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Identification of Possible Maternal Risk Factors for Development of Syndromic Oro-Facial Clefts

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Abstract: Context: The concept "epigenetics" highlights that environmental factors are able to trigger changes in gene activity. This confounds the search for aetiological factors of syndromic oro-facial clefts as it interplays between genetics and environmental stimulation. Subjects and Methods: The study makes use of a database of syndromic cleft patients over 33 years at the Department of Maxillo-Facial and Oral Surgery at the University of Pretoria. The ten most common clefting syndromes (Fairbairn-Robin triad, Demarque van der Woude syndrome, Holoprosencephaly, Naso-maxillo-acro dysostosis (Binder's syndrome), Goldenhar syndrome, Treacher-Collins syndrome, Trisomy 13 (Patau's syndrome), P63 Mutation associated clefting disorders, Trisomy 21 (Down's syndrome), Oro-Facial Digital syndromes) were included amounting to 517 patients. The nine most common maternal risk factors (Unknown Infection, Viral Infection, HIV, Medication, Smoking, Alcohol, Oligohydramnios, Vitamins, Hormones) were included totaling 398. Results: Fairbairn-Robin triad had a significant correlation with oligohydramnios, infection and medication. Demarque-van der Woude syndrome presented with a significant contribution from medication and Holoprosencephaly showed a significant correlation with vitamin supplementation. Conclusion: based on the results of this study Fairbairn-Robin triad appears to have a strong environmental component to the presentation thereof. Demarque-van der Woude was indicated to having a genetic-environmental interplay contributing to the presentation of the syndrome.

Keywords: Syndromic Oro-facial Clefts, Epigenetics, Maternal Risk Factors

1. Introduction

James Paget wrote in the Lancet (1882) that curiosities or changes could become the beginning of excellent knowledge. There remain many unanswered questions regarding the aetiopathogenesis of syndromic oro-facial cleft disorders.

A syndrome is defined as: "A group of signs and symptoms that occur together and characterize a particular abnormality or condition". [1] With improvements of molecular technology, more than 600 syndromes involving oro-facial clefts have been recognized. Chromosomal aberrations are the most common cause of oro-facial clefts and is followed by Mendelian / heterogenous abnormalities and teratogenic factors. [2]

The oro-facial cleft includes cleft lip with or without a cleft palate (CL/P) or as an isolated cleft palate (CP), these abnormalities may be syndromic/genetic disorders or non-syndromic. According to the literature about 70 percent of cases with CL/P and 50 percent of CP are non-syndromic. [3, 4] Although both CL/P and CL result in malformation of the midface, they differ in the context of embryology, etiology, associated abnormalities, candidate genes, and recurrence risk. [5]

The study of fetal midfacial anomalies has led to the detection of candidate genes and the recognition of environmental factors that affect fetal development.

Teratogen exposure has been postulated to represent a contributing factor in the development of malformations in fetuses with genetic predisposition. [5] This concept is termed "gene-environment interactions", the effects of which have not been fully elucidated. Specific gene variants have been selectively investigated one at a time, but such studies invariably result in the detection of a multitude of gene variations with unknown effect of environmental exposure. [6]

The concept "epigenetics" highlights that environmental factors are able to trigger changes in gene activity. This confounds the search for etiological factors of syndromic oro-facial clefts, as it is interplay between genetics and environmental stimulation. A way in which epigenetics can be passed to the next generation is during pregnancy, where a mother's habitus can change the epigenome (the epigenetic modifications in the genome) of her fetus. [7] Concerning cigarette smoking, gene-environment interactions are being investigated with current data indicating smoking and a fetal allele at TGF-alpha gene locus being a risk factor for oro-facial clefts. [8, 9] This assertion of "epigenetics" if further supported by the association between alcohol and Fetal Alcohol Syndrome and a confirmed link to syndromic CL/P. [10].

