cases, an influenced individual has one parent with the condition. Every so often, a person who has copy of the altered gene doesn't give any signs of Van der Woude syndrome [15].

4. Genetics of van der woude syndrome

4.1 IRF6 (interferon regulatory factor 6)

The IRF6 mass chromosome region may have its cytogenetic or molecular regions. The cytogenetic position of IRF6 is located at 1q32.2, which is the long arm of chromosome 1 at the position of 32.2. The location of irf6 molecules is the baseline set 209,785,617 to 209,806,175 on chromosome 1 (Homo sapiens Refreshed Explanation Delivery 109.20200228, GRCh38.p13) [6].

Figure 4. The cytogenetic location of IRF6 [6]

Changes in the IRF6 cause the van der Woude disorder [6,7,15]. IRF6 up to a place in the IRF factor. This quartation factor shares less DNA N-terminal helix-turn-helix restriction area and less C-terminal protein restriction space [10]. This family is known for its role in immune function. At the same time, IRF6 is required for craniophaasial morphogenesis and epidermal formation during embryonic development (MIM 607199) [9,11]. IRF6 provides guidelines to guide protein production, and these guidelines play an important role in its early development. This protein is a transcription factor, which means that the protein attaches to a specific DNA location and helps control certain actions [6,15]. The IRF6 protein is active inside the cell and can propagate to the head and face tissues. It is also associated with the development of different parts of the body, including the skin and genitals [6].

The expression IRF6 in human craniophaasial structures associated with normal palate and lip development is based on information obtained from the Craniofacial and Oral Quality Occlusal Organization (COGENE) Consortium. Information from the SAGE library is used to evaluate gene expression patterns in different human embryonic tissues (i.e., 26-day-old human embryonic tissue, 4-week anterior rhombomere, 4-week posterior rhombomere, 4-week frontonasal prominence, 5-week frontonasal prominence, 6-week mandible, and 8.5-week upper lip) [12]. Mutations in IRF6 cause Van der Woude to prevent the presence of duplicate genes in each cell that makes the protein work. Irf6 protein deficiency affects the development and maturation of facial tissue, carrying signs of Van der Woude's syndrome, such as OFC [6,15].

There are a sum of 219 IRF6 gene mutation, including 191 IRF6 gene mutation recognized in patients with VWS (Li et al. 2017). These mutation including missense or nonsense, control area, frameshift and different other various types of changes, however the dominant part have all the earmarks of being missense nonsense mutation. [7,14]. Kondo et al. Found changes in protein truncation (nonsense and frameshift) and missense conversion in VWS. The missense mutation situation provides the structure and function of IRF6. When we adjusted the IRF protein group, they noticed that IRF6 had two connecting domains, namely the spiral wing DNA binding domain (amino acid 13–113) and the protein binding domain (amino acids 226–394) named SMIR (Smad-interferon administrative factor–restricting space) [7].

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Figure 5. IRF6 quality structure. Exons (square) is drawn to separate it from exon 9, which is longer than its appearance. The parentheses connecting the exostron represent the connected intron, while the disconnection between 9 exons and 10 exons representing the intron is not included in the 1,621 nt available in the most famous 4.4 kb IRF6 recording. Untranslated sections are displayed in gray. The predicted IRF6 protein contains the spiral wing DNA binding domain (yellow) and the SMIR/IAD (green) protein binding domain. The arrow indicates the overall situation of protein cutting (above exo) and the missense mutation (below the exone) that causes polymorphic (green) VWS (blue). The arrow above exon 4 shows the nonsense mutation Glu92X identified in the vwS14 affected twin family. Amino acid changes for each missense mutation, a reference sign indicating that the change affects structures in contact with DNA [7].

Additional reporting by Gatta et al. Examined the IFR6 gene in the Italian VWS family and found nonsense mutations in exon 6, including the G650A transition and the formation of a stop kodon on a pile of amino acids 217 (W217X). So far, changes to the W217X have not been described in the two main studies, which do not take into account irf6 mutations in VWS, which can be said to be new mutations along these lines. In fact, compared to dna binding and the SMIR domain, most IRF6 mutations are included in exons 4 and 7, and only two nonsense mutations including exon 6 are described for specific C558A and G576A.

