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ORIGINAL RESEARCH ARTICLE

Cleft types, lower-lip pits, and lip pit surgeries in individuals with Van der Woude syndrome in Finland

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ABSTRACT

Background: Van der Woude syndrome (VWS) may display varied clinical features. We aimed to determine cleft types, lower lip pits, and lip pit surgeries in a large VWS cohort in Finland.

Materials and methods: This is a single-center retrospective, observational patient record study performed at national centralized cleft center that evaluated 151 individuals with VWS born between 1946 and 2019. Information regarding sex, cleft type, lip pit presence, and the number of lip pit surgeries were gathered from patient records.

Results: Sixty per cent of the individuals with VWS were female and 40% were male ($p < 0.01$). The majority (105/151; 70%) of the individuals with VWS presented with clefts in the palate region ($p < 0.01$). Cleft lip (CL) occurred in 7.3% and cleft lip and palate (CLP) in 21.5% and no cleft in 2.6% of individuals with VWS. Information on lip pits was available for 127/151 patients. Lip pits were present in 93% of patients. Lip pits were surgically removed more frequently in unilateral cleft lip and palate (UCLP) (84.6%) and bilateral cleft lip and palate (BCLP) (66.7%) compared with cleft palate (CP) (8.8%) ($p < 0.001$). Recurrent surgery for lip pits occurred more often in BCLP (46.4%) than in UCLP (6.7%) and CP (1.3%).

Conclusions: In Finland, cleft palate is the predominant cleft type in VWS. Cleft type distribution in VWS reflects the frequencies of non-syndromic clefts in Finland, deviating from trends observed in other countries. Lip pits are more commonly removed in UCLP or BCLP than in CP only. Furthermore, recurrent surgeries for lip pits occur more frequently in individuals with BCLP.

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Introduction

Van der Woude syndrome (VWS; ORPHA:888; OMIM 119300) is a rare genetic disorder characterized by a broad spectrum of clinical features, including variable cleft types and dental anomalies, such as tooth agenesis. The most characteristic feature of VWS is the presence of lips pits, small depressions in the lower lip [1]. VWS is one of the most common syndromic forms of clefts, and its estimated global occurrence is approximately 1/35,000 to 1/100,000 with an equal sex distribution [2].

Mutations in gene *IRF6* have been identified in approximately 70% of individuals with VWS, making it the most common cause of the disorder [3–5]. In addition, mutations in gene *GRHL3* account for 5% of the individuals with VWS [4, 6], whereas more recently identified PRKCI variants may be attributable to 2–3% of the individuals with VWS [7]. The causal mutation remains unknown in approximately 20% of individuals [7]. Furthermore, pathogenic single-nucleotide variants have also been detected in the regulatory regions of IRF6 in individuals with VWS [8]. The severity of the condition with VWS can vary widely even among individuals within the same family who carry the same genetic mutation. Recently, differences in DNA methylation have been reported to potentially explain the variability in VWS phenotype among family members [9, 10], underscoring the influence of genetic modifiers and other factors as causative elements.

IRF6 and GRHL3 are transcription factors that play critical roles in the development of the oral epithelium and skin [11]. Patients with VWS are more likely to experience wound complications and poorer surgical outcomes compared with those with non-syndromic clefts (i.e. clefts occurring without additional anomalies or symptoms) [12]. Various surgical techniques have been developed to improve lower lip appearance and to prevent pit recurrence [13].

Cleft lip (CL ± A) with or without cleft palate (CP) is usually observed twice as frequently as CP in VWS, mirroring the proportions seen in non-syndromic clefts [14]. The sex ratio is reported to be nearly equal in VWS for CP, CL, and CLP (cleft lip and palate) [4]. Lip pits occur in 86% of affected individuals [15] and are typically bilateral, symmetrically placed openings associated with minor salivary glands in the lower lip mucosa [15] (Figure 1a). Lip pit presence varies depending on cleft type; 37% of lip pits were observed with CLP, whereas 51% were observed in individuals with CP [16]. Lip appearances are variable also among family members and may less commonly manifest as single unilateral lip pits, conical elevations of the lip, or bulges located below the vermilion border [16]. Lip manifestations can be the only symptom of VWS. Lower lip pits in VWS may be symptomatic, cause discomfort due to saliva secretion, and affect aesthetics. They can have a significant impact on a person's quality of life and are removed if causing chronic discomfort.

