

# Associated syndromes and other genetic variations at a South African cleft lip and palate clinic

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## Key words

cleft lip and/or palate, facial cleft deformity, syndromes, genetic variations

## **Abstract: Curationis 32 (2): 53-58**

A retrospective study was done of data on all patients registered at one of the largest cleft lip and palate clinics in South Africa ( $n = 3174$ ). The associated syndromes and other genetic variations [(abbreviation:) ASGV] found in the population of persons suffering from facial cleft deformities (FCD) were analysed. 832 (26.2%) cleft lip and/or palate patients presented with ASGV. Fifty-seven different types of syndromes were recorded of which the Fairbairn-Robin appearance (FRA) (or Pierre Robin sequence) 169 (5.3%), the Demarquc-van der Woude syndrome 40 (1.3%), and the holoprosencephaly sequence cases 32 (1.0%) were the three most common ones. The three most common genetic variations found in the non-syndromic patients, were heart involvement 53 (1.7%), club foot 42 (1.3%) and various eye problems 39 (1.2%).

The main facial cleft deformity, namely the cleft lip, alveolus and palate (CLAP), was found in 26.2% of the ASGV-group. This particular cleft deformity was recorded at 39.7% in the FCD clinic. On the other hand, the hard and soft palate cleft (hPsP) group was found in 32.9% of patients who also had ASGV; in the total group of patients registered at the clinic, it accounted for only 16.6%. This means that ASGV occur less commonly in the CLAP group of patients, than in the hPsP group of patients.

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## Introduction

Clefts of the orofacial region are among the most common congenital anomalies, already known since ancient times and occur with differing frequencies in different population groups. Egyptian mummies with cleft palates have been excavated and it has been suggested that between 4000 to 2000 years B.C., the incidence was 1:1000 (Millard, 1976:58). This figure is similar to that of modern times. The accepted birth rate of facial cleft deformities in South Africa as described are 1:725 for Caucasians and 1:2380 for Black-Africans (Van Wyk, Bütow, van der Merwe, & Kleynhans, 1987:403).

Currently 3174 patients are registered at the University of Pretoria Cleft Lip and Palate or Facial Cleft Deformity (FCD) clinic. Patient flow is approximately 50-60 per month with an average of 750 patient consultations per annum. The FCD clinic has a strict treatment protocol, from birth to 18 years of age, according to which the patients are evaluated, followed up and treated according to specific stages during this 18-year period (Bütow, 1995:3; Bütow & van Wyk, 2007:298). After the primary constructive surgery, patients are not only followed up annually for assessment of function, facial growth and aesthetics, but also for the collection of any additional data on changes to the family and case history, in particular as far as associated syndromes and genetic variations (ASGV) are concerned (Burdi, 1977:262; Vallino-Napoli, Riley & Halliday, 2004:185).

## Material and Methods

A retrospective analysis was made of data on all patients registered at the FCD clinic. Descriptive statistics, which included average and percentage values, were compiled. This retrospective study included data on the total number of registered patients, the types of clefts and ASGV. A comparison was made between the total number of registered patients and those who presented with ASGV. All these specific parameters were analysed according to the Microsoft Excel programme (2003).

## Results

A total of 832 (26.2%) patients of the 3174 (total registered cases in the FCD clinic, indicated as an \* in calculations)

**Table 1: Cleft types – ASGV cases versus total clefts\***

Types of cleft	ASGV	Total clefts*
CL	4.0%	5.6%
CAL	9.5%	12.6%
CLAP	26.2%	39.7%
hP	0.6%	0.5%
hPsP	32.9%	16.6%
sP	20.8%	18.6%
COMBI	3.0%	4.5%
Oblique Facial	0	1.4%

also suffered from ASGV (Figure 1). The following ratios were recorded between the ASGV and the total population of cleft patients (with an \*) at the clinic: 4.0%/5.6%\* - cleft lip (CL); 9.5/12.6%\* - cleft lip and alveolus (CLA); 26.2%/39.7%\* - cleft lip, alveolus and palate (CLAP); 0.6%/0.5%\* - cleft hard palate (hP); 32.9%/16.6%\* - cleft hard and soft palate (hPsP); 20.8%/18.6%\* - cleft soft palate (sP) and 3.0%/4.5%\* - for cleft combinations (eg. CL + sP, without a cleft in the alveolus and/or

hP); 0%/1.4%\* - oblique (Table 1, Figures 2.1 & 2.2).

