DERMATOGLYPHIC ANALYSIS OF NON-SYNDROMIC ORAL CLEFTS CASES, UNAFFECTED FAMILY MEMBERS AND CONTROLS

by

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Non-syndromic oral clefts are a complex craniofacial anomaly with a multifactorial etiology involving both genetic and environmental effects. The risk of developing clefts is influenced by generalized embryological instabilities. Our hypothesis is that, due to a shared embryological chronology between the formation of the lip/palate and fingerprints in the first trimester, individuals with oral clefts may also show abnormal dermatoglyphics. Our subjects are from 5 sites, Hungary, Pittsburgh, Madrid, Texas and Patagonia. Our study follows a case-control design: 1) Cases: Individuals with CL, CLP or CP; 2) Unaffected family members from the case families; 3) True controls, genetically unrelated individuals with no family history of clefting. Our analyses were performed on three data sets: Data set 1—All cleft types, unaffected family members, and true controls (n=1502); Data set 2—Cleft lip with or without cleft palate: CL/P individuals, unaffected family members, and true controls (n=1228): and Data set 3—Cleft palate only: CP individuals, unaffected family members, the true controls (n=570).

We obtained fingerprints from all individuals in our study. Three raters designated the patterns as arch, loop and whorl. Chi-square analysis was done to evaluate the pattern frequency differences across sites, sex, and cleft types. Dissimilarity scores were calculated and tested for

significance using Student's t-test, ANOVA and regression analysis. Ridge counts were also analyzed. We set the level of significance to 0.05.

We found that pattern frequency differences exist across different sites and by sex, based on the cleft status. We further observed pattern differences between the types of non-syndromic CL/P. Arches were higher in cases and unaffected family members compared to the true controls. This difference was more pronounced among females compared to males. Cases had more pattern asymmetry than unaffected family members, who had a higher asymmetry compared to true controls when all cleft types were combined. No significant ridge count differences were observed among these groups.

These results support our hypothesis that individuals with oral clefts differ in their pattern frequencies and dermatoglyphic asymmetry, compared to controls.

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1.0 INTRODUCTION

1.1 NON-SYNDROMIC CLEFT LIP AND CLEFT PALATE

Clefting is a condition formed by the failure or improper fusion of tissues during the development process. In the oral region, clefts can occur in the lips or palate or both simultaneously. Cleft Lip with or without Cleft Palate (CL/P) belongs to a heterogeneous group of disorders that affect the oral cavity and the lips with a substantial rate of dysmorphogenesis. They are one of the most common birth defects worldwide. CL/P can present in isolation or as a part of other Mendelian syndromes, with gene-environment interactions or from teratogenic agents (Stanier P, 2004). Epidemiologically, CL/P has a wide variability across different geographical, racial and ethnic groups with a high prevalence rate of about 1 in 500 Asian and Native American population and low prevalence of 1 in 2500 among the African ancestry populations. The etiology of non-syndromic forms of clefts is controlled by both genetic and environmental components, making it a complex trait of study. (Scott et al., 2005, Dixon et al., 2011). Recent developments in exploring this complex etiology further have been through genome-wide association studies (GWAS), where the role of a host of genes like IRF6, VAX1, FGF8, and MSX1 have been intensively studied. Studies also support the roles of environmental risk factors like maternal smoking, alcohol intake, nutrition levels such as zinc deficiency, stress, which further increases the complexity of studying this condition (Honein et al., Deroo et al.,

2008, Munger et al., 2009). Studies such as the Pittsburgh Oro-Facial Cleft study, which started in 1993, are being done to evaluate and validate the presence of associated phenotypes in the familial transmission of non-syndromic CL/P. Phenotypes include dermatoglyphics, asymmetry, craniofacial morphologies, and subclinical features like the orbicularis oris muscle defects and velopharyngeal incompetence (Weinberg et al., 2005, Marazita, 2007). Cleft lip also has been analyzed in epidemiological studies to show gender differences, where males are more commonly affected than females. Cleft Palate on the other hand has been previously reported to show a female dominance (Greg et al, 1994). A laterality difference has also been found, with unilateral clefts occurring more commonly on the left side of the lip than the right side (Nagase et al., 2010, Dixon et al., 2011).

1.2 DERMATOGLYPHICS

1.2.1 Historical Background

The term dermatoglyphics is derived from two Greek words, *derma*-skin and *glyphe*-carve. It was coined by Cummins and Midlo in the year 1926 and is defined as the study of ridged skin on the palmar and plantar surfaces of human extremities. Fingerprints differentiate during the early fetal life and remain unchanged by age and environment. Thus, they serve to supply a record of growth disturbances that occur during the early prenatal life. Further, these traits can be obtained inexpensively and non-invasively, making them particularly useful in screening for diseases. Their strong inheritance pattern suggests that they can serve as potential genetic markers with considerable research in the future (Holt, 1968).

An artistic desire to reproduce the dermal patterns led to an early exploration of dermal ridges and creases. Archeological expeditions have shown artifacts bearing actual fingerprints and impressions of fingerprints as cave drawings, which date back to 5th century A.D. Fingerprint imprints, were used on documents for centuries, especially by the Chinese as legal evidence for land-sale contracts. Countries like India, Egypt and China have used dermal configurations in palmistry (Chamberlain and Mallery, 1895). However, the earliest scientific interest in the ridge configurations was shown by the Anatomists in the 17th century when they began studying the skin and its development. Bell, an anatomist in 1833, suggested that skin ridges provide firmer grasping and a steadier footing, offering an explanation for the functional advantages of dermal ridges in man. The 19th century saw the use of fingerprints for personal identification and law enforcement (Cummins and Mildo, 1945). Sir Francis Galton, a biologist, recognized the biological variability of fingerprints and demonstrated their permanence, which make them suitable markers for many scientific investigations especially in the field of medicine. He coined the terms arch, loop and whorl for classifying pattern types on the fingers. He was the first to study their inheritance mode by conducting genetic studies where he observed the fingerprint patterns among twins, siblings and genetically unrelated individuals. His data showed a high rate of concordance among related individuals as compared to controls (Galton, 1890). This biological perspective inspired many scientists in the beginning of the 20th century to investigate the mechanism and nature of fingerprint formation and their relevance to health and disease. Cummins was the first scientist to study dermatoglyphics in relation to medical disorders (Plato, Garruto and Schaumann, 1991).

1.2.2 Embryogenesis of Epidermal Ridges

The formation of the upper extremities occurs early in the first trimester when a visible bulge known as a limb bud develops around the 4th week of embryogenesis. This is followed by the formation of a hand paddle that occurs around 35 days. Fingers begin to separate from this paddle and around the 7th week, fetal volar pads become visible as mesenchymal elevations on each fingertip (Reed and Opitz, 1981). The volar pads regress around 10-11 weeks and this corresponds to the formation of the dermal ridges. They start out as localized cellular proliferations, which then project into the superficial layer of the dermis, forming shallow primary ridges. These primary ridges branch out and secondary ridges are formed. Ridge differentiation is studied to spread proximally from the fingertip to the palm in a radio-ulnar direction (Babler, 1981). Dermal ridges completely replace the volar pads by the 6th month. Bonnevie in 1924, postulated that configuration of the ridges is largely dependent on the size and position of the volar pads; smaller pads would lead to simpler patterns (arch) and prominent pads would lead to the development of more complex configurations (loops and whorls). She further studied that pads that were positioned symmetrically on the fingertip would give rise to a centered pattern (whorl) and the asymmetrical pads would give rise to loops (Bonnevie, 1924). Babler, in 1978, performed histologic studies that indicated the timing of formation of epidermal ridges. Whorl like pattern resulted earlier in development and arches were associated with a late ridge formation. He further postulated that height of the volar pad had no effect on the number of ridges. This confirmed Abel's hypothesis, which stated that populations with pattern frequency differences had similar ridge counts (Babler, 1991).

Various theories have been put forth to speculate the directions of the ridge configurations. Cummins (1926) proposed that the different directions of the ridges could be a result of physical and topographic growth forces like the tensions and pressures in the skin during early embryogenesis. Bonnevie (1929) however, associated the underlying arrangements of peripheral nerves to determine the fingerprint patterns. Penrose (1969) suggested that the ridges followed the lines of greatest convexity in the epidermis. It was in 1973 when Hirsch and Schweichel, laid out a summary of the factors inducing the direction of differentiation of the dermal ridges. From an inadequate supply of oxygen to the fetal epidermal tissues to deviations in the distribution of sweat glands, disturbances in the basal layer proliferation of the epithelium, disturbances in keratinization process, environmental factors such as external pressure on the fetal pads and even embryonic finger movements influences the ridge differentiation (Cummins, 1926, Penrose, 1969, Hirsch and Schweighel, 1973). Genetics plays an important role in influencing the epidermal ridge configurations. Hereditary basis of dermal patterns as studied by Galton (1892) showed the closer resemblance of dermatoglyphic traits among close relatives than among unrelated people. Heredity of dermatoglyphic features has now been widely accepted to conform to a polygenic system where individual genes contribute to an additive effect (Galton, 1892).

A more recent work on prenatal dermatoglyphics performed on human abortuses with chromosomal abnormalities have shown that there is definitely a delay in the development of epidermal ridges by more than 2 weeks as compared to what was observed in age-matched normal fetuses. Thus, ridges can be used as a screening tool in providing information about the abnormal fetuses. The contours of the volar pads and the dermal configurations were studied in

the rat models. The topography of the volar surface is essential in determining the arrangements of the ridges. A pre-natal study performed by Okajima and his colleagues in 1991, observed that the morphological features of the volar pads and flexion creases of rats were very similar to humans. They also laid emphasis on the chronology of the ridge formation. The development of ridges was considerably delayed in rats as compared to human fetuses. In humans, these ridge configurations are almost fully developed by 6 months whereas in rats they continue to develop postnatally. If these differences are taken into consideration, rats and even mice could serve as potential models to study the effect of several factors on the embryogenesis of dermatoglyphics (Kimura, Schaumann and Shiota, 2002).

Table 1: Chronology – Pre-natal Development of the Fingerprints in Humans

6 weeks post fertilization	Inter-digital notches on the hand plate
7 weeks	5 thick areas representing the finger rays; Separation of fingertips, the thumb separates from the rest of the fingers
8 weeks	Separation of the remaining fingers; Volar pads begin to develop
9 weeks	Thumb rotates. Flexion creases become apparent
10 weeks	Constrictions between the nail fields and the digital pads develop
11 weeks	Pads regress; a central depression can be seen in each digital pad
13 weeks	Pad regression is complete. Digital depressions disappear
12-14 weeks	Primary and secondary ridge formation
22-24 weeks	Complete formation of dermal configurations

1.2.3 Dermatoglyphic Terminologies

The basic classification system for dermatoglyphic patterns was proposed by Galton in 1892. He divided them into three main types: arches, loops and whorls, based on the number of triradii, which he described as triangular plots, formed by the divergence of adjacent ridges.