The objective of this study was threefold: (1) to evaluate the distribution of cleft types, (2) to investigate the prevalence of lower lip pits and (3) lip pit surgeries in a large cohort of individuals with VWS in Finland.

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Materials and methods

This single-center retrospective, observational patient record study focused on 155 individuals with VWS born between 1946 and 2019, treated at the Cleft Palate and Craniofacial Center, Helsinki University Hospital. Information regarding time of birth, sex, cleft type, presence and type of lip pits, and the number of lip pit operations were gathered from patient records, dental casts, x-rays, and photographs. Data collection spanned from birth to 18 years of age as this is the standard protocol at our cleft center, however for more recently born individuals the data collection was not complete. Individuals who had data collected until 16-years were included in the lip pit surgery evaluation. The cohort represents an almost complete national series of Finnish patients with VWS. Approximately, seven patients are missing, as they were treated at Oulu University Hospital, the second cleft unit in Norhern Finland, which began operating in 2006 (personal communication, prof. Harila). The diagnosis of VWS was set by an experienced plastic surgeon or clinical geneticist and was based on clinical findings and family history. Analyses were conducted using SPSS Statistics for Macintosh, Version 25.0 (IBM Corp.). Categorical comparisons were made with Fisher's exact test. Limit for statistical significance was set at $p < 0.05$.

Ethics

The research protocol received approval from Helsinki University Hospital (63-HUS/146/2023), and principles outlined in the Declaration of Helsinki were followed.

Results

Patients

After reviewing the files of 155 patients with VWS, four patients were excluded due to the presence of an additional underlying syndrome or insufficient patient records. Of these, one patient was excluded for having Turner syndrome, another for having popliteal pterygium syndrome, and two additional patients were excluded due to inadequate records. Among the remaining 151 included patients, 60% were female and 40% were male (Table 1), demonstrating a statistically significant sex difference ($p = 0.0144$).

Cleft types

The majority (105/151; 70%) of individuals with VWS presented clefts in the palate region (CP) ($p < 0.01$), comprising of cleft of the hard and soft palate (HSCP) 51.7%, cleft of the soft palate (SCP) 7.9%, submucous cleft palate (SMCP) 7.9%, and bifid uvula 2.0%. CL (uni- or bi-lateral, UCL ± A, BCL ± A) occurred in 7.3%, unilateral cleft lip and palate (UCLP) in 8.6%, bilateral cleft lip and palate (BCLP) in 11.9%, and no cleft in 2.6% of individuals with VWS (Table 1 and Figure 1b). Clefts were on the right side in 6/13 and on the left side in 6/13 of the UCLP individuals (this information was not available for one patient).

In the CP group, 59% were female (62/105) and 41% were male (43/105). Similarly, in the CL/P group, 62% (26/42) were female and 38% (16/42) were male ($p < 0.01$).

Table 1. Rates of cleft types and sex.

Cleft type	*n* (%)	Female, *n* (%)	Male, *n* (%)
CP			
HSCP	78 (51.7)	48 (61.5)	30 (38.4)
SCP	12 (7.9)	6 (50.0)	6 (50.0)
SMCP	12 (7.9)	6 (50.0)	6 (50.0)
Bifid uvula	3 (2.0)	2 (66.7)	1 (33.3)
CL/P			
UCL ± A	5 (3.3)	3 (60.0)	2 (40.0)
BCL ± A	6 (4.0)	5 (83.3)	1 (17.6)
UCLP	13 (8.6)	8 (61.5)	5 (38.5)
BCLP	18 (11.9)	10 (55.6)	8 (44.4)
No cleft	4 (2.6)	3 (75.0)	1 (25.0)
Total	151	91 (60.3)	60 (39.7)

HSCP: cleft of the hard and soft palate; SCP: cleft of the soft palate; SMCP: submucous cleft palate; BCL: bilateral cleft lip; UCL: unilateral cleft lip; BCLP: bilateral cleft lip and palate; UCLP: unilateral cleft lip and palate; CP: cleft palate; CL: Cleft lip.