The difference in the ratio of males and females between the ASGV (49.6 : 50.3) and the total cleft population\* of the FCD clinic was determined (53.6 : 46.4) (Figure 3).

The cleft cases with a positive family history in the ASGV versus the total population group\* was recorded: ASGV 23.2% / total population 26.4%\*. The following aspects were found (ra-

**Figure 1: Syndromes, single gene involvement, chromosome involvement and other genetic variations (ASGV)**

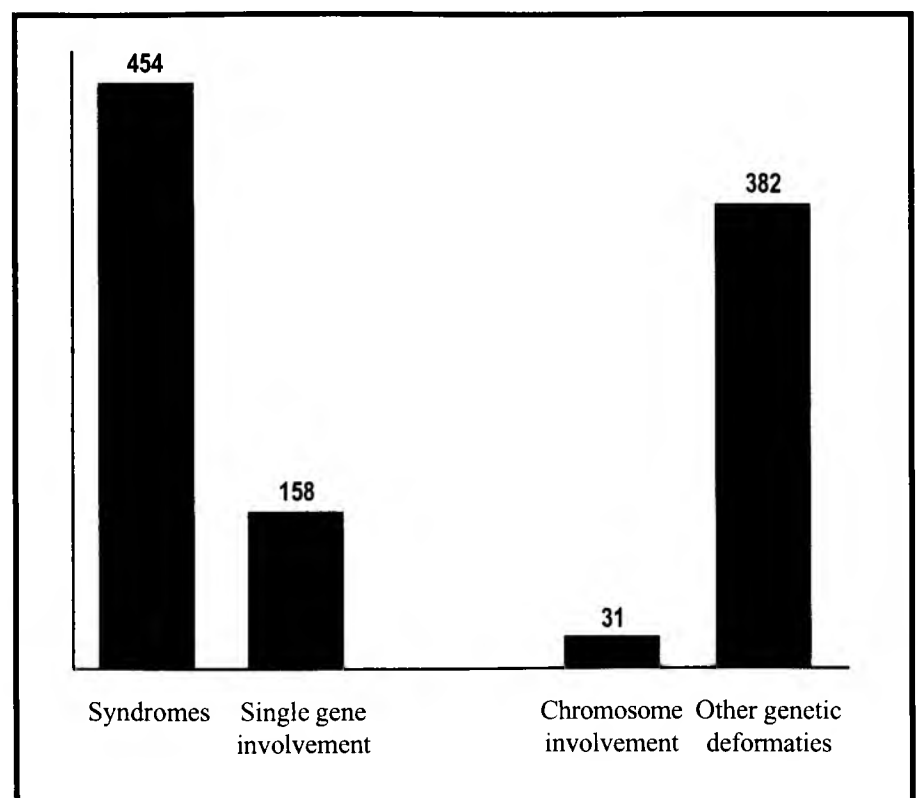


Figure 2.1: Number of cleft cases per category found in the ASGV

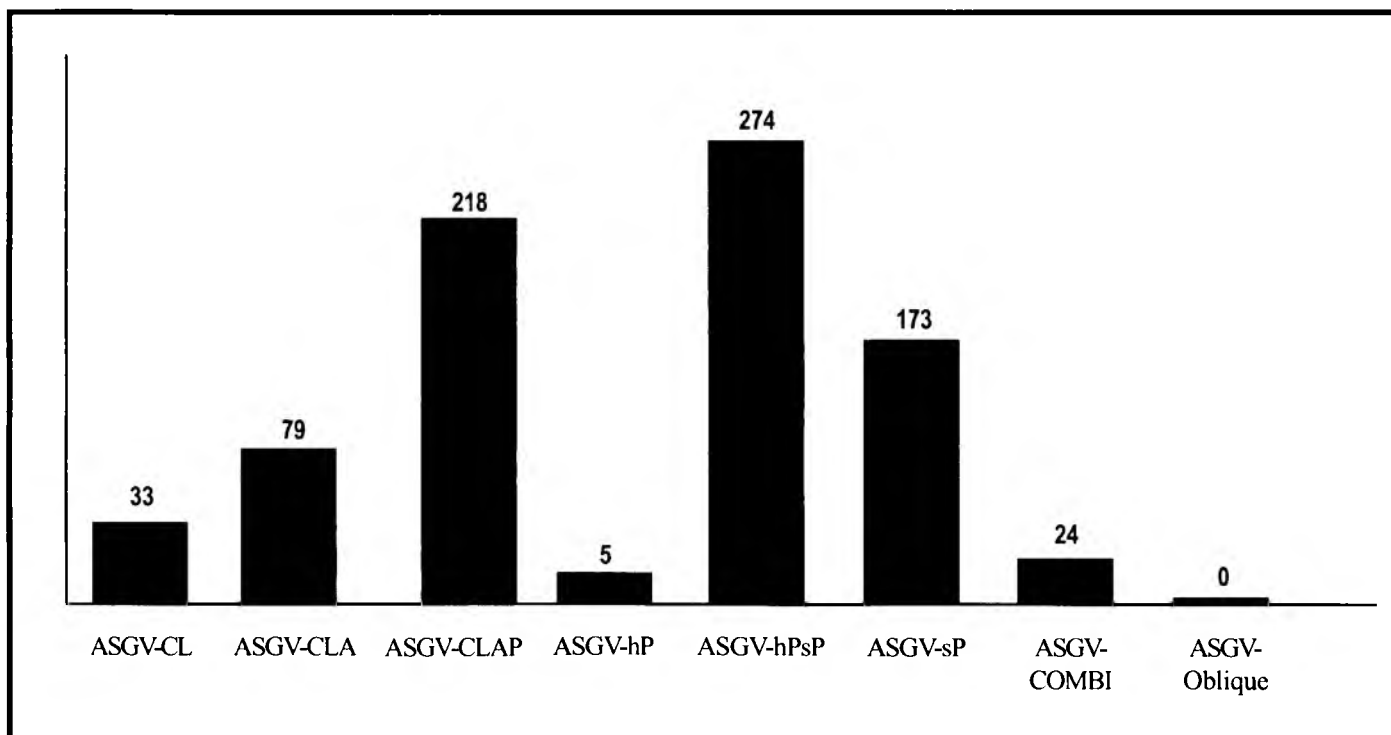
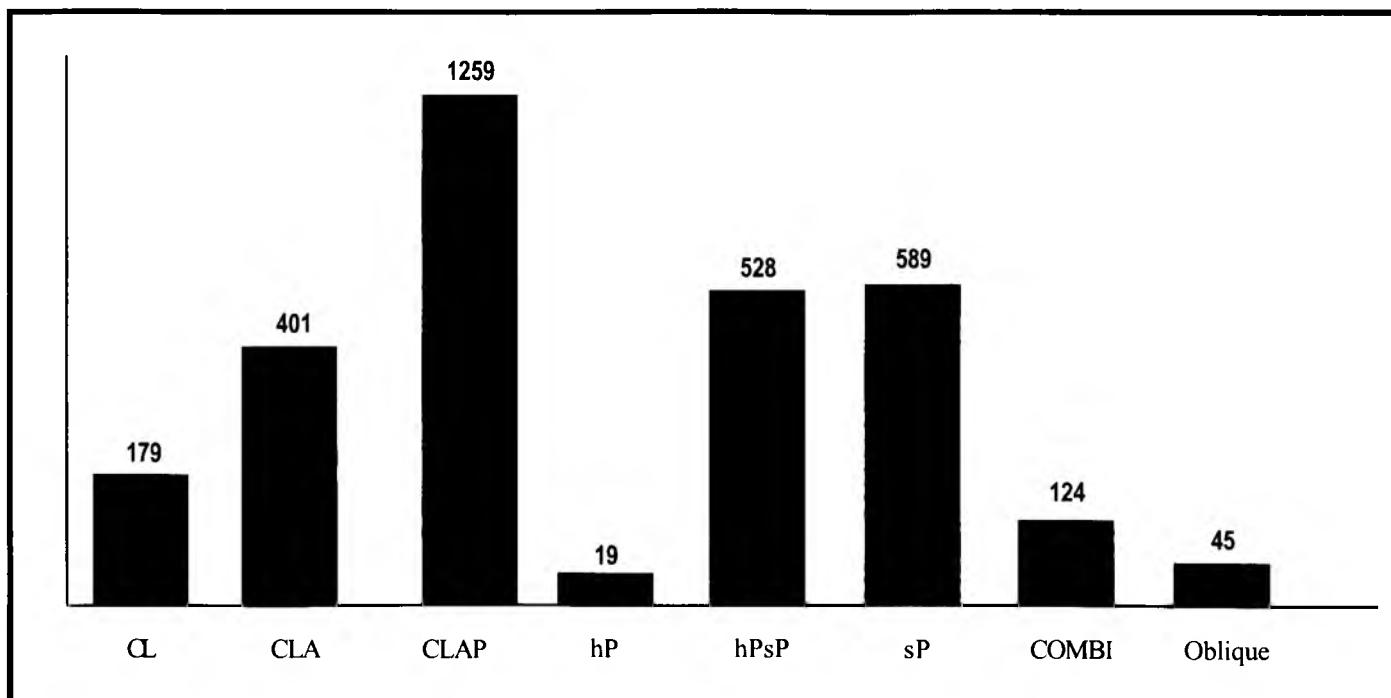