- **Center:** Except the arches, other pattern types have a central point around which the ridges organize themselves into different shapes.
- **Triradius:** Penrose in 1954 defined a triradius as a junction of three regions each containing systems of ridges, which are parallel in small fields of these regions. Increase in the number of triradii in the order of arch, loop, whorl, is an indication of an increase in the complexity of a pattern.
- **Pattern Intensity Index:** proposed by Cummins and Steggerda in 1935, this index is defined as the average number of triradii occurring on the fingers per individual. This means that a very high value of the index indicates a high frequency of whorls (Holt, 1968).
- **Ridge count:** Ridge counts, a quantitative measure, are calculated by drawing a line from the center to the triradius of the print, cutting through the ridges in-between them. The number of ridges that the line cuts through, including the center ridge and excluding the triradius, is the ridge count (Schaumann and Alter, 1976).
- **Pattern Types:** An individual can have the same pattern type on all 10 fingers or can have a mixed pattern type.

An arch has no triradius. It is composed of a succession of curved ridges. Hence, the ridge count is a 0. A variation in the arch pattern is the tented arch, which has a centrally situated triradius, but since it coincides with the center of a print, the ridge count remains 0.

Loops are the most commonly occurring patterns among most populations. A loop has one triradius, which could be situated on either the ulnar or the radial side of the print. An ulnar loop opens towards the ulnar margin of the hand and a radial loop opens towards the radial margin of the hand. Hence, loops have two ridge counts with one of the counts, corresponding to the direction to which they open being greater than 0 and the other count always remains a 0.

A whorl on the other hand has two triradii, one on the ulnar and one of the radial side. Thus whorls get two ridge counts, each greater than 0. Variations in the whorl patterns lead to three subtypes in whorls, symmetrical whorls which are composed of concentric ridges around a common center; Spiral whorls where the ridges are arranged spirally around the center, spinning out either in a clockwise or anticlockwise direction; Double-loop whorls, which have two loops, arranged in a whorl like pattern around two centers. (Holt, 1968)

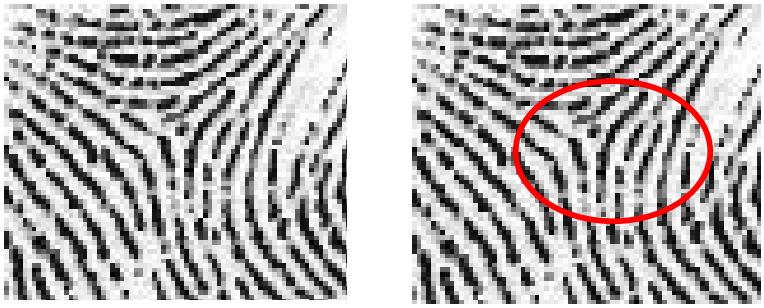


Figure 1: Representation of the Triradius in a Dermal Print

The red mark around the triradius of the print on the right side shows the confluence of 3 ridges.

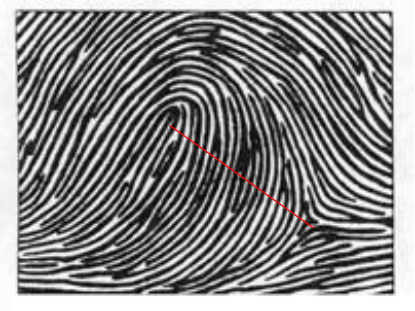


Figure 2: Counting the Number of Ridges

The ridges are counted by drawing a line connecting the center and triradius of the pattern on the print.

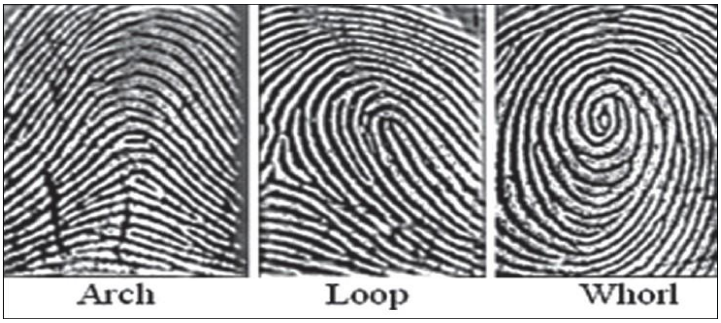


Figure 3: Basic pattern types- Arch Loop and Whorl

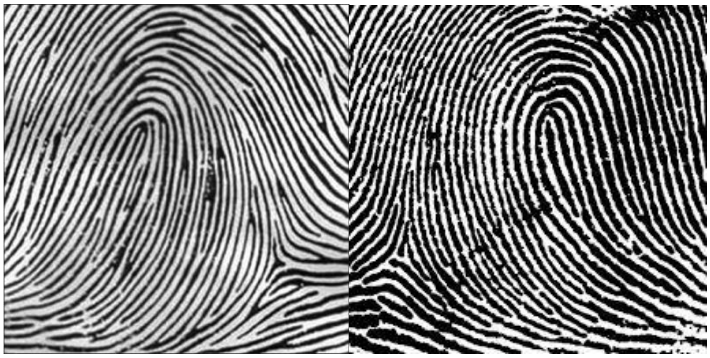


Figure 4: Directionality in Loops

They are classified as ulnar loops and radial loops based on the direction in which they open out.

1.2.4 Gender and Racial Variations in Fingerprints

1.2.4.1 Sex Differences

Many studies have shown the existence of a gender-based difference in the distribution of fingerprint patterns. Females have narrower ridges than males, which can be correlated to some extent with the relatively smaller size of their hands as compared to males (Cummins and Mildo, 1945). Females tend to have a higher percentage of arches, lesser number of radial loops and fewer whorls compared to males. Holt in 1968 first analyzed the gender differences in the pattern frequencies in a British population. He obtained fingerprints of 500 males and 500 females and classified the pattern types. The conclusions of his study are presented as percentages in table 2 below.

Table 2: Pattern Frequencies Based on Sex - Holt, 1968

Pattern	Males (n=500; 5000 fingers)	Females (n=500; 5000 fingers)
Arches	4.3%	5.7%
Ulnar Loops	61.5%	65.6%
Radial Loops	5.9%	4.8%
Whorls	28.3%	23.9%

Similar differences were observed between males and females from other studies performed by Bonnevie, Galton and others.

1.2.4.2 Racial Differences

Racial variations have also been studied in the frequencies of fingerprint patterns. Galton in 1892 compared prints from large samples of 5 populations: English, Welsh, Jews, Africans

and Basques. He found some statistically significant frequency differences of pattern types between the 5 races. Evaluations of samples of Chinese populations showed that they have the highest frequencies of whorls among all major racial groups (Holt, 1968; Neiswanger et al., 2002). This makes it important to have racially matched controls in any study. Among many studies that evaluated this difference, Plato in 1973 summarized the frequency differences in pattern types among the different racial groups and his results are presented in table 3 (Plato, 1973).

Table 3: Pattern Frequencies Based on Race – Plato, 1973

Racial group	N	Whorls (mean)	Ulnar Loops (mean)	Radial Loops (mean)	Arches (mean)
Caucasians	112	35.4	55.6	4.3	4.3
Africans	88	27.4	61.4	2.6	8.8
Native Americans	76	42.6	49.4	3.1	5.0
Orientals	55	46.7	48.1	3.0	1.8
Australasians	60	52.7	44.9	1.1	1.4
Asian Indians	7	42.6	51.8	2.2	3.4

Many other dermatoglyphic studies that followed also showed statistically significant differences among the different ethnic groups for pattern types. Although sex and ethnic differences exist for pattern types, this cannot be interpreted as being able to identify the sex / race of an individual from a palm print.

1.2.5 Common Patterns on Digits

Bonnieve in 1924 identified that certain patterns occur more commonly on certain fingers. She concluded that arches occur more frequently on the 2nd and 3rd digit while whorls

occur more commonly on the 1st, 2nd and 4th digit. Loops tend to occur more often on the 3rd and 4th digit when compared to other patterns. Her analysis was performed on a normal population with no birth defects or any known medical history. We do not find any other similar reports in studies that came later to find associations between dermatoglyphics and birth defects.

1.2.6 Dermatoglyphic Anomalies

Destruction of dermal patterns on the hands and feet can occur as a result of trauma or from certain inborn errors of the ridge patterns. Congenital dermatoglyphic malformations are classified as ridge aplasia; ridge hypoplasia; ridge dissociation and ridges-off-the-end (Holt, 1968).

Ridge aplasia is characterized by the complete absence of dermal ridges over the entire palmar surface of the hands and plantar surface of the feet. Studies performed by Baird in 1964 described 16 members of a family out of 28 members in 4 generations exhibiting ridge aplasia. Although this is regarded as a rare occurrence, it does throw light on the genetics behind this event. Two more patients with the same condition were described but they presented with medical disorders; one of them suffered from progeria and hydrocephalus with cleft palate, the other from a type of ectodermal dysplasia (Holt, 1968 and Baird, 1968). Ridge hypoplasia is characterized by ridges shorter in length. This is difficult to distinguish from an acquired ridge atrophy due to trauma. Ridge dissociation are severe anomalies of ridges that are frequently described in medical disorders like ectodermal dysplasia, malformation of fingers and birth defects. Ridges-off–the-end represent an interesting group where instead of running transversely,

ridges run distally off the edge of the fingertip. It is inherited as an autosomal trait and is not found to be associated with any medical disorders (Hedge, Rai and Mathew, 2005).

1.2.7 Dermatoglyphics in Medicine

As early as 1939, Cummins observed abnormal finger and palm print patterns in children affected with Down Syndrome, and this led many other pioneers in this field to study the altered dermatoglyphic patterns in other medical disorders (Cummins, 1939; Schaumann and Alter, 1976).

