Van der Woude syndrome with novel variants: a case series

LT Leung #, MB, ChB, **Stephanie KL Ho #,** MB, BS, **WC Yiu,** MSc, **Min Ou,** MPhil, **Jennifer YY Poon,** MB, ChB, **Shirley SW Cheng,** MB, ChB, **Ivan FM Lo,** MB, ChB, **HM Luk *,** MD (HK)

Department of Clinical Genetics, Hong Kong Children's Hospital, Hong Kong SAR, China

* Corresponding author: lukhm@ha.org.hk

# Equal contribution

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Case presentations

In January 2024, individuals presenting to the Department of Clinical Genetics at Hong Kong Children's Hospital with suspected pathogenic variants in the *IRF6* or *GRHL3* genes were assessed. Eight patients with molecularly confirmed Van der Woude syndrome (VWS) from four unrelated families were identified, aged between 17 and 58 years, with a male-to-female ratio of 5:3. All four index cases had an affected parent. Pedigrees of the four families are shown in online supplementary Figure 1.

Cleft palate was observed in 75% (n=6) of individuals, of whom two had bilateral cleft palate and two had submucous cleft palate. Lower lip pits were present in 62.5% (n=5). Cleft lip and/or alveolus was evident in four patients (50%), usually affecting both sides. Bifid uvula was observed in only one individual, while hypodontia was seen in two. One patient had ankyloglossia and two patients (25%) developed vitiligo.

The clinical findings are summarised in the Table. Clinical photos demonstrating oral findings from Family 4 are shown in the Figure.

A different variant was identified in each of the index patients in our cohort. Three harboured an *IRF6* (NM_006147.4) variant, while the remaining index patient had a variant in *GRHL3* (NM_198173.3). All variants were classified as likely pathogenic or pathogenic according to the American College of Medical Genetics and Genomics guidelines[1]. Two of the *IRF6* variants were missense variants, while the remaining one was a splice site variant. The only *GRHL3* variant identified in our cohort was a nonsense variant. All other variants in our cohort were novel, except *IRF6* c.52G>A p.(Val18Met) which has been previously reported.[2]

The molecular findings of our patients are summarised in the Table and online supplementary Figure 2.

Discussion

Orofacial cleft is a prevalent congenital defect with an estimated global occurrence of 1 in 500 to 1000 births and a comparatively higher incidence in Asia according to 2019 Global Burden of Disease data[3]. It is linked to both environmental and genetic factors. Most cases are non-syndromic, presenting a reduced risk of a genetic disorder, with orofacial clefts manifesting as isolated structural anomalies. Nevertheless, syndromic cases comprise approximately 30% of all cases, with an associated higher risk in patients with central cleft lip and/or palate (CL/P) or isolated cleft palate.[4] Cases may be familial or non-familial. According to a local study,[4] the diagnostic yield of genomic variants, including variants of uncertain significance, for non-syndromic orofacial clefts was only about 4%. In contrast, for syndromic cases, the detection rate of genomic variants is as high as around 70%. Among these, most variants have been detected by karyotyping or chromosomal microarray.[5] In view of this finding, genetic testing (ie, chromosomal microarray) is conventionally offered as first-line screening in patients with syndromic orofacial clefts. Whole exome sequencing is less commonly performed in Hong Kong's public clinical sector, although there is no international consensus. Clinical and molecular findings from our four families with VWS suggest that whole exome sequencing may be helpful in making a genetic diagnosis in patients with orofacial clefts. This is advantageous for both the patient and their family, as reproductive options such as preimplantation genetic diagnosis or prenatal diagnosis can be provided for at-risk individuals.

Van der Woude syndrome has historically been linked to pathogenic variants in *IRF6*, which encodes a transcription factor essential for the differentiation of skin, as well as breast and oral epithelium. Abnormal differentiation of the epidermis or oral periderm may be implicated in the pathogenesis of CL/P. The subsequent increase in the number of patients with CL/P has been accompanied by the discovery of a second gene, *GRHL3*. In vivo studies have demonstrated that *GRHL3* regulates the epidermal permeability barrier through action downstream of *IRF6*, explaining the phenotypic convergence.[6] Although it has been postulated that *GRHL3* is more likely associated with cleft palate and less

