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CHROMOSOME 18q DELETION SYNDROME: A LIP PHENOTYPES WITH MEDICAL SYNDROMES; A REVIEW STUDY.

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ABSTRACT

Occurrence of structural and the morphological characteristics of lip prints depend upon habitual activities of any individual, exposure of environmental factors, genetic defects, mainly involvement in consumption of illicit drugs/ alcohol. In most of the cases, it has been observed that some abnormalities occur due to genetic factors at the time of birth. Lip phenotyping helps us to determine morphometric features. Cleft lip/cleft palate is one among the craniofacial deformity that affects the phenotype of the lips. Chromosome 18q deletion syndrome is one of the syndromes causing cleft lip and cleft palate. Although aetiology of prints can be examined by ultrasound, amniocentesis yet the conclusion is established based on the affected chromosome with the help of genetic markers. This study is an attempt to find out the effect of chromosome 18q deletion and to determine identity of individual based on phenotyping[1]. It can provide important clue about perpetrator involve in sexual assault cases/homicide cases where saliva/ sweat of an individual is recovered from the deceased body. Palatoscopy helps in determination of personality through palatal rugae with an application of investigative techniques.

KEYWORDS: Lip phenotyping, Chromosome 18q deletion syndrome, Cleft lip, Cleft palate, Genetic markers etc.

INTRODUCTION

Lip phenotyping is one of the methods which helps in the study of morphological characteristics of the lips and helps in the identification of an individual. It has been studied that the shape of lip prints and its features differ based on the race/ gender of individual. Some abnormalities can be caused due to environmental factors, exposure of harmful activities such as alcohol addiction, smoking, consumption of drugs etc. Apart from this, genetic factors also play a major role in affecting the individual with abnormalities along with physical and mental disabilities[2]. The genetic defect is caused by chromosome mutations that includes addition, deletion and duplication. Such kind of mutation may lead to the craniofacial dysplasia's among which is cleft lip and cleft palate. Genetic markers are known as the DNA sequence that helps in the identification of the inherited disease and can link with the responsible gene. Genetic markers that is used for lip phenotyping is denoted as SNP's (Single Nucleotide Polymorphism[3,4]. Genome Wide Association Studies (GWAS) has also conducted a study with the help of SNP's

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genetic markers with the large sample size and also with the help of GWAS the cleft genes have also been discovered. It has also been denoted by the scientists that the cleft genes can also be identified through linkage analysis. Chromosome 18 is one of the chromosomes which consists of two copies in every individual. It consists of 78 million base pairs and represent abouts 2.5% of the total DNA in cells. It consists of 200-300 genes which provides instruction for the production of proteins and helps in performing variety of roles in the body. An occurrence of chromosomal mutation in any part of the chromosome may affect the gene and may lead to congenital abnormalities. Chromosome 18q deletion syndrome is also one of the abnormalities caused by chromosomal mutation known as deletion that occurs in the chromosome 18[5,6].

The below mentioned tabular column depicts some of the other kinds of syndromes, their phenotypes, type of mutation and the gene that undergoes mutation and affected.

TABLE 1.1 – Syndromes and their lip phenotypes along with the types of mutations and the gene responsible for it is mentioned.

SYNDROME	PHENOTYPE	MUTATION	GENE	REFERENCE
Floating Harbor	Narrow-short philtrum	Heterozygous	SRCAP	Patton et.al, 1991
Wiedemann - Steiner	Narrow-short philtrum	Missense	KMT2A	Stellaci et.al,2016
Williams - Beuren	Short philtrum	Deletion	CLIP2, ELN, GTF21, GTF21RD1 & LIMK1	Morris et.al, 2013
Pitt - Hopkins	Flat – Cupid Bow shape	Deletion	TCF4	Giuseppe Marangi & Marcella Zolino, 2015
Miller - Dieker	Narrow-short philtrum	Deletion	PAFAHB & YWHAE	J Q Miller, 1963
Ohdo (X-linked)	Narrow-short philtrum	Missense	MED12	Silfhout et.al, 2013
Kaufman oculocerbrofacial	Narrow-short philtrum	Biallelic	UBE3B	Goldstein et.al, 2016
Mandibulofacial Dysostosis	Thin vermillion	Sporadic	TCOF1, POLR1C & POLR1D	McElrath A D & Winters R, 2022
Geleophysic Dyslapsia	Narrow-short philtrum	Heterozygous	ADAMTSL2	J Spranger et.al, 1984
Prader - Willi	Thin Upper Lip	Deletion	SNRPN & NDN	Genetic Home Reference, 2014