Maternal illnesses have also been linked to birth defects with diffusion of metabolites or antibodies across the placenta having a toxic effect on the fetus. [11] Physical agents such as heat (hot tub, maternal fever or sauna) and radiation has been implicated in birth defects. [12, 13] Drug use and exposure have been linked with fetal malformations, although the precise teratogenic agent is difficult to identify on its own. A study of FDA-approved drugs used therapeutically between 2000 and 2101 concluded that 98% drugs approved for human use to have an indeterminate teratogenic risk. [14] Other factors influencing the magnitude of the element's effect include the dose and duration as well as the timing of embryonic development. [6].

The results of this study depend to a large extent on the reliability of the information volunteered and the willingness of the mother to participate. A distinct trend in under-reporting of the exact dosage or frequency of illicit substance use in early pregnancy has emerged in the current literature. [15] This is the reason we have elected to use a simple "yes/no" answer pertaining to drug/substance use in this study.

2. Subjects and Methods

This study is retrospective and considers the data obtained over a 33-year period of time (August 1983-May 2017), which comprises the patient records of 4451 patients who presented with oro-facial cleft disorders at the University of Pretoria. Data Analysis and Interpretation was via a two-sample t-test as well as proportion analysis and the associated 95% confidence interval for most outcomes. The comparison was made between the identified risk factor for a particular syndrome, versus the same risk factor and the remaining syndromes.

The ten most common syndromes/genetic disorders presenting to the Oro-Facial Cleft Clinic at the University of Pretoria was evaluated. Nine common risk factors were identified according to frequency as reported by mothers of the affected children.

2.1. The Ten Syndromes/Genetic Disorders in Order of Incidence Is

1. Fairbairn-Robin triad
2. Demarque van der Woude syndrome
3. Holoprosencephaly
4. Naso-maxillo-acro dysostosis (Binder's syndrome)
5. Goldenhar syndrome
6. Treacher-Collins syndrome
7. Trisomy 13 (Patau's syndrome)
8. P63 Mutation associated clefting disorders
9. Trisomy 21 (Down's syndrome)
10. Oro-Facial Digital syndromes

2.2. The Nine Risk Factors Are as Follow

1. Unknown Infection
2. Viral Infection
3. HIV
4. Medication
5. Smoking
6. Alcohol
7. Oligohydramnios
8. Vitamins
9. Hormones

2.3. The Interpretation of Risk Factors Is as Follow

2.3.1. Unknown Infection

These are infections reported by the mother, which could either be fungal, bacterial, or not a typical viral infection. The patient did receive an anti-fungal or anti-biotic treatment and in some exceptions no medication.

2.3.2. Viral Infection

Influenza was the most prominent within this category, with single other cases of acute viral infections.

2.3.3. HIV

This was deliberately mentioned separately from "Viral Infections" due to the difference in management and disease presentation from that of a viral influenza.

2.3.4. Medication

Medication included all medication apart from vitamins.

2.3.5. Smoking

Mother smoking during the first trimester.

2.3.6. Alcohol

Mother consuming alcohol during the first trimester.

2.3.7. Oligohydramnios

As reported by the mother or on the medical records from the treating practitioner.

2.3.8. Vitamins

Supplements as given by the local clinic or as taken by the mother without medical recommendation.

2.3.9. Hormones

Contraceptive medication or infertility medication.

The top ten most common syndromes presenting to the Oro-facial Cleft Deformity Clinic's patients was assessed and the amount of patients included, totaled 517. Patients that presented with multiple syndromes phenotypically were excluded. The total number of risk factors counted was 398, with some patients reporting to have more than one risk factor.

3. Results

Six results proved to be significant; for Fairbairn-Robin triad; Unknown Infection had a P-value of 0.032 with a 95% CI [0.923, 0.186]; Viral infections for Fairbairn-Robin triad with a P-value of 0.0009 with a 95% CI [0.109, 0.208] and lastly for Fairbairn-Robin triad; Medication with a P-value of 0.000 and a 95% CI [0.318, 0.451].

For Demarque-van der Woude syndrome; medication had a significant impact with a P-value of 0.0001 and a 95% CI [0.038, 0.162].