Lip pits

Lip pit information was available for 135/151 patients. Lip pits were present in 93% (125/135) of VWS patients. The prevalence of lip pits by cleft type was 93% with HSCP, 90% with SCP, 82% with SMCP, 33% with bifid uvula, 100% with CL ± A, 100% with BCLP, and 100% with UCLP (Table 2). A small number of patients (10/135) showed a single lower lip pit, 5/10 of which had CP, 2/10 had SCP, 2/10 had UCL, and 1/10 had UCLP (Table 3). The single pit was observed on the left side of the lower lip in 5/10, on the right side in 3/10, and in the middle in 2/10 of the individuals (Table 3).

No statistically significant sex differences were detected in lip pit prevalences between groups when cleft types were grouped into clefts of the palate region (CP), BCLP, and UCLP. Groups of individuals with BCL, UCL, and the patients with no cleft were excluded from the sex analysis due to the small number of study individuals.

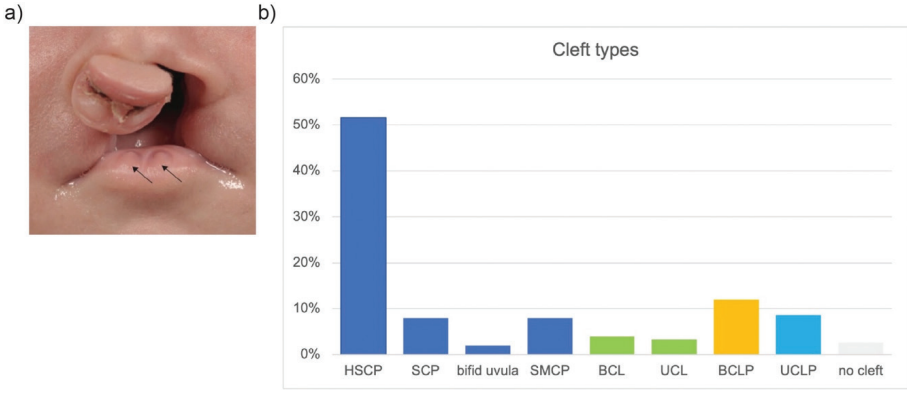

Figure 1. (a) Characteristic bilateral symmetrical lower lip pits in an individual with VWS and BCLP. The black arrow points to the lip pit. (b) Distribution of cleft types in patients with VWS. HSCP: cleft of the hard and soft palate; SCP: cleft of the soft palate; SMCP: submucous cleft palate; BCL: bilateral cleft lip; UCL: unilateral cleft lip; BCLP: bilateral cleft lip and palate; UCLP: unilateral cleft lip and palate; VWS: Van der Woude syndrome.

Table 2. Rates of lip pits according to cleft type.

Cleft type	Lip pits *n* (%)		
	Yes	No	Total
HSCP	62 (95)	5	67
SCP	9 (90)	1	10
SMCP	9 (82)	2	11
Bifid uvula	1 (33)	2	3
UCL ± A	5 (100)	0	4
BCL ± A	6 (100)	0	6
UCLP	13 (100)	0	13
BCLP	16 (100)	0	16
No cleft	4 (100)	0	4
Total (*n*)	125	10	135

HSCP: cleft of the hard and soft palate; SCP: cleft of the soft palate; SMCP: submucous cleft palate; BCL: bilateral cleft lip; UCL: unilateral cleft lip; BCLP: bilateral cleft lip and palate; UCLP: unilateral cleft lip and palate.