Abnormal dermatoglyphic patterns were more closely followed in limb abnormalities. A few such disorders include the thalidomide embryopathy, where the teratogen thalidomide, which was used in the 1950s as a drug to alleviate the symptoms of morning sickness in pregnant women, leaves children with severely malformed limbs (phocomelia). The abnormal dermatoglyphic traits seen in such children include the absence of the axial triradii and abnormal palmar flexion creases. Syndromes such as Fanconi's anemia, Trisomy 18, and Holt-Oram syndrome are associated with an absence or hypoplastic thumbs. The ridge configurations in palms of the affected individuals are distorted, triphalangeal thumb is a characteristic trait, and abnormal dermatoglyphics are present. Anonychia is a condition where the absence or hypoplasia of the nails results in the extension of ridged skin, altering the patterns on the fingers.

Several chromosomal abnormalities like the autosomal trisomies are also associated with abnormal dermatoglyphics. Down Syndrome is commonly associated with a single transverse

flexion crease on the palms. There is a marked increase in ulnar loops and significantly lowered ridge counts on the fingertips of the affected individuals. Trisomy 18 is associated with increased percentages of arches among the affected individuals.

Late 1950's saw the extension of dermatoglyphic studies to other conditions like cleft-lip and palate, rubella, leukemia, celiac disease, diabetes, schizophrenia, oral cancer, dental caries, and so on. The aim of these association studies is to understand the developmental instabilities, the genetic basis of diseases, and to exploit dermatoglyphics as a potential marker for screening susceptible individuals, under the assumption that dermatoglyphic patterns may act as sensitive indicators of developmental stability (Schaumann and Alter, 1976).

1.3 DERMATOGLYPHICS AND ORAL CLEFTS

Several studies have explored the relationships between dermatoglyphic patterns, their asymmetry, and clefting of the orofacial region. They have demonstrated a relationship between CL/P and dermatoglyphic pattern types and asymmetry in several populations. Gender based differences have also been demonstrated (Holt, 1968; Hedge, Rai and Mathew, 2005; Scott et al, 2005). One underlying justification for these studies is the developmental overlap in the chronologies of the formation of the lip and palate and dermatoglyphics, in utero.

The development of lip and the primary palate is completed by seventh week of intrauterine life and the secondary palate by the 12^{th} week in humans. The dermal ridges also

form around the 6th week and complete their development by the 12th or 13th week (Hedge, Rai and Mathew, 2005).

Dermatoglyphics, being sensitive indicators of intrauterine anomalies, can provide valuable information to decipher the genetic etiology behind the dysmorphogenesis in oral clefts. The presence of a cleft may also be associated with some generalized developmental instabilities, which may possibly result in asymmetry that is observed in cleft lip. The left side is more commonly affected than the right side for unilateral cleft lip (Scott et al, 2005). Phenotypically, developmental instabilities could manifest as exaggerated levels of dermatoglyphic asymmetry or altered frequencies of pattern types or both (Jahanbin et al, 2010).

Silver in 1966 investigated 39 white boys and girls with CL/P against their controls for dermatoglyphic variations. He obtained the 3rd inter-digital palmar pattern, individual fingerprint patterns and the hallucal pattern on the ball of the foot. He did not find statistically significant differences among any of the individual patterns between different sexes and he concluded that embryogenesis of CL/P may be independent of the production of the abnormal dermatoglyphic patterns. However, his sample size is quite small and was not conclusive.

Vormittang et al in 1979 demonstrated that fingerprint pattern types differed based on the cleft laterality. Their study favored the view that differences exist in the dermatoglyphic patterns between familial CL (P) and isolated CP. They studied the patterns from 107 CL (P) cases and 17 isolated CP cases from Austria. With respect to their right unilateral CL (P) cases, increased number of arches and a reduced number of whorls were characteristic features, while increased

number of arches and a reduced number of ulnar loops were associated with the patients having bilateral CL (P). The total ridge count showed a high value for female CL (P) patients that surpassed the male CL (P) cases and the control group. Further, a higher total ridge count was observed in familial CL (P) patients as compared to the isolated CP patients.

A study of a large sample of Chinese population was performed by Neiswanger et al in 2002 to assess the dermatoglyphic asymmetry in CL/P. Three dermatoglyphic measures—pattern frequencies, total ridge counts, and atd angles — were obtained and asymmetry scores were calculated for right and left hands for each of these three measures. Their rationale was that developmental instability manifests itself phenotypically as some form of asymmetry. An exaggerated presentation of asymmetry between the dermatoglyphic patterns of the left and right hands may reflect unstable genetic control during development (Adams and Niswander, 1967; Woolf and Gianas, 1977). Their results with regards to pattern frequency differences agreed with Silver (1966) in that they did not find any significant differences between pattern types of cases, controls and unaffected relatives. Their sample confirmed Holt's findings that the Chinese population had a higher frequency of whorls among all major racial groups. However, their asymmetry analysis found significantly more asymmetry in the pattern types of probands who had a positive family history of clefting, suggesting that a genetic load may impact developmental stability (Neiswanger et al, 2002).

Studies comparing the dermatoglyphic pattern frequencies between CL/P cases and their unaffected relatives from China and Philippines show that this relationship occurs in different populations. Scott et al, (2005) performed the first study to demonstrate population-specific

associations between CL/P and dermatoglyphics. They identified two forms of heterogeneity: within each population and between populations. Within-population heterogeneity results differed in both populations. Within the Chinese population, CL/P cases showed significantly more radial loops compared to their unaffected relatives, but the Filipino cases had more ulnar loops. Between-population pattern frequencies differed across China and the Philippines. Thus, they conclude that their results may exhibit developmental instability and underlying population-based differences in disease-causing alleles (Scott, et al., 2005).

Even though Silver (1966) and Neiswanger et al. (2002) did not find significant pattern differences between cleft cases, controls and unaffected family members, other investigators continued to analyze this trait. An Indian group in 2005 found significant pattern differences between their cleft cases and control group. They reported that children with oral clefts had an increased frequency of ulnar loops compared to the controls, who reported with an increased frequency of whorls. Fluctuating asymmetry of the atd angle of the cases was also found to be increased significantly compared to the controls. Fluctuating asymmetry is the random differences between the two sides of quantitative traits in an individual. It increases in magnitude when there is an inability to maintain developmental homeostasis. Thus, based on their results they concluded that any genetic damage during development could manifest itself through abnormal dermatoglyphics thus increasing their usefulness as a diagnostic tool for preliminary investigation of diseases with a suspected genetic etiology. Hence, their findings continued to increase the interest in this type of study (Mathew, Hedge and Rai, 2005).

Several studies were performed in 2013 to evaluate the dermatoglyphics in cleft cases, their parents and control groups. In one study with a sample of 294 Indian subjects, an increased frequency of loops and arches and decreased frequencies of whorls were observed in cases compared to their parents. The authors concluded that these significant differences make dermatoglyphics suitable as a tool to evaluate genetic etiology and for genetic counselling (Saxena, David and Indira, 2013). An Iranian study which included 55 patients with non-familial CLP and their unaffected parents (38 fathers and 47 mothers) and a control group of 60 unaffected children and their parents (37 fathers and 50 mothers), showed significant differences in the pattern frequencies among non-familial cleft lip and palate (CLP) cases and control children (p value = 0.022) as well as unaffected fathers of CLP patients and their control group (p value= 0.02). However, no enhanced fluctuating asymmetric between the different groups was observed, indicating a low degree of developmental instability in this deformity. (Eslami, Jahanbin and Ezati, 2013). A cross- sectional study performed on Indian subjects, examined dermatoglyphic patterns and dental abnormalities in 90 CL/P cases and age-appropriate controls. They demonstrated highly significant differences in loops and whorls between the study and the control group, with the loops increased in the study group and the whorls decreased. The dental anomalies were increased in CL/P group and decreased among children with CP alone. They conclude that a gene-mediated etiology in clefting can be supported by any deviation in the dermatoglyphic characteristics indicating a genetic difference between the cases and the control groups (Maheshwari et al, 2013).

The most recent work published in this field was in 2015 by a Brazilian group where they analyzed the fluctuating asymmetry in a Brazilian sample of 51 affected trios and 50 unaffected

control trios. The affected trios were comprised of non-syndromic CL/P subjects with their unaffected parents. They observed statistically significant difference between the atd angles of the fathers of the affected trio group indicating developmental deviations and instabilities (Leite BD et al, 2015).

Thus, the continued interest in trying to establish the association between dermatoglyphics and oral clefts is based on the principle that there may be some sort of embryological instability during the formation of the clefts, which may reflect in other parts of the body like the dermal ridges, which is influenced by genetics.

1.4 HYPOTHESIS

Our hypothesis is that, due to a shared embryological chronology between the formation of the lip/palate and fingerprints in the first trimester, individuals with non-syndromic clefts may show abnormal dermatoglyphic patterns, ridge counts, and/or asymmetries.

2.0 MATERIALS AND METHODS

In an attempt to study the extended phenotypic features that may be associated with, non-syndromic clefting, we chose to evaluate the dermatoglyphic pattern and ridge count differences in our data set.

2.1.1 SAMPLE

Our initial data set was taken from the Pittsburgh Oral-Facial Cleft Study. It included 1550 individuals from 5 different sites. The cleft status of the affected individuals was evaluated by clinicians trained to distinguish between syndromic and non-syndromic clefting. Since our study focuses on the non-syndromic cleft types, we excluded 32 subjects who were diagnosed with Van der Woude syndrome. Our final sample sizes from each site were Hungary (n=679), Pittsburgh (n=460), Texas (n= 195), Madrid (n= 117) and Patagonia (n=51).

Three groups of individuals were available for analysis:

1) Cases: Individuals with CL, CLP, or CP. There could be more than one individual with a cleft from a single family.

2) Unaffected family members from the case families (UFM).

3) True controls (TC) or genetically unrelated individuals who had no family history of clefting. All five sites have unaffected family members, but only Pittsburgh and Hungary also have true controls.

2.1.2 STUDY DESIGN

Our study followed a case-control design with the two control groups described above. We chose our subject groups based on the hypothesis that cases affected with clefts have the risk genes and may have had an environmental push towards developing clefts. The unaffected family members may or may not have the risk genes or the environmental exposure, thus making them ideal candidates for study, in between cases and true controls. Because they share more genetics with the cases compared to the true controls, we can expect their dermatoglyphic pattern frequencies and instabilities to be intermediate, if there is a genetic association between clefting and dermatoglyphics.