Although mutations in exon 6 are rare and not in dna binding or the SMIR domain of the IRF6 gene, through and through the formation of a kodon stop in exon 6, the protein does not have a complete SMIR domain. Applies to VWS models that cause mutations. In addition, the location of irf6 mutations in the VWS family confirms that protein cutting mutations are common in VWS, and supports speculation that haploid insufficiency carries the VWS phenotype. What is striking is that also in today's family, transformation produces a variety of phenotypes in the family, thus affirming the expressive ability of VWS variables. In short, this report confirms the relationship between IRF6 and VWS, supporting changes in irf6 pathogenic function in this syndrome and the key of this gene that pretends to be in the orofacial improvement stage.

In addition, we found a new mutation that can cause functional damage to the SMIR domain, thus confirming that the IRF6 gene can be affected by various changes. This suggests that molecular analysis of VWS patients should be based on direct sequence screening for all qualities, since in addition to exons 4 and 7, mutations can also be distributed outside the gene. Further reports from Italy's VWS family will shed light on whether the W217X will speaks to the Italian changes [14].

4.2 GRHL3 (Grainyhead Like Transcription Factor 3)
GRHL3 at cytogenetic area 1p36.11, which is the short (p) arm of chromosome 1 at position 36.11 and molecular locations base pairs 24,319,333 to 24,364,482 on chromosome 1 (Homo sapiens Refreshed Comment Delivery 109.20200228, GRCh38.p13) [3].
There is a group of three human genes in striate head 3 or GRHL3 (MIM 608317), which encode orthologist transcription Drosophila quality grainy head. This gene family is necessary for the development and repair of the epidermal barrier layer. In zebrafish, GRHL1 and GRHL3 have been shown to be necessary for the formation of the cortex, which is a temporary layer of epithelial cells located on the surface of a developing embryo. In zebrafish skin development also requires interferon regulation factor 6 (IRF6), and legally regulates GRHL3 expression. In addition, excessive GRHL3 expression partially maintains pericyte development in zebrafish embryos that express the dominant negative form of IRF6. This information indicates that GRHL3 is an important part of the line under IRF6 [9].

By focused exome sequencing in 8 affected and 3 unaffected individuals from a huge Finnish family with Van der Woude condition mapping to chromosome 1p34 (VWS2; 606713), Peyrard-Janvid et al. (2014) recognized heterozygosity for a 2-bp addition in the GRHL3 quality (608317.0001) that isolated with infection in the family and was not found in controls. Screening of 44 extra VWS families who were negative for causative changes in the IRF6 quality (607199) uncovered heterozygous GRHL3 transformations in 7 of them [9].

Peyrard-Janvid et al. (2014) examined the impact of GRHL3 changes on Grhl3 work in zebrafish and watched abrogation of periderm improvement, reliable with a dominant negative impact. In mouse, all of the 6 organisms lacking GRHL3 displayed unusual oral periderm and 1 (17%) created cleft palate. Examination of the oral phenotype of double-heterozygote (IRF6 +/−; GRHL3 +/−) murine embryos neglected to exhibit epistasis between the 2 genes, recommending that they work in isolated however concurrent pathways during palatogenesis [9].

Previous research has shown that Irf6 deficiency in mice can cause orofacial cleft through at least two pathological mechanisms: abnormal cortical differentiation and failure of the medial peripheral rupture of epithelium (MEE). MEE can be described normally in embryos requiring GRHL3, causing normal components IRF6 and GRHL3 to fail to differentiate through the epidermis, thereby improving the function of the cortex that was recently thought to produce lips and sense of taste [9].