Lip pit surgeries

Information on lip pit surgeries was collected from the records of patients that were over 16 years of age at the time of the study. These criteria were fulfilled by 96 patients. Lip pits were surgically removed more frequently in UCLP (72.7% (8/11)) and BCLP (72.7% (8/11)) compared with clefts in the palate region (14.9% (11/74)), and the difference was significant ($p < 0.001$) between the UCLP and CP groups and between the BCLP and CP groups, but no difference was detected between the UCLP and BCLP groups (Table 4). No sex differences between the groups were detected.

Recurrent surgery for lip pits occurred more often in BCLP (62.5% (5/8)) than in UCLP (12.5% (1/8)) and CP (9% (1/11)). The mean age at primary lip pit surgery was 10 years (range 10 months–29 years, $n = 27$) and 13 years (range 6–30 years, $n = 7$) for recurrent surgery. The timing of lip pit surgery was set individually and based on the wishes of the patient and/or family rather than a standardized protocol. Lip pit removal was most often scheduled in conjunction with other cleft-related procedures (e.g. alveolar bone grafting, speech correcting surgery, or secondary scar revision). The number of patients who had recurrent surgery was too small to yield statistically reliable results.

Discussion

The treatment of patients with cleft has been centralized in Finland since the 1940s, initially at a single unit in Finland. In 2018, a second unit was established, located in northern Finland. This centralization has facilitated the maintenance of extensive longitudinal patient registries, which include patient records, radiographs, and cast models. Consequently, this has enabled the compilation of this large longitudinal cohort of individuals with VWS.

Table 3. Correlation of single lip pit location, sex, and cleft type.

Gender	Cleft type	Lip pit location		
		Median	Left side	Right side
F	UCLP/L	x		
F	UCL/L		x	
F	CP		x	
F	CP		x	
M	SCP			x
F	CP		x	
M	UCL/L	x		
F	CP			x
F	CP		x	
F	SCP			x

SCP: cleft of the soft palate; UCL: unilateral cleft lip; UCLP: unilateral cleft lip and palate; CP: cleft palate.

In this study, we found that CP is the most prevalent cleft type in individuals with VWS in Finland. A female-to-male ratio of 3:2 was detected. Lip pits were present in 93% of patients, and lip pits were removed more often when patients exhibited UCLP or BCLP compared with the patient group with clefts in the palate region. Recurrent surgeries were performed more often to patients with BCLP than UCLP or CP.

Cleft palate is the most prevalent cleft type in VWS

In Finland, the distribution of non-syndromic cleft types differs when compared with non-Finnish European populations. In Finland, the incidences of isolated CP and CL/P were 12.1 and 9.3 per 10,000 births, respectively, in 2013–2019 [17]. Cleft types in this study (CP 70% and CL/P 30%) showed similar distributions as the general distribution of non-syndromic cleft types in Finland (CP 60% and CL/P 40% [18]). This aligns with a previous study from Finland with 79 patients with VWS, where the prevalences for CP alone and CL/P were 58 and 42%, respectively [16]. In addition, a previous genetic study of VWS comprising five Finnish lineages reported that CP was present in 90% and CLP in 10% of affected individuals [19]. Three of these lineages were linked to the IRF6 region [19]. Moreover, CP was observed in all individuals in a large Finnish lineage with GRHL3 variants [6]. In this study, only one individual was diagnosed with an additional syndrome, which is consistent with VWS being typically and isolated genetic condition that does not commonly coexist with other, unrelated syndromes.

Cleft prevalences with VWS in other countries appear to be the opposite of prevalences in Finland; the prevalence for CP in VWS ranges from 5 to 31% while CL/P prevalence ranges from 30 to 83% [20–24]. The large study by Burdick included 864 patients with VWS and reported that only 16% of individuals with VWS have CP, while 37% have CL or CLP [14].