For Holoprosencephaly; Vitamins was significant with a P-value of 0.011 and a 95% CI [0.150, 0.350].

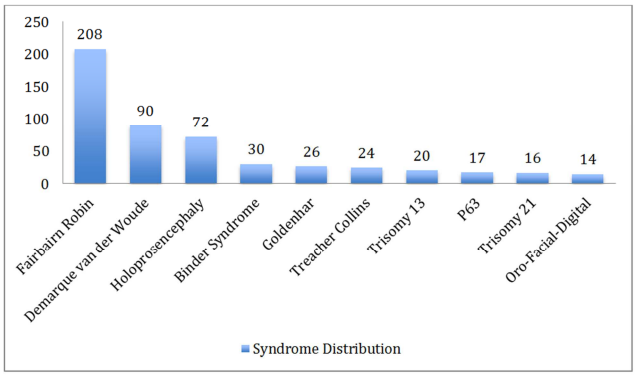

Figure 1. *The frequency distribution of the ten evaluated syndromes.*

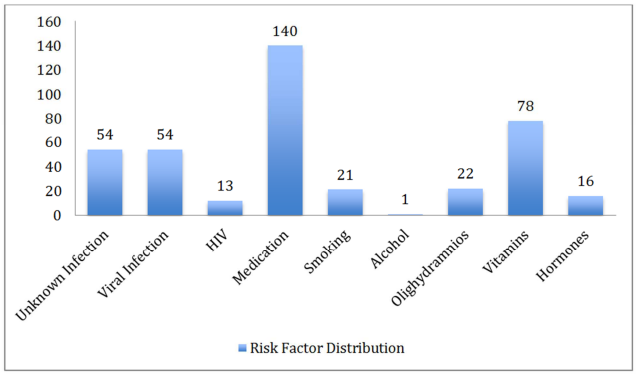

Figure 2. *The evaluated maternal risk factors according to presenting frequency.*

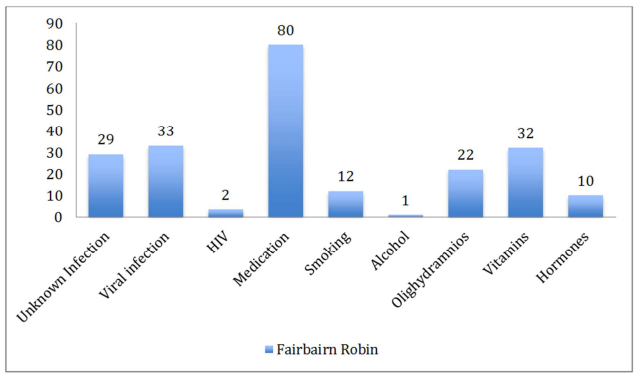

Figure 3. *Frequency of maternal risk factors associated with Fairbairn-Robin triad.*

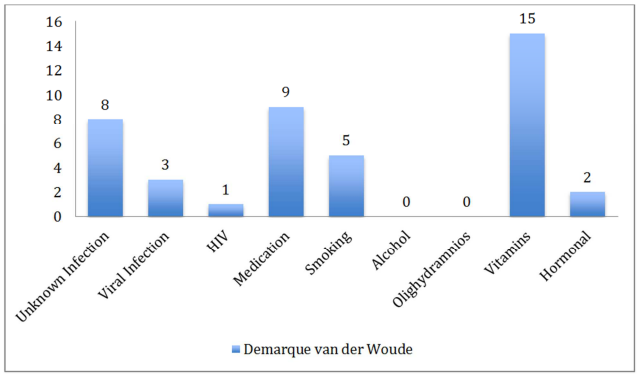

Figure 4. *Frequency of maternal risk factors reported for Demarque-van der Woude syndrome.*