Figure 2.2: Number of cleft cases per category registered at the FCD clinic



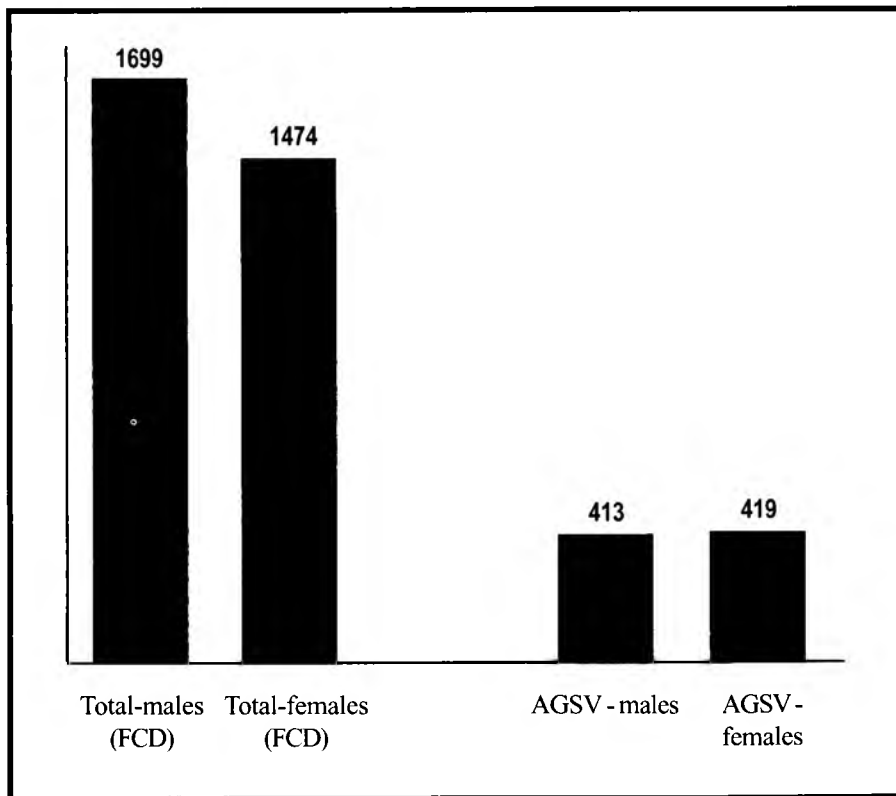
tio): mother with FCD – 2.4% / 2.8%\*, father with FCD – 2.8% / 3.0%\*, sibling (brother/sister) with FCD – 3.6% / 3.5%\*, first - degree cousin with FCD – 1.8% / 2.1%\* and distant family member with FCD – 12.6% / 14.9%\* (Figures 4.1 & 4.2).