TABLE. Clinical and molecular findings of the patients

Family	F1		F2		F3	F4		
Individual	II:1	I:1	II:1	I:1	II:1	II:2	II:1	I:1
Sex	M	M	F		F	F	M	M
Age at last consultation	19 y 3 mo	49 y 11 mo	16 y 2 mo	47 y 8 mo	11 y 6 mo	17 y 7 mo	25 y 11 mo	57 y 10 mo
Affected parent	Yes	Yes	Yes	Nil	Yes	Yes	Yes	Yes
Gene	*IRF6*		*IRF6*		*IRF6*	*GRHL3*		
Variant	c.52G>A		c.247C>G		c.-3-1G>A	c.682A>T		
Protein change	p.(Val18Met)		p.(Leu83Val)		p.?	p.(Lys228*)		
Location	Exon 3		Exon 4		Intron 2	Exon 4		
Reported in literature	Yes		Nil		Nil	Nil		
Inheritance	Paternal	N/A	Paternal	N/A	Paternal	Paternal	Paternal	N/A
Lower lip pits	+	+	+	N/A	+	+	Nil	Nil
Cleft lip and/or alveolus	Bilateral cleft lip and alveolus	Bilateral cleft lip	Bilateral cleft lip and alveolus	Bilateral cleft lip	Nil	Nil	Nil	Nil
Cleft palate	Bilateral	Bilateral	Nil	N/A	+	Right submucous cleft palate	Submucous cleft palate	+
Cleft uvula	N/A	N/A	N/A	N/A	Nil	Bifid uvula	N/A	Nil
Hypodontia	+	N/A	+	N/A	Nil	N/A	N/A	N/A
Others	ADHD, ankyloglossia, maxillary hypoplasia, mild genial hypoplasia	Vitiligo; past cleft-related jaw surgeries done	Bilateral eye high myopia and astigmatism	Ankylosing spondylitis	Congenital torticollis	Vitiligo		

Abbreviations: ADHD = attention-deficit hyperactivity disorder; F = female; M = male; N/A = not available

likely with cleft lip, CL/P and lip pits, the number of affected patients remains too small to draw definitive conclusions about genotype-phenotype correlations. In our cohort, all three individuals with a *GRHL3* variant had cleft palate (mostly submucous), no cleft lip, and only one had lower lip pits. These findings appear to align with previous reports.[2,4,5]

According to the literature, approximately 60% of VWS cases show familial occurrence.[7] All index individuals in our cohort had an affected parent. The concurrence of lower lip pits and CL/P has been reported as the most common clinical features among patients with VWS, affecting 80% of cases.[8] In total, 75% and 62.5% of our patients had cleft palate or lower lip pits, respectively. Cleft lip and/or alveolus was evident in 50% of individuals. These findings are comparable with figures described in previous studies.[2,4,5] Disease-causing variants in both genes have also been associated with dental anomalies, including hypodontia, dental aplasia, and malocclusion. Bifid uvula, hypodontia and ankyloglossia were also observed in our cohort. It is known that individuals with VWS exhibit highly variable expressivity, ranging from isolated lower lip pits to bilateral CL/P. As highlighted by Family 4 in our cohort, lower lip pits were identified only in individual II:2, but not in her elder sibling (II:1) or father (I:1). This again demonstrates the broad intrafamilial variability.

An enriched prevalence of vitiligo was also observed in our cohort. Although not previously reported in patients with VWS, two patients (one harbouring an *IRF6* and one a *GRHL3* variant) in our cohort had vitiligo. In individual F1 I:1, vitiligo was diagnosed during adulthood; in individual F4 II:2, at 16 years of age. Our observation points to a possible disease association, with the argument that interferon regulatory factors play a significant role in the immune system by functioning as major transcriptional regulators of type I interferon.[9] Further research has revealed that *IRF6* regulates a subset of toll-like receptor 3 responses in human keratinocytes and may play a role in keratinocyte and/or immune cell functions during cell damage and wound healing. Alternatively, *GRHL3* is a transcription factor critical for epidermal differentiation and skin barrier repair. A possible association of dysfunction in interferon regulatory factors or *GRHL3* with autoimmune