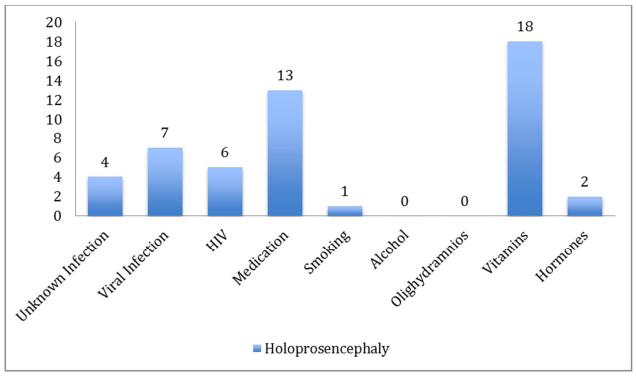

Figure 5. *Holoprosencephaly with reported associated maternal risk factors by frequency.*

4. Discussion

The patients that presented to the Oro-facial Cleft Deformity Clinic University of Pretoria for the past 33 years were evaluated. The ten most common syndromes/genetic disorders that was identified were; Fairbairn-Robin triad (a subdivision of Pierre Robin sequence [18]), Demarque-van der Woude syndrome, Holoprosencephaly, Goldenhar syndrome, Naso-maxillo-acro-dysostosis [19] (Binder syndrome), Oro-Facial-Digital syndrome, Trisomy 21, Trisomy 13, Treacher Collins and p63 – related genetic disorders (Ankyloblepharon Ectodermal Dysplasia (AED); Ectodermal-Ectrodactyly-clefting syndrome (EEC); Rapp-Hodgkins syndrome).

The risk factors that were identified included; unknown infection, viral infection, HIV, medication, smoking, alcohol, oligohydramnios, vitamins and hormones.

Within the literature a number of genetic and teratogenic causes were identified to contribute to syndromic manifestations. The associated syndromes will now be discussed separately in chronological order from most common to the least common. The main clinical findings of each syndrome will be mentioned, as well as findings contributing to the etiopathogenesis of each syndrome.

4.1. Fairbairn-Robin Triad

In 1923 Pierre Robin discussed the clinical presentation of glossoptosis together with micrognathia and described its management. [16] Fairbairn has at this stage already presented the triad of micrognathia, cleft palate with airway compromise and glossoptosis in 1846. [17] In the presence of an oro-facial cleft together with the other features as described by Pierre Robin, the entity will be further referred to as Fairbairn-Robin triad (FRT) [18]. Some theories prevail as to the cause of the growth disturbance present with Pierre Robin sequence [20]. The three theories entail the presence of oligohydramnios or polyhydramnios alone (mechanical restriction or obstruction) [21], or a combination of a metabolic disorder together with secondary intrauterine mechanical obstruction or restriction. [22] Within the study model, 208 patients presented with Fairbairn-Robin triad. Oligohydramnios was noted in 22 of the cases with no other syndromes having a mother reporting oligohydramnios. Unknown infection was stated in 29 cases and viral infection (commonly diagnosed as influenza) in 33 of cases. Medication as a risk factor was documented in 84 of the 208 Fairbairn-Robin triad cases. The reporting of oligohydramnios coincides with the literature [21], and this study supports the theory.

4.2. Demarque-Van Der Woude Syndrome

This syndrome according to the Online Mendelian Inheritance in Man (OMIM) database, Demarque-van der Woude syndrome (DVWS) is one of the most common syndromic clefts, affecting 2% of all oro-facial clefts. Popliteal Pterygium syndrome (PPS) is considered a more severe form of DVWS. Up to date this DVWS and PPS has been associated with mutations in the interferon regulatory factor 6 (IRF6) in about 70-75% of cases, with the grainy-head-like 3 (GRHL3) accounting for between 3-5%. The remaining 20% are speculated about. [23, 24] IRF6 is required for skin, limb and craniofacial development. [25-27] GRHL3 is required for development and repair of the epidermal barrier layer. [28-30] Phenotypically the IRF6 associated DVDW presents more with cleft lip and the GRHL3 associated DVDW presents with a cleft palate. The lip pits are more common with IRF6 than with GRHL3 mutations (76% versus 52%) but not significantly so. [22] Within this study 90 patients presented with Demarque-van der Woude syndrome. The significant risk factor reported on was medication with a total of 11 mothers stating usage of medication within their first trimester of pregnancy.