Owing to the etiological differences between CL/P and CP, many of our analyses were performed on three different data sets:

- Data Set 1—All cleft types: The complete sample, including all cleft individuals, their unaffected family members, and the true controls from Hungary and Pittsburgh (n=1502)
- Data Set 2—Cleft lip with or without cleft palate: CL/P individuals, their unaffected family members, and the true controls from Hungary and Pittsburgh. (n=1228)
- Data Set 3—Cleft palate only: CP individuals, their unaffected family members, and the true controls from Hungary and Pittsburgh. (n=570)

The cases and unaffected family members from data set 1 were split into two subgroups for data sets 2 and 3, while the complete set of true controls was included in all three data sets. A few individuals had an unknown cleft type; they and their unaffected family members were included in the first data set but deleted from the second and third data sets.

2.1.3 FINGERPRINT DATA

- **Collection**

  Fingerprints were collected from our 5 sites after obtaining informed consent. Rolled prints of each finger were taken individually using the standard ink method, in which each finger is inked and then rolled on paper to obtain a complete print with clear triradii, and labelled for both digit and left or right hand. Any print, which did not appear clearly on the first attempt, was obtained again to ensure that we had recognizable prints of all fingers.

- **Rating**

  Three trained raters independently scored the patterns on each finger into arch, ulnar loop, radial loop, whorl, accidentals, or others. For the purpose of this analysis, we combined the radial and ulnar loops into a single "loop" group, and the accidentals and others into a single 'others' group. The patterns were arbitrated by a fourth rater to re-evaluate any disagreements in the rating process, and a sub-set of prints was spot-checked. Three independent raters counted the ridges and the mean and standard

deviation was obtained. If the standard deviation was greater than 2.0, the count was staffed and/or arbitrated. Counts with standard deviation that remained > 2.0 after this process were called unknown. Raters were blinded to the affection status of the subjects. Unrecognizable prints due to scars or printing errors were coded with a -8888.

- **Cleaning**

Microsoft Access was used to clean and manage our data. A number of cleaning queries were run, including checking for missing prints that were coded as -8888 and re-arbitrating them, wherever possible. Pattern and count discrepancies were checked and resolved as follows. For any pattern rated as an arch, the corresponding ridge count should be '0' for both the radial and the ulnar counts. Similarly, loops must have a '0' on either the radial or the ulnar count (a radial loop will have a '0' on the radial side). Whorls must have two non-zero counts, one each on the radial and the ulnar side. Since the ridge counts were calculated by three raters for each print, a mean was obtained for the final count. The mean was rounded up to the nearest whole number if it was either equal to or exceeded 0.5 and rounded down to the nearest whole number otherwise.

Pattern types

We used the arch, loop and whorl pattern types for all our analyses. The "other" prints were deleted from the analysis of pattern frequencies, and individuals with at least nine known pattern types were included.

- **Non-syndromic CL/P types**

The cases in the data set 2, CL/P, have a unilateral cleft lip either with or without cleft palate (right or left) or a bilateral cleft lip with or without cleft palate. We studied the distribution of arch, loop and whorls among these case sub-types in data set 2 only.

- **Pattern Asymmetry**

Pattern asymmetry between right and left hands was determined by an average dissimilarity score. We assigned a score of '0' when the fingerprint pattern type was identical on the right and the left hands for the same digit. A score of '1' was assigned when the patterns differed on the same digit between the two hands. The pattern groups used for this analysis were arch, loop, whorl, and other; radial and ulnar loops were scored as identical loops, following Woolf and Gianas (1976). Thus, summing up the score over all the five pairs of digits, the dissimilarity score could range from 0 (when all 5 pairs of digits had the same patterns) to 5 (when all 5 pairs of digits had different patterns). Only individuals with ten known pattern types were included.

- **Ridge Counts: ARC and TRC**

We calculated two ridge count variables for each individual in the data set, an absolute ridge count and a total ridge count. Absolute ridge count (ARC) is the sum of all the ridge counts (radial count + ulnar count = 20 counts) on the 10 fingers. Total ridge count (TRC) is calculated by taking the highest of the two ridge counts (radial or ulnar count) per finger and summing them up for all 10 fingers per individual. Only individuals with ten known pattern types were included.

2.1.4 STATISTICAL ANALYSIS

Our final data set was constructed in Microsoft Excel (version 15.13.1) with nine main variables—site, affection status, sex, pattern types on each finger, cleft types among cases, ridge-counts on each finger, ARC, TRC, and pattern dissimilarity scores. We formulated the variable "affection status" from the two variables "cleft family history" and "cleft type." The variable "cleft types" included the cleft lip types of unilateral (left and right) and bilateral, as well as cleft palate.

For each of the three data sets, we performed qualitative and quantitative analysis. For most of the analyses, only arch, loop and whorl pattern types were studied. Descriptive statistics were performed using Microsoft Excel (version 15.13.1). Summary statistics, as well as tables and bar graphs for visual representation of the summary data, were created using Microsoft Excel. The individual data sets were then imported into SAS (9.4) for statistical analysis (Cary, 1990).

I. Pattern Types

- **Identifying Common Patterns on Certain Digits**

We identified common patterns on each digit based on Bonnevie's work in 1924. Holt, Galton and Bonnevie suggested that certain patterns are more commonly found on certain fingers relative to the others. We first started by calculating the percentage of arch/loop/whorl on each digit and compared them to the overall percentage of arch/loop/whorl in each of our 3 data sets. This was done for Hungary and Pittsburgh

alone, since only these two sites have true controls, which are the most representative of the general population.

- **Pattern Types and Clefting**

Chi-square tests were used to determine associations between the different categorical variables. For smaller samples like Patagonia, Fischer's exact test was used to test the pattern frequency differences. For each of the 3 data sets, differences in pattern frequencies (arch, loop and whorl) were analyzed first across the site variable, and then by sex. Finally, pattern frequency differences based on affection status were analyzed, accounting for differences in site and sex. The frequency of patterns was also analyzed among the cleft sub-types in data set 2, CL/P, by site and sex.

- **Pattern Asymmetry**

Mean dissimilarity scores were obtained for each of the three data sets. The analysis of these scores for significant differences in their means was done as follows:

1. For Hungary and Pittsburgh, two types of tests were done:
    a) ANOVA between the 3 groups of affection status: cases, true controls and unaffected family members.
    b) Student's t-test between the cases and TC
2. For all 5 sites, two types of tests were done:
    a) Student's t-test between cases and UFM
    b) Regression analysis between the cases and UFM accounting for differences in site and sex.

II. Ridge Counts

Means and standard deviations of absolute ridge counts (ARC) and total ridge counts (TRC) were obtained. Two types of statistical tests were performed for mean ARC AND TRC for each of the 3 data sets:

1) For Hungary and Pittsburgh, ANOVA to test the differences in their means between cases, UFM, and TC.
2) For all the 5 sites, t-tests to test the differences in their means between cases and UFM.

For all the above analyses, the level of significance was set to 0.05 (alpha=0.05) to test for any significant statistical differences.

3.0 RESULTS

3.1 DESCRIPTIVE STATISTICS

This section describes the sample distributions for the three data sets, based on our three main variables—site, sex, and affection status. Table 4 presents the sample sizes for each site by sex for each of the three data sets. For data sets 1 and 2, Hungary and Pittsburgh have more females than males, while there are more males in Patagonia. For Madrid and Texas, males and females have an approximately equal distribution. Note that true controls are included in all three data sets for Hungary and Pittsburgh, which inflates the number of people in data set 3 for these sites. Thus, the actual number of cases in the CP data set is relatively small for all five sites.

Table 4: Sample Distribution across 5 Sites by Sex

Site	Sex	Data Set 1: All Cleft Types		Data Set 2: CL/P		Data Set 3: CP Only	
		n	%	n	%	n	%
Hungary	Males	312	45.95%	245	45.62%	114	43.02%
	Females	367	54.05%	292	54.38%	151	56.98%
	Total	679		537		265	
Pittsburgh	Males	203	44.13%	164	44.32%	106	40.15%
	Females	257	55.87%	206	55.68%	158	59.85%
	Total	460		370		264	
Patagonia	Males	31	60.78%	29	61.70%	2	50.00%
	Females	20	39.22%	18	38.30%	2	50.00%
	Total	51		47		4	
Madrid	Males	56	47.86%	46	49.46%	10	41.67%
	Females	61	52.14%	47	50.54%	14	58.33%
	Total	117		93		24	
Texas	Males	99	50.77%	92	50.83%	6	46.15%
	Females	96	49.23%	89	49.17%	7	53.85%
	Total	195		181		13	
TOTAL		**1502**		**1228**		**570**	

Table 5 presents the sample sizes for the three groups of subjects, based on their affection status, by sex, for the three data sets. For the cases, data sets 1 and 2 show more males than females, while there are equal numbers of males and females in data set 3. There are 299 TC in all three data sets, and 62% are female. For the UFM, all three data sets have more females than males.

Table 5: Sample Distribution across Affection Status by Sex

Groups	Sex	Data Set 1: All Cleft types		Data Set 2: CL/P		Data Set 3: CP only	
		n	%	n	%	n	%
Cases	Males	210	57.22%	163	60.15%	46	49.46%
	Females	157	42.78%	108	39.85%	47	50.54%
	Total	367		271		93	
True Control, (TC)-Hungary and Pittsburgh	Males	114	38.13%	114	38.13%	114	38.13%
	Females	185	61.87%	185	61.87%	185	61.87%
	Total	299		299		299	
Unaffected Family Member, (UFM)	Males	377	45.10%	299	45.44%	78	43.82%
	Females	459	54.90%	359	54.56%	100	56.18%
	Total	836		658		178	
TOTAL		**1502**		**1228**		**570**	

3.2 DATA CLEANING

Our qualitative analysis included analyzing the pattern frequency differences based on different variables. For this purpose, we further cleaned the data sets to include only those people with at-least 9 recognizable patterns. In Data set 3, CP cases that were reported as unknown (n=3) were removed from the analysis. For dissimilarity scores and ridge count analysis, we included only those subjects with recognizable patterns and ridge counts on all 10 fingers. The final sample sizes for the different analyses and data sets are presented in Table 6.

Table 6: Sample Sizes for Analyses and Data Sets

Analysis	Data Set 1: All Cleft types	Data Set 2: CL/P	Data Set 3: CP only
Pattern frequency	1502	1228	570
Dissimilarity score and Ridge count	1426	1158	548

3.3 PATTERN DATA

3.3.1 IDENTIFYING COMMON PATTERNS ON CERTAIN DIGITS

As shown in Table 7 for data set 1, we observed that certain patterns occur more commonly on certain fingers. To show this, Table 7 is color coded as follows. For each digit, red represents those patterns that are lower in percentage than the overall percentage of that pattern and green represents patterns that have a higher percentage than the overall percentage of that pattern. For example, for cases in Hungary, the overall percentage of arches is 6%. Each digit that is over 6% shows a relative increase in arches and is colored green.