The high prevalence of CP among Finnish individuals with VWS may be influenced by population-specific genetic or epigenetic factors. A risk variant for CP in an IRF6 enhancer, enriched in the Finnish population, was recently identified [25], and may partly explain the high incidence of CP in this nearly nationally comprehensive VWS cohort. Differences in the spectrum or distribution of pathogenic variants in IRF6, GRHL3, or PRKCI between Finnish and non-Finnish populations could also contribute to the contrasting cleft-type distributions. In addition, Finnish-specific DNA methylation patterns might modulate phenotype expression and help to explain the predominance of CP observed here. These considerations underscore the need to account for genetic variation and genetic modifiers in future studies aimed at elucidating the molecular basis of VWS in Finland.

Female-to-male ratio with VWS is 3:2

The sex distribution of VWS in this study with females comprising 60% and males 40% of the sample differed from the previously reported equal sex distribution in other countries [14]. When examining the sex distribution of VWS across cleft types, we observed that

Table 4. Rates of lip pit surgery and recurrent lip pit surgery.

Cleft type	Lip pit surgery, *n* (%)		*P*	Lip pit surgery by gender, *n* (%)		Recurrent surgery, *n* (%)
	No	Yes		Females	Males	
Palatal clefts	63 (85.1)	11 (14.9)	0.001*	5 (45)	6 (55)	1 (9)
UCLP	3 (27,3)	8 (72.7)		6 (75)	2 (25)	1 (12.5)
BCLP	3 (27.3)	8 (72.7)		5 (62.5)	3 (37.5)	5 (62.5)

BCLP: bilateral cleft lip and palate; UCLP: unilateral cleft lip and palate.

*Fisher's exact test.

nearly 60% of individuals with clefts of the palate region were female. However, in the case of CL/P, the sex distribution was reversed compared with that typically observed in non-syndromic clefts in Finland. Females were more frequently affected than males, which is consistent with previous findings of female predominance in VWS in both the CP and CL/P groups in Finland [16].

The rate of lip pit removal varies according to cleft type

Lip pits were removed in 72.7% of individuals with UCLP and BCLP, whereas lip pits were removed in only 14.9% of individuals with CP. The smaller number of lip pit removals in the CP group may be related to the fact that fewer surgical procedures are generally performed on this group. The threshold for a separate lip pit removal operation may be higher compared with situations where pit removal is performed alongside another procedure such as rhinoplastia or lip scar revision.

Recurrent surgery for lip pits were performed more frequently in the BCLP group (62.5%) than in the UCLP (12.5%) or CP (9%) groups. This may be because of more prominent lip anomalies in the BCLP group compared with the UCLP and CP groups, leading patients with BCLP to perceive lip pit removal as more necessary. Another possible explanation is that patients in the BCLP group may undergo more secondary surgeries involving rhinoplasty and lip scar revisions, which may lower the threshold for also removing pits in the lower lip.

Strengths and limitations

The primary strength of this study is the large cohort of individuals with this rare condition. The data, consisting of standardized records from a nationally centralized center, were collected over a 73-year period. However, a notable limitation is the relatively small number of patients in the cleft subgroups, which precludes the statistical comparisons among these subgroups. In addition, the statistical power in the analyses involving recurrent lip pit surgeries is limited because of small sample sizes, restricting the reliability of the conclusions drawn for these subgroups. In the mid-20th century, individuals with SMCP or bifid uvula were not necessarily referred to hospitals. Furthermore, in most situations the diagnosis was based on clinical findings particularly with those born in the last century, and only few individuals underwent genetic testing for VWS. This suggests that individuals with clefts but without lip pits may have been under-represented in the study group. The specific reasons for lip pit removal were not documented in many patient records. Instead, patient discomfort with their lip pits was the primary indication for surgical removal.

Conclusions

To conclude, in Finland, CP is the predominant cleft type in VWS. The distribution of cleft types (CP 70% and CL/P 30%) in VWS reflects the frequencies of non-syndromic clefts in Finland (CP 60% and CL/P 40% [19]), deviating from trends observed in many countries where incidence of CL/P is usually higher than CP. Lip pits are present in 93% of individuals with VWS and are more commonly removed in UCLP or BCLP than in CP only. Furthermore, recurrent surgeries for lip pits occur more frequently in individuals with BCLP.

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Declaration of interest statement

The authors report that there are no competing interests to declare.

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