4.3. Holoprosencephaly (HPE)

HPE is the most common human forebrain malformation with an estimated prevalence of 1 in 250 conceptuses. [31, 32] Several genetic mutations have been linked to HPE, with the phenotypical range varying so much a specific mutation cannot be linked to all. Upon evaluation of the Gli2 gene encoding for the Hedgehog pathway is has been established that mice with single allele Gli2 mutations exhibit increased severity and penetrance when exposed to a low dose teratogen (Tamoxifen). [33] A single allele mutation of Gli2 is usually silent. Hh (Hedghog) signaling is important for two reasons, firstly it acts as a mitogen enabling expansion of medial forebrain tissue and secondly, separation of the initially singular eye field. SHH ligand secreted from the notochord and floor plate of the neural plate and tube specifies ventral neuroprogenitor cells. Galen et al., indicated that the normally silent genetic and environmental factors can interact to produce a severe HPE outcome. Another study evaluating the effects of prenatal alcohol exposure in the context of Gli2 heterozygosity also underlined that this functional predisposition in combination with the environmental factor as causing severe birth defects. [32] This highlights the emerging consensus that HPE as with other birth defects are likely to result from the interactions between genetic and environmental factors. [31] Holoprosencephaly presented in 72 patients. Vitamin supplementation was reported in 18 cases and this was noted as significant. It is difficult to draw a conclusion from this finding though, since the variety of supplementation cannot be determined. Very few patients could name the supplement. This was the syndrome that presented with the highest count of HIV patients (5/72), but this was not significant.

4.4. Naso-Maxillo-Acro-Dysostosis (Binder's Syndrome)

Naso-maxillo-acro-dysostosis [19] or Binder's syndrome also known, as nasomaxillary dysplasia, is a congenital malformation. It was first described in 1882 by Zuckerkandl [35], but Binder reported three patients with six recognizable characteristics; arhinoid face, abnormal position of nasal bones, intermaxillary hypoplasia with associated malocclusion, reduced or absent anterior nasal spine, atrophy of the nasal mucosa and absence of the frontal sinus. [36] The severity of the syndrome would be determined by the amount of features present. [19] The etiology of the syndrome is still unknown with some suggested etiologies including; inhibition of the ossification center that forms the lateral and inferior borders of the piriform aperture during the fifth and sixth gestational week, this causes hypoplasia of the upper jaw. The other possible causes include birth trauma [39], genetic factors [38], and possibly vitamin K deficiency. [39, 40] 30 Patients presented with the diagnostic signs of Binder's syndrome with clefts. The most common risk factors that were indicated was medication (10/30) and viral

infection (6/30), but not of these proved to be significant.

4.5. Goldenhar Syndrome

Goldenhar syndrome (GS) was first described by Maurice Goldenhar in 1952, it is described by many synonyms of which oculo-auriculo-vertebral syndrome, facio-auriculo-vertebral syndrome or Goldenhar-Gorlin syndrome are some. [41, 42] GS is recognized by impaired development of structures such as the eyes, ears, lip, tongue, palate, mandible, maxilla and deformation of the teeth structures. These structures derive from the first and the second pharyngeal arches. Abnormalities of the heart, kidneys, central nervous system or the skeleton and vertebral defects are seen. There is a spectrum of abnormalities ranging from mild to severe. The etiopathogenesis is still poorly understood but suspected to be multifactorial and dependent on genetic and environmental factors. Cases were described as either autosomal dominant or recessive inheritance [43-48], with recurrence risk being 2-3%. Most cases are described as being sporadic. Hypothesis about the development involves abnormal development of vasculature in the 4^{th} week of pregnancy when the 1^{st} and 2^{nd} pharyngeal arches develop. External factors involved in the development of GS includes vasoactive medications, smoking, cocaine, exposure to thalidomide, hormonal therapy, and Tamoxifen interfere with the development of the 1^{st} and 2^{nd} pharyngeal arches. Increased risk has been associated with diabetic mothers and mothers with hypothyroidism, celiac disease, vaginal bleeding during pregnancy or premature births. [49] A significant correlation was noted between pregnancy at an older age of both parents and the frequency of GS in their children. In vitro fertilization and multiple pregnancies especially with monozygotic twins showed an increased incidence of GS. [50, 51] The total number of patients with Goldenhar syndrome with clefts was 26. The two most common risk factors identified was medication (6/26) and unknown infection (4/26). None of these risk factors proved to be significant.