The 832 patients who presented with both a facial cleft deformity, as well as an associated syndrome or other genetic variation (ASGV), could be cat-

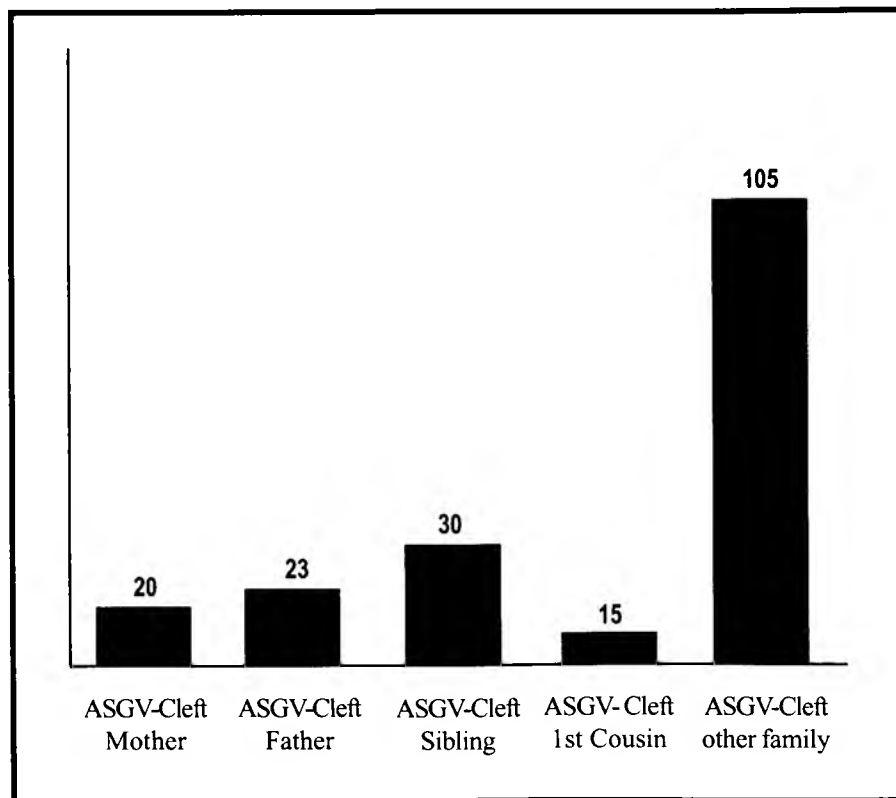
egorised into the following most frequent congenital deformities: Fairbairn-Robin Appearance (FRA), 169: 20.3% (5.3%\*); Fairbairn-Robin Appearance/Stickler, 16 2.0% (0.5%); Demarque-van der Woude syndrome, 40: 4.8% (1.3%\*); Fairbairn-Robin Appearance/Demarque-van der Woude, 7: 0.8% (0.2%\*) holoprosencephaly sequence, 32: 3.8% (1.0%\*); Goldenhar syndrome and oto-mandibular dysos-

tosis, 19: 2.3% (0.6%\*); Teacher-Collins syndrome, 14: 1.7% (0.4%\*); nasomaxillo-acro-dysostosis or Binder syndrome, 18: 2.2.% (0.6%\*); trisomy 13 or Patau syndrome, 13: 1.6% (0.43%\*); ectrodactyly-ectodermal dysplasia-clefting and ankyloblepharon-ectodermal dysplasia-clefting syndrome, 9: 1.1% (0.3%\*); oro-facial digital (type II) or Mohr syndrome, 6: 0.7% (0.2%\*) and popliteal pterygium syndrome, 7:

**Figure 3 : Ratio between males and females, in the ASGV group and in the total cleft population of the FCD clinic.**



**Figure 4.1: Positive family history of ASGV**



0.8% (0.2%\*). Chromosomal anomalies in cleft lip and/or palate cases were found in 31: 3.7% (1.0%\*). These 31 cases included trisomy 13, 13: 1.6% (0.4%\*); trisomy 21,