For cases, TC, and UFM from both Hungary and Pittsburgh, arches occur more frequently on the 2^{nd} and 3^{rd} digits while whorls occur more commonly on the 1^{st}, 2^{nd} and 4^{th} digits. Loops occur more often on the 3^{rd} and 5^{th} digits when compared to other patterns. There are only three instances in which the left and right hand differ, and they all occur in the case group. In Hungary, arches occur more commonly on the left thumb, but less on the right, and whorls occur more commonly the right index finger, but less on the left. In Pittsburgh, arches are more common on the left middle finger, but less on the right. Similar results were found for data sets 2 and 3.

Table 7: Pattern Distribution across Ten Fingers for Data Set 1 – All Cleft Types

				Digit 1		Digit 2		Digit 3		Digit 4		Digit 5	
Aff	Site	Type	Overall	R1	L1	R2	L2	R3	L3	R4	L4	R5	L5
Case	Hungary	Arch	6%	1%	7%	14%	11%	9%	9%	1%	4%	1%	2%
		Loop	63%	50%	47%	48%	59%	74%	71%	56%	58%	82%	84%
		Whorl	31%	49%	46%	38%	30%	17%	20%	43%	38%	17%	14%
	Pittsburgh	Arch	6%	4%	4%	9%	13%	6%	12%	4%	4%	2%	2%
		Loop	65%	46%	63%	52%	54%	79%	70%	48%	58%	86%	84%
		Whorl	29%	51%	33%	39%	33%	15%	17%	49%	38%	11%	14%
TC	Hungary	Arch	5%	1%	2%	13%	14%	10%	7%	2%	4%	0%	2%
		Loop	67%	52%	58%	55%	56%	76%	79%	55%	58%	85%	84%
		Whorl	29%	47%	41%	33%	30%	15%	15%	43%	38%	15%	14%
	Pittsburgh	Arch	6%	2%	4%	13%	13%	6%	9%	2%	4%	3%	2%
		Loop	67%	49%	60%	60%	60%	79%	75%	56%	58%	86%	84%
		Whorl	27%	50%	36%	27%	28%	14%	16%	42%	38%	11%	14%
UFM	Hungary	Arch	5%	3%	4%	12%	12%	6%	10%	2%	4%	1%	2%
		Loop	65%	52%	62%	51%	53%	76%	68%	54%	58%	84%	84%
		Whorl	30%	46%	34%	38%	35%	18%	22%	44%	38%	15%	14%
	Pittsburgh	Arch	6%	2%	4%	11%	9%	9%	10%	6%	4%	2%	2%
		Loop	72%	60%	64%	65%	62%	79%	77%	60%	58%	89%	84%
		Whorl	22%	38%	32%	24%	29%	11%	13%	34%	38%	8%	14%

(AFF: Affection status; TC: True control; UFM: Unaffected family member)

3.3.2 PATTERN TYPES AND CLEFTING

i. Based on the Variable- Site:

Tables 8-10 show the results from the Chi square analysis that was done to test the differences in the frequencies of patterns (arch, loop, and whorl) across the 5 sites for data sets 1 – 3, respectively. All percentages are rounded off to the nearest integer. In both data sets 1 and 2, Hungary and Patagonia showed higher frequency of whorls while Madrid showed a higher frequency of arches. Pittsburgh, Texas and Madrid seem to have a higher frequency of loops (p value <0.0001 in both data sets). In data set 3, CP only, Hungary, Madrid and Patagonia had an increased frequency of whorls while Madrid showed a decreased frequency of arches. Loops were increased in Texas and Madrid (p value= 0.0003).

Table 8: Distribution of Arch, Loop and Whorl across 5 Sites. Data Set 1 – All Cleft Types

Site	Arch		Loop		Whorl		Total
Hungary	359	5%	4352	65%	1994	30%	**6705**
Pittsburgh	275	6%	3133	69%	1151	25%	**4559**
Texas	111	6%	1323	68%	501	26%	**1935**
Madrid	107	9%	847	73%	207	18%	**1161**
Patagonia	20	4%	306	61%	178	35%	**504**
TOTAL	**872**	**6%**	**9961**	**67%**	**4031**	**27%**	**14864**

(χ^2 =118.0008, p value < 0.0001)

Table 9: Distribution of Arch, Loop and Whorl across 5 Sites. Data Set 2 – CL/P

Site	Arch		Loop		Whorl		Total
Hungary	263	5%	3413	64%	1627	31%	**5303**
Pittsburgh	215	6%	2524	69%	924	25%	**3663**
Texas	108	6%	1210	67%	478	27%	**1796**
Madrid	104	11%	679	74%	139	15%	**922**
Patagonia	19	4%	282	61%	164	35%	**465**
TOTAL	**709**	**6%**	**8108**	**67%**	**3332**	**27%**	**12149**

(χ^2 = 161.7887, p value < 0.0001)

Table 10: Distribution of Arch, Loop and Whorl across 5 Sites. Data Set 3 – CP only

Site	Arch		Loop		Whorl		Total
Hungary	156	6%	1750	67%	713	27%	**2619**
Pittsburgh	161	6%	1763	67%	698	27%	**2622**
Texas	3	2%	109	84%	17	13%	**129**
Madrid	3	1%	168	70%	68	28%	**239**
Patagonia	1	3%	24	62%	14	36%	**39**
TOTAL	**324**	**6%**	**3814**	**68%**	**1510**	**27%**	**5648**

(χ^2= 29.4416, p value = 0.0003)

Thus, we conclude that pattern frequencies differ by site.

ii. Based on the Variable-Sex:

Without taking affection status and site differences into account, we analyzed the distribution of pattern frequencies by sex. Our results show that there is an increased frequency of whorls in males in data set 1 (p value= 0.0002) and in data set 2 (p value=0.0245). In data set 3, CP only, however this difference is not statistically significant (p value=0.2413). This is presented in tables 11-13.

Table 11: Distribution of Arch, Loop and Whorl by Sex. Data Set 1: All Cleft Types

	Arch		Loop		Whorl		Total
Females	499	6%	5379	68%	2050	26%	**7928**
Males	373	5%	4582	66%	1981	29%	**6936**
Total	**872**	**6%**	**9961**	**67%**	**4031**	**27%**	**14864**

(χ^2 = 17.0284, p value= 0.0002).

Table 12: Distribution of Arch, Loop and Whorl by Sex. Data Set 2: CL/P

	Arch		Loop		Whorl		Total
Females	398	6%	4339	67%	1710	27%	**6447**
Males	311	5%	3769	66%	1622	28%	**5702**
Total	**709**	**6%**	**8108**	**67%**	**3332**	**27%**	**12149**

(χ^2 = 7.4143, p value= 0.0245)

Table 13: Distribution of Arch, Loop and Whorl by Sex. Data Set 3: CP Only

	Arch		Loop		Whorl		Total
Females	193	6%	2235	68%	845	26%	**3273**
Males	131	6%	1570	67%	655	28%	**2356**
Total	**324**	**6%**	**3805**	**68%**	**1500**	**27%**	**5629**

(χ^2 = 2.8432, p value= 0.2413)

Thus, we conclude that pattern frequencies in data sets 1 and 2 differ based on sex.

iii. Based on the Variable-Affection Status, by Site and Sex:

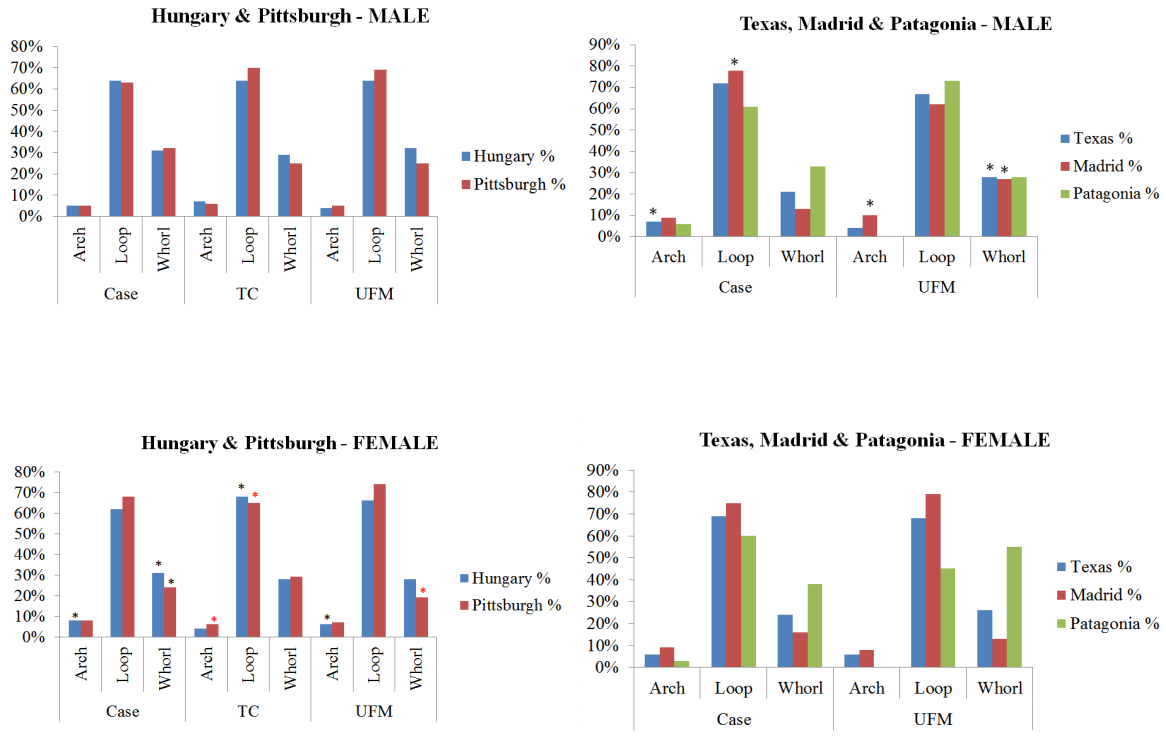
Based on the above results, we analyzed the pattern frequencies by affection status (case, UFM, and TC), accounting for the differences in site and sex. This was done by running separate chi-square analyses for each site and sex, resulting in 10 analyses for each data set.

The results are represented graphically in Figure 5. Statistically significant results are represented by an asterisk on the bars. The black asterisk represents a significant increase in frequency of a pattern and the red represents a significant decrease.