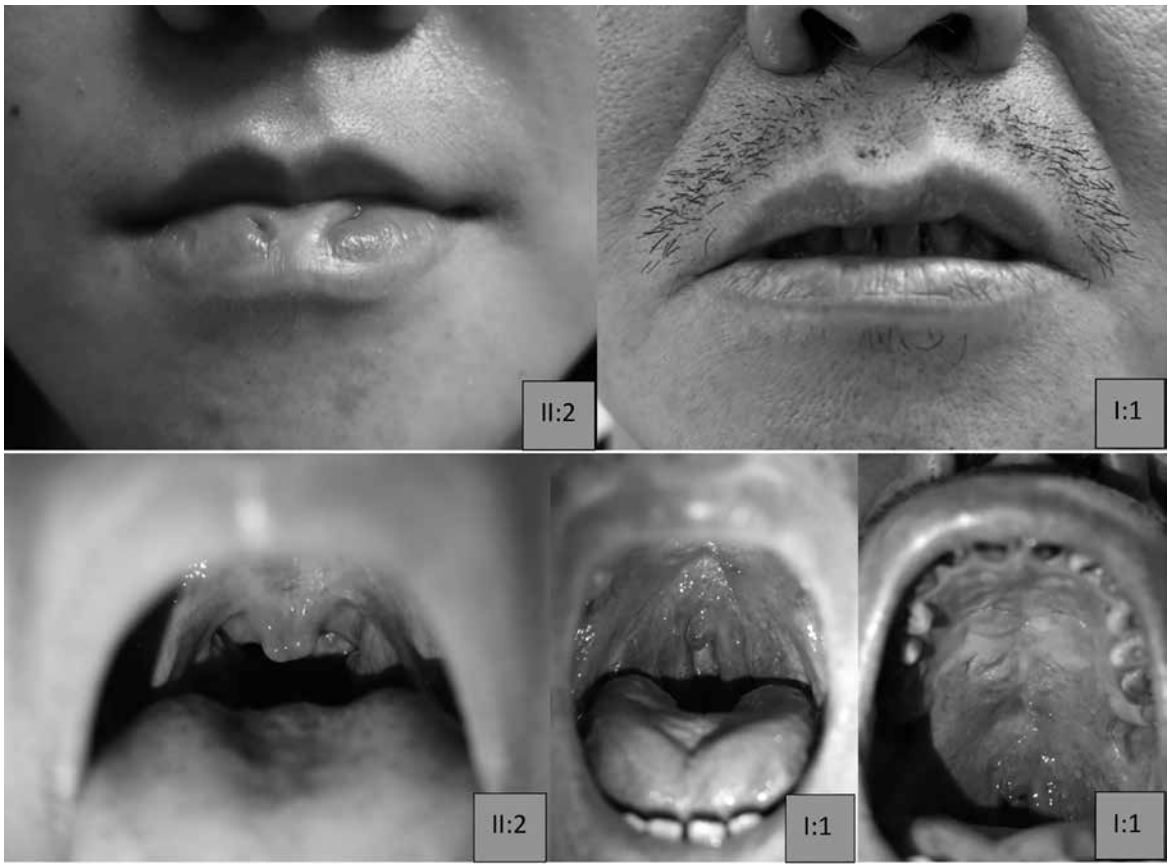

FIG. Clinical photos of patients II:2 and I:1 from Family 4 (daughter and father, respectively). Patient II:2 presents with lower lip pits, bifid uvula and a right submucous cleft palate. Patient I:1 has a history of repaired cleft palate

dermatological conditions such as vitiligo cannot be excluded. Further studies are required to confirm a potential correlation.

All *IRF6* and *GRHL3* variants found in our cohort, except one, were novel. In previous VWS reports, missense variants in *IRF6* were mainly clustered in exons 3, 4, 7, and 9, whereas truncating variants were evenly distributed across the whole gene.[10] One novel *IRF6* variant in our cohort was a missense variant in exon 4, while another was a splice site variant in intron 2. No specific genotype-phenotype correlation was established in our current study due to the limited sample size.

Due to the highly variable expressivity and incomplete penetrance, it is essential for clinicians to remain vigilant in diagnosing individuals with a relatively mild phenotype. Referral to clinical geneticists for consideration of genetic testing is beneficial for affected individuals with familial occurrence of CL/P or when other features suggest a syndromic diagnosis. In view of the limited number of individuals identified in our cohort, future studies may be needed to establish clearer genotype-phenotype correlations, explore a potential association with vitiligo, and evaluate the diagnostic efficacy of whole exome sequencing.

Author contributions

Concept or design: LT Leung, SKL Ho.
Acquisition of data: WC Yiu, M Ou, JYY Poon, SSW Cheng, IFM Lo, HM Luk.
Analysis or interpretation of data: LT Leung, SKL Ho, WC Yiu.
Drafting of the manuscript: LT Leung, SKL Ho, IFM Lo, HM Luk.
Critical revision of the manuscript for important intellectual content: IFM Lo, HM Luk.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors disclosed no conflicts of interest.

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Ethics approval

This study was conducted in accordance with the Declaration of Helsinki. The patients/their legal guardian provided written informed consent for participation and publication of this case report.

Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine or the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2412455).

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