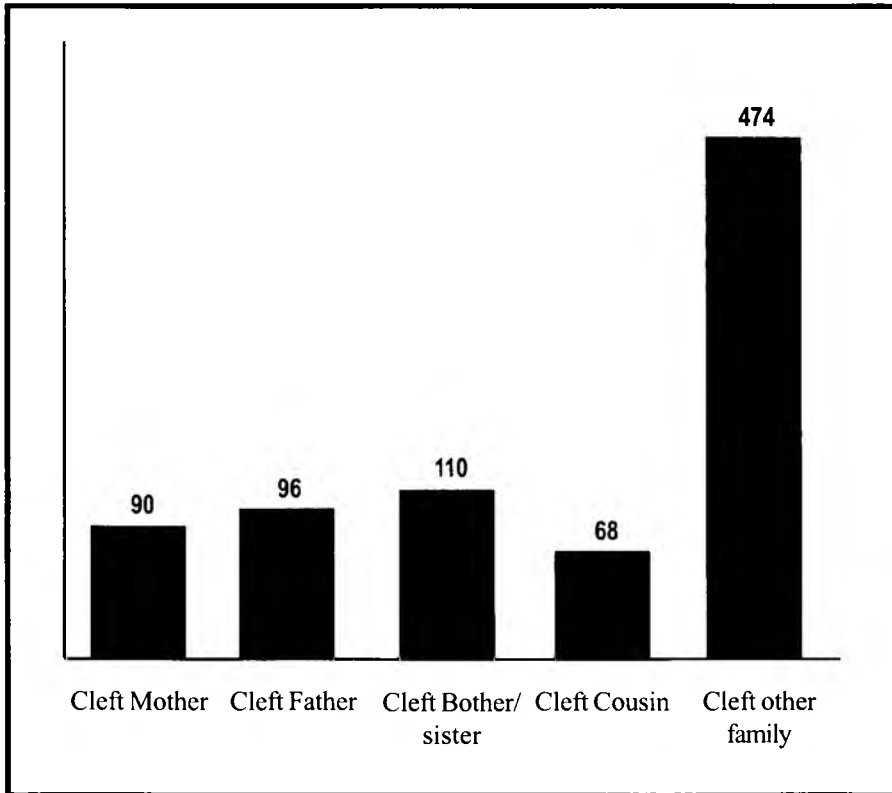
6: 0.7% (0.2%\*); trisomy 18, 2: 0.3% (0.1%\*) and structural anomalies of chromosome 22 as well as other structural anomalies, 5: 0.6% (0.1%\*) (\* = total cleft population).

A number of syndromes, with a facial cleft deformity (excluding chromosomal anomalies), are associated with single gene defects (Cobourne, 2004:7). In the ASGV group, there were 158 19.0% (5.0%\*) cases associated with these single gene defects and the most common types seen at the clinic, were: Demarque-van der Woude syndrome (40: 4.8%), Treacher Collins syndrome (14: 1.7%), ectrodactyly-ectodermal dysplasia-clefting syndrome (ECC) (6: 0.7%), popliteal pterygium syndrome (6: 0.7%), oral-facial-digital or Mohr syndrome (6: 0.7%), velo-cardio-facial or Shprintzen syndrome (6: 0.7%), Waardenburg syndrome (4: 0.5%), pyknodysostosis (3: 0.4%) and ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC) (3: 0.4%). Sporadic disorders such as holoprosencephaly sequence (32), Goldenhar (17), naso-maxillo-acro-dysostosis or Binder syndrome (16), Binder/Fairbairn-Robin appearance (2), amniotic band syndrome (6), Klippel-Feil (2), and fronto-nasal dysplasia (4) were also found. Tessier clefts, which are also sporadic in origin (lateral-facial, oblique-facial and other cranio-facial clefts) were identified in 47 cases. Two prominent teratogenic agents were found in the study: maternal smoking (12) and maternal alcohol intake (11). Other isolated congenital abnormalities associated with the ASGV group were counted for 384 of the 832: 46.0% [12.0%\*], with the ten main associated abnormalities as: heart defects/involvements, 53: 6.4% (1.7%\*); pinnae and inner ear defects/involvements, 44: 5.3% (1.4%\*); clubfoot 42: 5.0% (0.3%\*); eye defects/involvements, 39: 4.7% (1.2%\*); hypertelorism, 24: 2.9% (0.7%\*); myopathy/muscle dystrophy, 19: 2.3% (0.6%\*); haemangioma, 8: 0.9% (0.2%\*); hydrocephalus, 9: 1.1% (0.3%\*); amelogenesis imperfecta, 5: 0.9% (0.2%\*) and esophageal atresia or stenosis, 8: 1.0% (0.2%\*).

## Discussion

The objective of this retrospective study was to evaluate the data on patients suffering from cleft lip and/or palate as well as syndromes and other congenital abnormalities, and to compare this data with the rest of the patients suffering from cleft lip and/or palate only, as recorded in a large South African facial cleft deformity clinic.