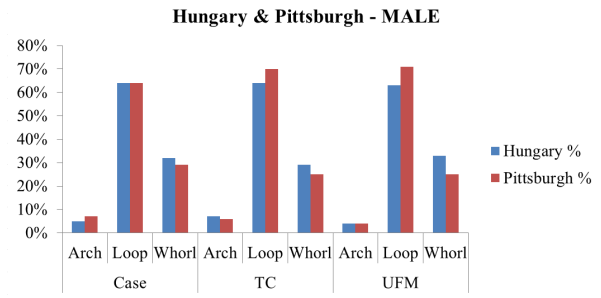
Figure 5: Distribution of Arches, Loops &Whorls in Males and Females in all 3 Data Sets

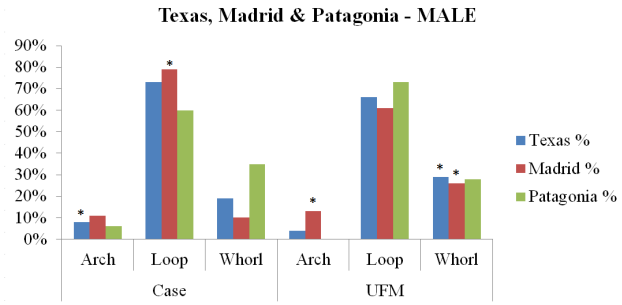
[TC: True control (Control group 1); UFM: Unaffected family member (Control group 2)]

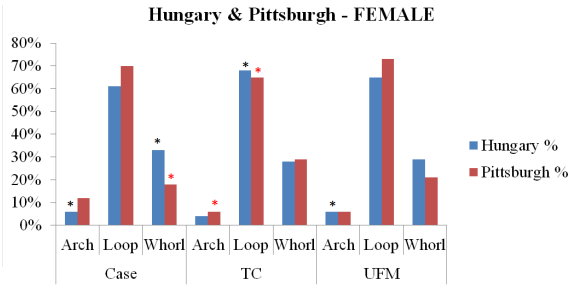
Data Set 1: All Cleft Types

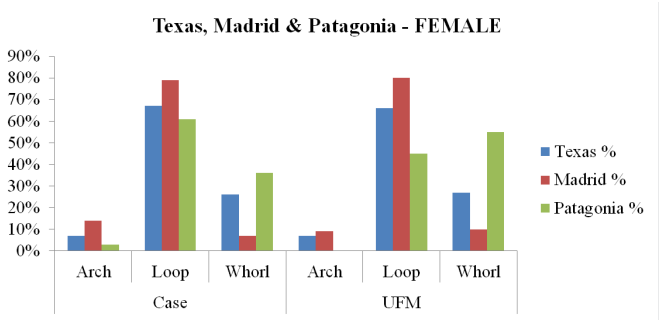


Data Set 2: CL/P

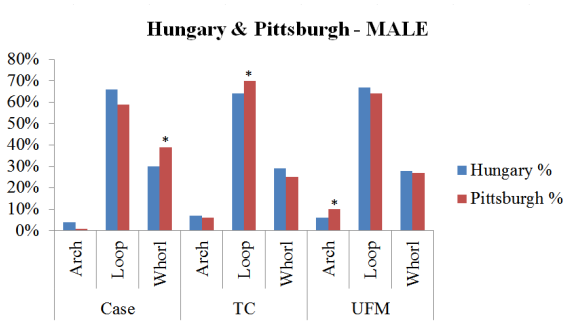


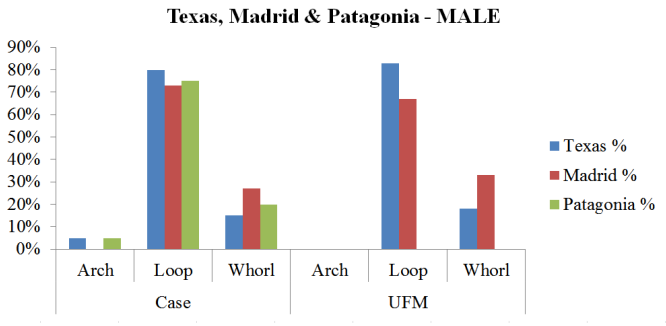


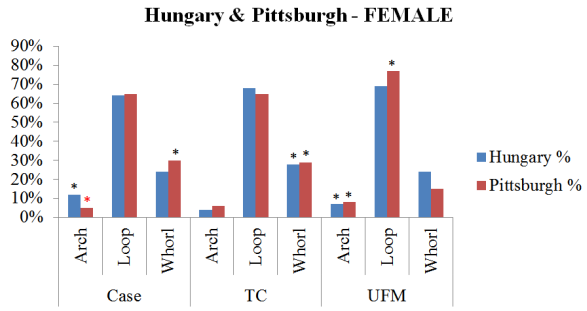


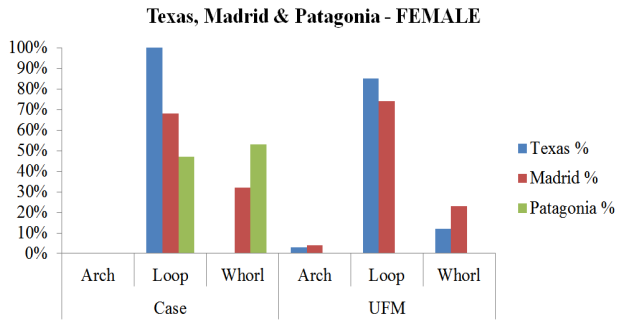


Data set 3: CP Only









The p values for the significant results are presented in Table 14.

Table 14: Significant P Values for Pattern Frequency Diff. by Site, Sex & Affection Status

	Data Set 1: All Cleft types	Data Set 2: CL/P	Data Set 3: CP only
Females	**Hungary*:** 0.0066 **Pittsburgh*:** <0.0001	**Hungary*:** 0.0401 **Pittsburgh*:** <0.0001	**Hungary*:** 0.0002 **Pittsburgh*:** 0.0001
Males	**Madrid**:** 0.0004 **Texas**:** 0.0088	**Madrid**:** 0.0002 **Texas**:** 0.0032	**Pittsburgh*:** 0.0002

*Included cases, TC and UFM, a 3x3 chi square test with 4 degrees of freedom (df)

** Included cases and UFM, a 3x2 chi square test with 2 df

Table 15 below, summarizes the significant differences in the pattern frequencies by site and sex.

Table 15: Summary of Pattern Frequency Differences among Cases, TC and UFM

15.a Females:

Site		Data Set 1			Data Set 2			Data Set 3		
		A	L	W	A	L	W	A	L	W
Hungary	**Cases**	↑	↓	↑	↑	↓	↑	↑	↓	(↓)
	TC	↓	↑	(↓)	↓	↑	(↓)	↓	(↑)	↑
	UFM	↑	↑	(↑)	↑	(↓)	(↑)	↑	↑	↓
Pittsburgh	**Cases**	↑	↓	(↑)	↑	(↑)	↓	(↓)	↓	↑
	TC	(↓)	↓	↑	↓	↓	↑	(↓)	↓	↑
	UFM	(↑)	↑	↓	(↓)	↑	↓	↑	↑	↓

( ) indicates marginal increase or decrease in frequency

(A=Arch, L=Loop, W=Whorl)

In data sets, 1 and 2, among females in Hungary, arches and whorls are increased among cases and UFM compared to TC. Loops were decreased. This was more pronounced in cases than in UFM. By contrast, in Pittsburgh, loops were increased in cases and UFM and whorls decreased, compared to TC. Arches also increased in cases compared to TC. Note that TC in Pittsburgh has a decreased frequency of loops, which is in contrast to what is found in Hungary. In data 3, CP only, among females, cases and UFM had an increased frequency of arches and TC had an increased frequency of whorls in Hungary. In Pittsburgh, there was a slight decrease in the frequency of arches among cases and an increase in whorls. UFM had an increase in the frequency of arches and loops while the TC exhibited an increase in frequency of whorls.

15.b: Males:

Site		Data Set 1			Data Set 2			Data Set 3		
		A	L	W	A	L	W	A	L	W
Madrid	Cases	↓	↑	↓	↓	↑	↓			
	UFM	↑	↓	↑	↑	↓	↑			
Texas	Cases	↑	↑	↓	↑	↑	↓			
	UFM	↓	↓	↑	↓	↓	↑			
Pittsburgh	Cases							↓	↓	↑
	TC							↓	↑	↓
	UFM							↑	↓	↓

( ) indicates marginal increase or decrease in frequency

(A=Arch, L=Loop, W=Whorl)

For data sets 1 and 2, for males in Texas, the frequency of arches increased and the frequency of whorls decreased among cases compared to UFM. Loops were slightly elevated. In Madrid, frequency of loops increased and whorls decreased in cases compared to UFM.

For data set 3, male cases in Pittsburgh had an increase in frequency of whorls and unaffected relatives had an increase in frequency of arches. TC had an increase in frequency of loops.

We must remember that the occurrence of arches, loops, and whorls on the digits are not independent of each other and hence an increase/decrease in two patterns impacts the frequency of the third pattern.

iv. Pattern Types in Non-syndromic CL/P:

For data set 2, among cases, the distribution of pattern types was analyzed based on the cleft types, which yielded statistically significant results reported below in Table 16.

Table 16: Distribution of Patterns Based on Cleft types among Cases.

(LCL/P: left cleft lip; RCL/P: right cleft lip; Bilateral: bilateral cleft lip/palate)

	Arch		Loop		Whorl		Total
LCL/P	80	5%	992	66%	433	29%	**1505**
RCL/P	36	6%	441	68%	174	27%	**651**
Bilateral	73	10%	475	64%	192	26%	**740**
Total	**189**	**7%**	**1908**	**66%**	**799**	**28%**	**2896**

(χ^2 = 19.333, p value = 0.0007)

We find an increase in frequency of whorls in cases with unilateral cleft lip on the left side and an increase in frequency of arches in cases with bilateral cleft lip. This analysis does not consider site or sex differences in the sample.

Based on our previous analysis on pattern types, however, we know that pattern types differ by site and sex. Hence, we further analyzed the distribution of pattern types among cases based on differences in site and sex. Table 17 shows the distribution of the pattern frequencies by site and sex. Table 18 presents the significant p values from the chi square analysis of the same, and Table 19 summarizes the significant results.