4.6. Treacher-Collins' Syndrome (TCS)

This is an autosomal dominant craniofacial malformation is known to be caused mainly by the TCOF1 gene. [52] A rare autosomal recessive form has been noted on the literature though. [53, 54] These patients are symmetrically affected, with characteristic hypoplasia of the zygomas and mandible, worth malformed ears, associated hearing loss due to atresia of the external ear canal. These patients also present with downward slanting palpebral fissures and lower eyelid coloboma.

The study by Hao did suggest a possible genetic heterogeneity or a variety of mechanisms leading to the syndrome. Some of the patients in their study diagnosed with TCS did not express a TCOF1 mutation. Two hypotheses are that there may be another gene located close to TCOF1 that is responsible for TCS or those nonsequential factors that can modulate the expression of TCOF1 for instance the methylation of gene or the mi-RNA regulation. Further research is still needed to explain these alterations. [52] Treacher-Collins' syndrome with clefts was diagnosed in 24 patients that presented to the University of Pretoria Oro-facial Cleft Clinic. Of these a mere two mothers indicated the use of medication within the first trimester as well as two indicating the use of vitamins.

4.7. Trisomy 13

Trisomy 13 was first discussed by Thomas Bartholin in 1657 and cytogenetically described by Klaus Patau in 1960. It is a rare (1/5000) syndrome with a high mortality during the first four months. Trisomy 13 is caused primarily by maternal nondisjunction (increased risk with advanced maternal age) with a secondary cause being unbalanced robertsonian translocation with a high recurrence in parental carriership of 13/14 or 13/15 balanced robertsonian translocation. [55] Lastly a postzygotic mosaic trisomy 13 is rare at 5% and can present with a mild phenotype and a longer survival. [53] The phenotypical features include small for gestational age, central nervous system anomalies, midline facial defects as well as urogenital malformations. 20 Patients presented with Trisomy 13 with clefts. The associated risk factors were indicated in single affected patients, thus none of these parameters were found to be significant.

4.8. TP63 Mutation Associated Clefting Disorders

TP63 is present in an array of isoforms. Heterozygous TP63 mutations in human syndromes include; Ankyloblepharon-Ectodermal Dysplasia –Clefting (AEC), Ectrodactyl-Ectodermal Dysplasia-Clefting (EEC), Limb-Mammary syndrome (LMS), Acro-Dermato-Ungual-Lactimal-Tooth syndrome (ADULT), Rapp-Hodgkin syndrome (RHS), and Split-Hand/Foot Malformation have been written up. Only AEC, EEC and RHS will be included due to the clefting component. Only AEC presents with severe epidermal erosions. It is suggested that impaired fibroblast growth factor (FGF) signaling plays a role with the dermal expression of AEC. Studies have shown that the AEC mutant p63 prevented transcription induction of zinc finger protein 750 (ZNF750), associated with familial psoriasis in two families. Forced expression of ZNF750 saved impaired epidermal differentiation resulting from AEC mutant p63. [56] The number of patients diagnosed with these three syndromes was 17. Six of these patient's mothers indicated having medicinal usage within the first trimester, but still this was not sufficient enough to be significant.