**Figure 4.2: Positive family history of the total cleft population of the FCD clinic**



A possible of more than 300 different syndromes may be associated with a facial cleft deformity (Coleman & Sykes, 2001: 10; Cobourne, 2004: 7), of which only 57 different types have been documented in the 3174 total cleft population at this FCD clinic.

The data of the ASGV (832: 26.2%) found in cleft lip and/or palate patients, was categorized into the following groups: total syndromes (454: 14.3%); single gene involvement with these syndromes (158: 5.0%); chromosome involvement (31: 1.0%) and other genetic abnormalities (excluding syndromes) (382: 12.0%). Two very different types of cleft formation were recorded separately: median facial cleft (43: 1.3%), including (32: 1.0%) holoprosencephaly sequence patients) and oblique facial cleft (45: 1.4%). In North-Eastern France a study has reported a high prevalence of 36.7% of infants born with oral clefts, who had associated congenital defects (Stoll, Alembi, Dott, & Roth, 2000: 41).

The most common syndrome was the Fairbairn-Robin appearance (FRA), included the Stickler syndrome (Hoogendijk & Bütow, 2008: S15), which occurred in 192: 20.3% cases. The FRA has been described as a cleft palate deformity, involving both the hard

and soft palate (hPsP). A cleft of the soft palate (sP) only, is very rare. This sequence is further associated with the tongue positioned in the cleft, resulting in glossoptosis, microglossia and micrognathia. The newly born therefore presents with severe breathing and feeding problems (Fogh-Andersen, 1971: 52). The Demarque-van der Woude syndrome was recorded as the second most common syndrome with 40: 4.8%. Any type of cleft may be associated with this syndrome, which includes a lower lip pit or fissure, with its accompanying sinuses and the inclusion of accessory mucus/salivary glands (Redelinghuys & de Witt, 1994: 39). The third most common recorded disorder in the ASGV group were patients with a holoprosencephaly sequence 32: 3.8%. Holoprosencephaly sequence babies are born without a premaxilla, prolabium and anterior midline nasal structures. Furthermore, microcephaly, due to failure of the developing forebrain into two separate hemispheres, forms part of this disorder (Putman & Postlethwaite, 1994: 153). The most prevalent type of cleft (39.7%) recorded in the total cleft population of the FCD clinic data was the cleft lip, alveolus and palate (CLAP), however, only 26.2% presented with

this type of cleft in the ASGV-group. In contrast, the hard and soft palate cleft (hPsP) accounted for 32.9% of cases, the most prevalent type, in the ASGV-group, whereas only 16.6% were found in the total cleft population. There were not much differences between the CL, CLA, hP, sP and the combination of clefts categories, between the ASGV and the total cleft population groups. There is a slight difference in the gender profile between the ASGV and the total cleft population group. The ASGV group included a higher number of siblings (brother and/or sister) who had cleft deformities, than that of the total cleft population group (3.6% vs 3.5%\*). This means that the sibling of someone born with a cleft lip and/or palate (with or without an ASGV), has a higher chance of suffering from an ASGV, should he or she also be born with a cleft lip and/or palate.

## Conclusion

Data collected from associated syndromes and other genetic variations (ASGV) in a population of facial cleft deformity patients registered at one of the largest cleft lip and palate clinic in South Africa were analysed in this retrospective study. A total of 832 (26.2%) patients of the 3174 cleft lip and palate cases presented with ASGV. Only 57 different types of syndromes were recorded, which is about one tenth of the total number of internationally documented cleft lip and/or palate syndromes. The Fairbairn-Robin appearance (FRA), the Demarque-van der Woude syndrome, and the holoprosencephaly sequence cases were the three most common ASGV.

Only 26.2% cleft lip, alveolus and palate cleft (CLAP) patients presented in the ASGV-group, whereas this was the most prevalent type of cleft recorded in the total cleft population of the FCD clinic (39.7%\*). However, 32.9% hard and soft palate cleft (hPsP) patients were found in ASGV, in comparison to the 16.6%\* found in the total cleft population group. This means, in South Africa, it would seem as if ASGV are less commonly associated in patients with complete clefts (CLAP), however, far more commonly found in patients with palatal clefts (hPsP).

There was differences in the involvement concerning gender, however, a sibling born with a cleft lip and/or pal-

ate (with or without an ASGV), has a higher chance of suffering from an ASGV, should there be a brother or sister with a facial cleft deformity.

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