Table 17: Distribution of Arch, Loop and Whorl among Cases by Site and Sex in CL/P

		LCL/P						RCL/P						BILATERAL					
Site	**Sex**	**Arch**		**Loop**		**Whorl**		**Arch**		**Loop**		**Whorl**		**Arch**		**Loop**		**Whorl**	
Hungary	**Female**	12	4%	179	61%	104	35%	11	9%	86	73%	21	18%	9	9%	47	47%	44	44%
	Male	15	5%	296	63%	98	32%	6	4%	96	60%	58	36%	10	6%	114	65%	52	30%
Pittsburgh	**Female**	9	15%	48	80%	3	5%	4	13%	18	60%	8	27%	6	9%	44	65%	18	26%
	Male	6	3%	116	64%	58	32%	1	2%	34	69%	14	29%	13	17%	48	62%	17	22%
Madrid	**Female**	2	4%	42	84%	6	12%	0	0%	26	96%	1	4%	13	43%	17	57%	0	0%
	Male	13	15%	69	78%	6	7%	0	0%	31	78%	9	23%	3	15%	17	85%	0	0%
Patagonia	**Female**	3	4%	39	56%	28	40%	2	4%	35	76%	9	20%	0	0%	23	77%	7	23%
	Male	7	6%	71	60%	40	34%	1	2%	30	61%	18	37%	6	8%	46	58%	27	34%
Texas	**Female**	2	3%	53	67%	24	30%	6	20%	15	50%	9	30%	1	5%	18	90%	1	5%
	Male	6	4%	98	72%	33	24%	3	8%	28	70%	9	23%	11	14%	61	76%	8	10%
Total		75	5%	911	66%	400	29%	34	6%	399	68%	156	26%	72	11%	435	64%	174	26%

Table 18: Significant Results from the Chi Square Analysis of Pattern Distribution among Cases by Site and Sex

	Site	**Data Set 2: CL/P**
Females	Hungary Pittsburgh Madrid Texas	$p<0.0001$ $p=0.0137$ $p<0.0001$ $p<0.0001$
Males	Pittsburgh Madrid Texas	$p=0.0025$ $p=0.0017$ $p=0.0027$

Both female and male cases from several sites show a significant difference in the distribution of patterns. For females in Hungary, there is a significant decrease in the frequency of whorls among cases with right CL/P. In Pittsburgh, the frequency of whorls is significantly decreased among cases with left CL/P. In Madrid, frequency of arches was significantly increased among cases with bilateral CL/P. In Texas, frequency of arches was significantly increased among cases with Bilateral CL/P.

For males, in Pittsburgh, there was a significant increase in the frequency of arches and decrease in the frequency of whorls in cases with Bilateral CL/P. In Madrid, the frequency of arches increased significantly in cases with left CL/P and there were no whorls in cases with Bilateral CL/P. In Texas, significant increase was seen in the frequency of arches in the cases with bilateral CL/P and decrease in whorls among cases with right CL/P.

Table 19: Summary of the Distribution of Patterns among CL/P Cases

		LCL/P			RCL/P			BILATERAL		
		A	L	W	A	L	W	A	L	W
Females	Hungary	↓	↓	↑	↑	↑	↓	↑	↑	↓
	Pittsburgh	↑	↑	↓	↑	↓	↓	↓	(↓)	↑
	Madrid	↓	↑	(↓)	-**	↑	↓	↑	↓	↑
	Texas	↓	(↑)	↑	↑	↓	(↑)	(↓)	↑	↓
Males	Pittsburgh	↓	(↓)	↑	(↓)	↑	↓	↑	(↓)	↓
	Madrid	↑	(↓)	↓	-**	(↓)	↑	(↑)	↑	-*
	Texas	↓	↓	↑	(↓)	(↑)	↓	↑	↑	↓

-*: there are no whorls in Bilateral CL/P cases among males in Madrid.

-**: there are no arches in RCL/P among males and females in Madrid

( ) indicates marginal increase or decrease in frequency

(Left CL/P (LCL/P), Right CL/P (RCL/P) and Bilateral CL/P (Bilateral))

When bilateral CL/P was removed from this analysis and chi-square analysis was re-run to analyze the pattern frequency differences between LCL/P and RCL/P, there were no significant results. Sample sizes get small when we split by site and sex and so these results must be taken very carefully.

3.3.3 PATTERN ASYMMETRY

Table 20 shows the mean dissimilarity scores for the three data sets and the 5 sites.

For data set 1, all cleft types, the t test results are as follows:

a) For Hungary and Pittsburgh, the cases and TC differed significantly in their pattern asymmetry. ($p=0.0158$)
b) For all 5 sites, cases and UFM differed significantly in their pattern asymmetry ($p=0.0053$)
c) The results from the regression analysis of all 5 sites, accounting for differences in sex showed that cases and UFM differed significantly in their pattern asymmetry ($p=0.0069$), and between males and females ($p=0.0473$).
d) Males had a higher asymmetry than females (μ: 1.23 vs μ:1.07)

No significant results at $p<0.05$ were found for data sets 2 and 3, although for data set 2, results were marginally significant at a p value of 0.059 between cases and UFM.

Table 20: Mean Dissimilarity Scores by Site in 3 data sets

	Data Set 1: All Cleft Types			Data Set 2: CL/P			Data Set 3: CP Only		
Site	**Case**	**TC**	**UFM**	**Case**	**TC**	**UFM**	**Case**	**TC**	**UFM**
Hungary	**1.3025**	**1.0583**	**1.1597**	**1.231**	**1.058**	**1.175**	**1.477**	**1.058**	**1.115**
Pittsburgh	**1.3086**	**1.1214**	**1.0396**	**1.319**	**1.121**	**0.993**	**1.333**	**1.121**	**1.161**
Madrid	**1.0000**	**-NA-**	**0.9000**	**0.920**	**-NA-**	**0.954**	**1.222**	**-NA-**	**0.667**
Patagonia	**1.2439**	**-NA-**	**1.0000**	**1.237**	**-NA-**	**1.000**	**1.333**	**-NA-**	**-***
Texas	**1.2326**	**-NA-**	**1.0395**	**1.256**	**-NA-**	**1.049**	**0.667**	**-NA-**	**0.900**

-* no UFM with 10 recognizable patterns

[TC: True controls, Hungary and Pittsburgh, UFM: Unaffected family members of cases]

3.4 RIDGE COUNTS

Tables 21 and 22 show the mean ARC and the mean TRC for the 3 data sets and 5 sites. For data set 1, results from the t-test analysis for ridge count analysis of all 5 sites was statistically significant only in Patagonia with a p value of 0.0434 (ARC analysis) and 0.0157 (TRC analysis). All other p values were not statistically significant.

No significant results were found for data sets 2 and 3.

Table 21: Mean and Standard Deviations: ARC

		Data Set 1: All Cleft Types			Data Set 2: CL/P			Data Set 3: CP only		
Site		**Case**	**TC**	**UFM**	**Case**	**TC**	**UFM**	**Case**	**TC**	**UFM**
Hungary	**n**	**160**	**119**	**369**	**115**	**119**	**273**	**44**	**119**	**96**
	Mean	**170.31**	**171.14**	**173.92**	**176.08**	**171.13**	**178.68**	**154.39**	**171.13**	**160.36**
	SD	**82.98**	**71.28**	**79.21**	**87.28**	**71.28**	**80.11**	**69.88**	**71.28**	**75.36**
Pittsburgh	**n**	**77**	**164**	**194**	**43**	**164**	**139**	**33**	**164**	**55**
	Mean	**177.82**	**168.48**	**164.23**	**169.88**	**168.48**	**168.58**	**188.94**	**168.48**	**153.24**
	SD	**73.15**	**78.99**	**75.77**	**74.15**	**78.99**	**76.34**	**72.52**	**78.99**	**73.86**
Madrid	**N**	**35**	**0**	**81**	**26**	**0**	**66**	**9**	**0**	**15**
	Mean	**138.69**	**-NA-**	**143.75**	**122.42**	**-NA-**	**137.68**	**185.67**	**-NA-**	**170.47**
	SD	**63.33**	**-NA-**	**76.38**	**60.55**	**-NA-**	**72.71**	**47.40**	**-NA-**	**88.62**
Patagonia	**n**	**37**	**0**	**5**	**34**	**0**	**5**	**3**	**0**	**0**
	Mean	**171.89**	**-NA-**	**250.80**	**172.91**	**-NA-**	**250.8**	**160.33**	**-NA-**	**-NA-**
	SD	**80.01**	**-NA-**	**73.56**	**83.02**	**-NA-**	**73.56**	**36.14**	**-NA-**	**-NA-**
Texas	**n**	**39**	**0**	**146**	**36**	**0**	**138**	**2**	**0**	**8**
	Mean	**137.38**	**-NA-**	**156.70**	**133.83**	**-NA-**	**157.25**	**160.5**	**-NA-**	**147.25**
	SD	**69.64**	**-NA-**	**76.61**	**70.31**	**-NA-**	**77.77**	**55.86**	**-NA-**	**55.58**

Table 22: Mean and Standard Deviations: TRC

		Data Set 1: All Cleft Types			Data Set 2: CL/P			Data Set 3: CP Only		
Site		**Case**	**TC**	**UFM**	**Case**	**TC**	**UFM**	**Case**	**TC**	**UFM**
Hungary	**n**	160	119	369	115	119	273	44	119	96
	Mean	131.51	136.36	136.16	134.65	136.36	138.84	122.68	136.36	128.56
	SD	46.91	41.35	45.66	47.78	41.35	45.45	44.29	41.35	45.65
Pittsburgh	**n**	77	164	194	43	164	139	33	164	55
	Mean	142.43	134.77	135.53	139.05	134.77	138.63	146.91	134.77	127.71
	SD	46.38	47.91	48.94	51.40	47.91	47.63	40.06	47.91	51.73
Madrid	**N**	35	0	81	26	0	66	9	0	15
	Mean	122.97	-NA-	120.73	111.19	-NA-	116.67	157	-NA-	138.6
	SD	45.85	-NA-	51.27	45.35	-NA-	51.87	27.46	-NA-	45.95
Patagonia	**n**	37	0	5	34	0	5	3	0	0
	Mean	129.78	-NA-	184	124.79	-NA-	184	129.67	-NA-	-NA-
	SD	45.64	-NA-	39.62	47.31	-NA-	39.62	23.54	-NA-	-NA-
Texas	**n**	39	0	146	36	0	138	2	0	8
	Mean	112.49	-NA-	124.44	109.53	-NA-	123.94	144	-NA-	133
	SD	44.42	-NA-	44.53	44.64	-NA-	44.78	32.53	-NA-	41.57

4.0 DISCUSSION

We performed qualitative and qualitative dermatoglyphic analyses of non-syndromic clefting on 1550 individuals from 5 sites from the POFC study. Owing to differences between CL/P and CP, we felt it was important to look at 3 different data sets — an all cleft type data set and CL/P separately from CP only. The frequencies of fingerprint patterns (arch, loop and whorl) differ between our 5 sites and between males and females. Thus, after accounting for these differences, we observed several notable trends between cleft status and pattern types. In females in both Hungary and Pittsburgh, we observed pattern frequency differences in all 3 data sets, while in males differences were observed in Madrid and Texas for data sets 1 and 2 and in Pittsburgh for data set 3. Because non-syndromic CL/P is the most common cleft type that has been analyzed with respect to fingerprints, we also examined cleft types in more detail in data set 2 and found pattern frequency differences between left, right and bilateral CL/P for females from all sites except Patagonia and for males in Pittsburgh, Madrid and Texas.