5. Epigenetic associated with van der woude syndrome

Epigenetics is the study of inherited gene expression changes that do not include changes in the basic DNA sequence, which ultimately leads to phenotype adjustment without genotype adjustment. Natural variables or specific mutations can trigger these changes. Some of the elements that contribute to epigenetic mechanisms are DNA methylation, chromatin remodeling, histon modification and non-coding RNA regulation. The various components that control epigenetic changes will not remain isolated, and there are reasonable relationships and interdependence between variables [16].

The first is DNA methylation, in which methyl groups are officially added to cytokine residues that are in the setting of cytosine guanine (CpG). For example, many CpG sites form cpg islands, and cytokines are dimethylated. Methylation of CpG sites in the promoter's area is associated with gene decay. DNA methylation turns off genes. Amplification of methyl channels is controlled inside cells and performed by an enzyme called DNA methyltransferage [16].
The second epigenetic modification is histone adjustment. The center of one nucleosome is made out of DNA folded over a histone octamer that comprises of 2 duplicates of the significant sorts of histones H2A, H2B, H3, and H4. A post-translational alteration of histone proteins usually happened along the way. It occurs in the tail of the histon that forms the nucleosome. They helped build the nucleosome. Therefore, the tail of each of these histones juts to the side. Each of these tails has a different point, where various chemical signals involve the implementation of complex epigenetics. Various chemicals can be added to the tail section to produce acetylation, methylation, phosphorylation, ubiquity and sulfonilation [16].

Recent studies have shown that epigenetic systems silence genes associated with non-coding RNA. Non-coding RNA or ncRNA is a functional RNA that has been transcribed from DNA but has not been converted into a protein. Some of them are divided into miRNA, siRNA, piRNA and Inc RNA. This NCRNA controls the quality or retention of hinges at the transcription and post-transcription levels. NCRNA involved in epigenetic processes is divided into two main categories. Short ncRNA (less than 30 nt) and long ncRNA (more prominent than 200 nt). Three important categories of short non-coding RNA are microRNA (miRNA), short interfering RNA (siRNA) and piwi-interacting RNA (piRNA). These two important groups appear to play a role in heterochromatin formation, histon modification, DNA methylation targeting, and gene silencing [16].

Epigenetic changes are central to numerous cell cycles and fundamental to numerous organism function, for example, engraving, X chromosome inactivation, cell reprogramming and senescence. Be that as it may, if these adjustments happen inappropriately, they can prompt major antagonistic wellbeing impacts, for example, malignancy or inherent sicknesses. Besides, the chance of switching epigenetic alterations speaks to an expected objective of novel therapeutic strategies and medication design.

Study affirms the function of a known IRF6 haplotype, which downregulates its appearance, as a causal quality for VWS, and raises the chance of epigenetic guidline of IRF6 articulation that should be affirmed. It also gives a model that VWS phenotype may happen in any event, when more than one variation meet up on a similar chromosome if practically they cause haploinsufficiency. And for the first time, the expression assays, both in vitro and in vivo, plainly exhibit that this variation haplotype essentially brings down the articulation level of IRF6. It is intriguing that a piece of IRF6 intron 1 including the change could tie to a repressor consequently bringing down its expression as demonstrated [17].

6. Conclusion
Van der Woude syndrome (VWS) is the most famous orofacial slit syndrome. The main indications of VWS are congenital orofacial fissures and lower lip openings. Van der Woude’s syndrome is found in autosomal dominant inheritance models, with high permeability and expressive variables. VWS resulted from conversions in IRF6 or GRHL3, which played an important role in early development. IrF6 proteins are dynamic in cells that encourage the growth of head and face tissues. It is also associated with the increasing variety of parts of the human body including the skin and genitals. IRF6 gene mutations include missense, control region, frameshift, and many other types of mutations. Irf6 protein deficiency affects the development and maturation of facial tissues, carrying signs and manifestations of Van der Waard syndrome (for example, OFC). It has been proven that GRHL3 is necessary for cortical development and is an important part of the IRF6 cortical repair pathway. This study confirms the function of known IRF6 haplotypes, which reduce their appearance, to the caesal quality of the VWS, and increases the likelihood of epigenetic guidelines of IRF6 articulation to be emphasized.
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