4.9. Trisomy 21

First described by John Langdon Down in 1866. The incidence is 1/700 births. The risk increases exponentially with increased maternal age and mothers younger than 20. 95% is caused by maternal nondisjunction during meiotic division. 4% is caused by parental balanced robertsonian translocation between chromosomes 13 or 14 and 21. 1% is

caused by postzygotic mitotic nondisjunction, these are mosaic trisomy 21 babies and can have a milder phenotype. Phenotypical features include; enlarged tongue, flattened skull, epicanthal folding, brushfield spots in the iris, small low set ears with a prominent overlapping of the anti-helix. A variety of other cardiac and gastro intestinal malformation can also be present. Hands presents with a simian crease (40%) and a distal position of the palmar axial triradius (84%) with clinodactyly of the fifth finger (83%). The feet present with a sandal gap and syndactyly of the second and third toe. [55] the amount of patients affected by trisomy 21 with clefts was 16. Medicinal use, together with HIV positivity and Vitamin supplementation was the main risk factors. None of the risk factors contributed significantly.

4.10. Oro-facial Digital Syndrome (OFD)

OFD syndrome will be discussed as a type 1 (OFD1) and a type 2 (OFD2), but at least 9 different forms have been described. [57] OFD1 was first reported by Mohr in 1941 [58] and later defined as oro-digital-facial dysostosis by Papillon-Leage and Psaume (1954) [59] and further discussed by Gorlin and Psaume in 1954. This syndrome is X-linked dominant and primarily lethal in male embryos. The incidence is estimated at 1:50000 live births and is caused by a mutation in the OFD1 gene (CXORF5 gene) [60], coding for a centrosomal protein located at the basal body of the primary cilium. This leads to abnormal Hedgehof signal transduction and errors in cell cycle control. [60] Phenotypically these patients may present with congenital heart defects, median cleft palate, cleft lip, lingual hamartomas, hypertelorism, short palpebral fissures, pseudocleft of the upper lip, low set ears, postaxial polydactyly, pre-axial polydactyly of the feet, also an array of other possible signs including microphthalmia and hydrocephalus. Only five live born male patients have been mentioned in the literature. [61]

OFD2 (Mohr's syndrome) is an autosomal recessive disease presenting characteristically with malformations of the oral cavity including tongue nodules, cleft and high arched palate, missing teeth, a broad nose and cleft lip. The features associated with the digits include clinodactyly, polydactyly, syndactyly, brachydactyly and duplication of the hallux. Other features that may present include conductive deafness, choroidal coloboma, renal and congenital heart defects. OFD2 presents with a rare incidence of 1 in 300000 live births. This is a clinical diagnosis with the molecular genetic component still unknown. [57] Oro-Facial Digital syndrome diagnosed patients accounted for 14 of the syndromic oro-facial cleft patients. No risk factor was indicated to even be remotely significant.

The majority of the syndromes discussed above still presents with questionable origins. The prospect exists that there is an array of contributing factors partaking in the development of these syndromes and their clinical features.

5. Conclusion

This study indicated that there is a significant correlation between Fairbairn- Robin triad (FRT) and Oligohydramnios presenting with a result of P= 0.000, Infection (unknown infection (P = 0.033) and viral infection (P= 0.001). Medication also contributed with a P-value of 0.000. The assumption can be made that the mother presented with an infection and then received medicinal treatment therefore. The question arises; did the medication cause the oligohydramnios and this in turn the FRT?

Significant results were also obtained for Demarque-van der Woude with the risk factor of Medication (P=0.0001). It may be that medications contribute to the mutation of IRF6 or GRHL3.

Lastly Holoprosencephaly presented with a p-value of (P=0.0113) for vitamins. Because vitamins involves such a wide variety of possible contributing components, the authors would like to refrain from drawing any conclusions hereof. The amount taken or whether or not it was done under medical recommendation/supervision is unknown.

A future study pertaining to exact type of medication or vitamin supplementation still remains to be done on a large scare. This study aimed to improve the understanding of the implication epigenetics can have on oro-facial-clefting syndromes.

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