All 5 sites had both cases and UFM but 2 sites (Hungary and Pittsburgh) also had a 3rd group of genetically unrelated true controls. Thus, we ran some of our analyses differently for Hungary and Pittsburgh, compared to Madrid, Texas, and Patagonia. We had a fairly large sample size of 1550 individuals. Since every individual has 10 fingerprints, this resulted in a sample of 15,500 fingerprints. Even so, some of the sample sizes became small in data set 3 (CP

only) and when we had to split down by sub-divisions, for example bilateral versus unilateral cleft lip. For most of our analyses, we followed what has been done in previous research by treating the fingerprints as independent, although clearly they are not, because 10 prints come from one individual. Cases and UFM came from the same families, so they showed a genetic relationship, which is another deviation from the assumption of independence.

Other groups have reported that unaffected relatives of CL/P cases may exhibit differences in their pattern frequencies from true controls (Weinberg et al., 2001; Ward et al., 2002). Thus, any variation in the expression of the trait among the unaffected family members may fall in the range between the cases and the true controls. This difference may be attributed to certain alleles responsible for clefting that segregate within families (Marazita and Neiswanger, 2002).

- **Pattern Type Frequencies and Clefting**

Table 23 summarizes the results of our analyses of pattern type frequencies from Tables 13 and 14 for data set 2, non-syndromic CL/P. It also includes information on sample sizes to facilitate comparison to literature. The ( ) in some of the cells in the table indicate marginally significant increase or decrease in frequency.

Table 23: Summary of Pattern Frequency Differences by Site and Sex for Non-syndromic CL/P in the POFC Study

S.No	Site / Population	Study Groups	N	Arch	Loop	Whorl
1	Hungary	Cases	118			
		M	66			
		F	52	↑	↓	↑
		UFM	295			
		M	132			
		F	163	↑	↓	(↑)
		TC	124			
		M	47			
		F	77			
2	Pittsburgh	Cases	47			
		M	31			
		F	16	↑	(↑)	↓
		UFM	148			
		M	66			
		F	82		↑	↓
		TC	175			
		M	67			
		F	108			
3	Madrid	Cases	26			
		M	15		↑	↓
		F	11			
		UFM	67			
		M	31			
		F	36			
4	Texas	Cases	39			
		M	26	↑	(↑)	↓
		F	13			
		UFM	142			
		M	66			
		F	76			
5	Patagonia	Cases	41			
		M	25			
		F	16			
		UFM	6			
		M	4			
		F	2			

Table 24 summarizes the statistically significant findings ($p<0.05$) in the pattern frequency differences from other studies of non-syndromic CL/P. We included all information available from their studies. For example, in study number 1, Balgir in 1993 reported that the frequency of loops was increased and frequency of whorls decreased in cases relative to the controls, but did not include information on sex.

Table 24: Summary of Literature on Fingerprint Pattern Frequencies and CL/P

S.No	Site / Population	Study Groups	N	Arch	Loop	Whorl	References
1	Indian	Cases	52		↑	↓	Balgir, 1993
		Controls	50				
2	Chinese	Cases	500				Neiswanger et al, 2002
		M	320				
		F	180				
		Unaffected Relatives	421				
		M	**210**		↓ (Ulnar)*	↑	
		F	211				
		Controls	66				
		M	37				
		F	29				
3	Chinese	Cases			↑ (Radial)*		Scot et al, 2005
		M	299				
		F	157				
		Unaffected Relatives					
		M	46				
		F	118				
	Filipino	Cases	**97**		↑ (Ulnar)*		
		M	66				
		F	31	↑**		↓**	
		Unaffected Relatives	90				
		M	33				
		F	57				
4	Iran	Parents of Cases	90				Jahanbin et al, 2010
		M	45	↑			
		F	45	↑		↓	
		Parents of Controls (M+F)	90				
5	Indian	Cases	45		↑	↓	Maheshwari et al, 2013
		Controls	45				
6	Indian	Cases	48	↑	↑		Saxena et al, 2013
		Controls	50				
		Parents of Cases	96	↑	↑		
		Parents of Controls	100				

*This result is significant only for the type of loop provided (ulnar /radial)

** Arches are increased and whorls are decreased in both cases and unaffected relatives in the Filipino sample, relative to other studies in the literature.

From our study, we observe that males and females differ in the distribution of their pattern frequencies. Affected females and their unaffected relatives in Hungary and Pittsburgh have more arches compared to true controls. This corresponds with other studies conducted by Scott et al, 2005, Jahanbin et al, 2010 and Saxena et al, 2013. Among males from Madrid and Texas, cases have a lower frequency of whorls than unaffected family members do. This agrees with the findings of Neiswanger et al in 2002.

We do not see consistencies even in the literature. With an exception of Neiswanger et al, 2002, who had a larger sample of UFM compared to controls, most of the studies showed that loops increased among cases and whorls decreased. Arches increased among cases and unaffected relatives. Most of our data is consistent with this, except in Hungary females, where loops are decreased and whorls are increased.

Looking at CL/P cases in more detail, we see that the type of cleft—left, right or bilateral—may influence these results. For example, arches are increased in bilateral CL/P as compared to left and right CL/P. Between unilateral left and right CL/P there are pattern frequency differences. We see these differences across males and females as well as in multiple ethnic groups. Thus, these results justify why we perform our analyses by site and sex.

Embryological evidence suggests that whorls manifest earlier in digit development while arches appear later (Babler, 1991). In congenital abnormalities like autism where there is delay in growth and development, the frequency of arches is found to be increased. (Walker, 1977; Chary et al, 1996). In contrast, Sotos syndrome, a skeletal overgrowth syndrome, has an increase in the frequency of whorls (Gorlin et al, 2001). In our study, we see that arches, which are considered slow developing patterns, are higher in number among cases and the unaffected relatives compared to the controls, thus providing an indirect suggestion of a developmental delay.

- **Pattern Asymmetry**

  As clefting has been described previously as a developmental disturbance and we are studying its association with fingerprint patterns, we could speculate that more pattern dissimilarity might exist among the cases when compared to their unaffected relatives and true controls.

  Our group did not find any significant differences at $p<0.05$ between cases, UFM and TC in the CL/P data set. However, there is a trend for increased pattern asymmetry in cases (mean= 1.22) over UFM (mean =1.08) in all 5 sites, although this is only marginally significant at a p value of 0.0599. When we ran the same analysis in our data set 1, all cleft types, this trend became significant at $p=0.0053$. Referring to Table 20, we see that cases in CP group (data set 3) have higher mean dissimilarity scores, which may be contributing to the increase in the significance in data set 1.

For data set 1 in the sites that had true controls, Hungary and Pittsburgh, we found that cases and true controls differed significantly with respect to their pattern asymmetry ($p = 0.0158$). Since we had significant differences between cases and UFM, we included sex differences. The results of our regression analysis showed that pattern asymmetry not only differed between cases and UFM ($p = 0.0069$) but also that, males in general, (mean = 1.203) had more asymmetry compared to females (mean= 1.071), with a significant p value of 0.0473.

When we look at the literature, we see that Woolf and Gianas, 1976 and Kobliansky et al in 1999, have shown that true controls and unaffected relatives of CL/P patients have the same degree of asymmetry. While comparing among cases, Woolf and Gianas also observed that familial cases differed from sporadic cases with regards to their pattern asymmetry. Scott et al in 2005 reported that dissimilarity scores differed between cases and unaffected relatives. Jahanbin et al, 2010 reported that pattern dissimilarity between controls and unaffected relatives was significant among females and not among males. Neiswanger et al in 2002 reported that probands with a positive family history of clefting showed significantly more pattern asymmetry than the probands who had a negative family history (sporadic cases), unaffected relatives or controls.

- **Ridge counts**

Except in Patagonia in data set 1, which is a relatively small sample in our study, we did not find any statistically significant differences in the TRC or ARC between the different cleft statuses for all three data sets. While ARC sums the two values for the

ridges, TRC takes into account only the highest ridge count value for each finger. Arches account for about 6% of entire our data set and whorls, about 27%. Arches do not contribute to TRC since they have no ridge counts. Patagonia has the highest percentage of whorls in our data set (35%) and lowest percentage of loops (61%) when compared to rest of the sites. Probably the larger of the two counts of whorls in Patagonia is larger than the ridge count for the loop, thus contributing to the significance observed in TRC. Our results are consistent with the bulk of the literature in which no differences are observed in TRC and ARC, with an exception of Jahanbin et al, 2010, who found that only females differed in their total ridge counts.

- **Future directions**

Our study is a preliminary analysis of the three pattern types. We find significant differences in pattern frequencies with some consistencies across the literature. One of the biggest strengths of our study is the large sample sizes compared to the other studies in the literature.

More information on the relationships between our variables: site, sex, affection status and cleft types, can be obtained by running a regression analysis, which is in progress. We are also trying to identify the relationship between the laterality in loops, radial and ulnar, and cleft status. In addition, because of the fact that 10 fingers come from the same person, we are trying to find ways to analyze pattern differences taking all 10 fingers into account.

5.0 CONCLUSION

Our results suggest that pattern frequency differences exist across different sites and by sex, based on the cleft status. We further noticed pattern differences between the types of non-syndromic CL/P. Arches were higher in cases and unaffected family members compared to true controls, who are representative of the general population. This difference was more pronounced among females compared to males. Cases had more pattern asymmetry than unaffected family members, who had a higher asymmetry compared to true controls when all cleft types were combined. No significant ridge count differences were observed among the cases, true controls and unaffected family members.

Thus, these results support our hypothesis that individuals with non-syndromic oral clefts may show abnormal dermatoglyphic patterns and/or asymmetries.

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