CHROMOSOME 18q DELETION SYNDROME

Chromosome 18q deletion syndrome is also known as Cohen syndrome. It was first discovered by M. Michael Cohen Jr. and his colleagues in the year 1973 by analyzing the patients and after a long study conducted by other scientists it was then confirmed by Carey and Hall in the year 1978. It is an autosomal recessive disorder which is caused by the chromosomal

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mutation in the body. It is caused by a gene name COH1. COH1 is an ortholog of VPS13B protein present in Saccharomyces cerevisiae. Deletion mutation is the observed to the major cause of this syndrome that takes place in homozygous or compound heterozygous state. The COH1 gene consists of various kinds of splice forms and reaches up to 62 exons. It encodes with the protein 4022aa whose domain structure and the similarities presents a role in protein sorting and vesical mediated transport. It has been identified that it consists of two peroxisomal matrix protein targeting signal 2 (PTS2) consensus sequences along with which in contrary to the known peroxisomal proteins with a PTS2 signals are located in the in an atypical position[7]. Twenty-two different types of VPS13B pathogenic genetic variants have been identified in people affected with Cohen syndrome. It denoted that the offspring of an individual is considered to be an obligate heterozygote (carriers).

The deletion of chromosome 18q is also a part of mutation where the chromosome is deleted from its particular location. This deletion may occur due to diseases or even due to exposure to harmful environmental factors as it is not necessary that it should be caused only due to genetic factors. Various kinds of defects are caused and one among them is craniofacial deformities such as cleft lip or cleft palate. It is also identified that the major type of mutation that occurs in the gene are nonsense and frameshift mutations. Genome Wide Association Studies (GWAS) performed a study with large number of samples and classified the features of lip phenotype for different kinds of syndromes[8]. In chromosome 18q syndrome it is known to have a narrow or short philtrum and based on their classification it is identified that most of the individuals consists of smooth – short philtrum or short-upturned philtrum. In some cases, people consist of narrow cleft palate. It has been concluded that the diagnosis of the syndrome is difficult due to the variation that occurs. In some cases, it can be analyzed using ultrasound technique and amniocentesis where the amniotic fluid is removed and tested for the chromosomal abnormality[9]. The ultrasound technique is performed as it consists of non-radiation risk and is also considered as the safest diagnostic tool. It has been observed that the diagnosis of this congenital abnormality is difficult to diagnose especially in infants but can be easily identified during the age of 7yrs to 14yrs which is considered as the schooling age.

IDENTICAL FEATURES OF CHROMOSOME 18Q DELETION SYNDROME IN BODY SITES

The facial dysmorphism is observed with people affected with congenital anomalies. In such cases there are various kinds of identical features that may cause facial dysmorphism. In chromosome 18q deletion syndrome as well-known one of the common facial dysmorphism is cleft lip and cleft palate. These are also differentiated in various kinds. According to studies, during the late infancy or pre-schooling age the individual affected with this syndrome appears to have relatively short philtrum, a small opened mouth along with downturned corners and thick lower lip and marked mentolabial sulcus[10]. At the age of 3yrs to 6yrs, they are appeared to have short philtrum with lower lip thicker. During late childhood or adolescence, they are observed with short philtrum upturned along with maxillary prognathia and open mouth expressions along with the appearance of prominent central incisors. Some may consist of open mouth appearance

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due to short lower lip. In case of palate, a high and narrow palate is observed. A smooth philtrum along with prominent upper central incisors are observed. The appearance of the mouth is unique with a short-upturned philtrum. The upper lip is thin and does not cover up the frontal part of the teeth which gives an open-mouthed appearance. These distinctive features vary from infants and young child affected by this syndrome.

SYNDROMATIC VS NON-SYNDROMATIC CLEFT LIP/PALATE

Apart from cleft lip and palate, people are affected with mental retardation and other physical abnormalities as a part of this syndrome. They face difficulty in communication, feeding, etc. since there is a dependency on a third person. In infants, neonatal feeding problems since they are hypotonic during the first month of life. The facial features are not much evident in infants and appear to be a normal child with mild symptoms whereas a healthy infant appears to be in normal conditions. Children of pre-schooling age face a delay in speech development and are prescribed speech therapy. It is observed that the growth and development of the syndromic individual delays and may face abnormalities in comparison with the non-syndromic people[11,12]. The diagnoses and the prescription of medications should be attentive. The maturity level of the individual will be low when compared with a normal person. Overall, special attention and care along with protection should be given to them along with some psychological guidance when compared with a normal individual.

CLINICAL ASSESSMENT

Based on growth and development, such people attain a slower development and it varies based on the individual. According to National Cohen Syndrome Database (NCSD)[13,14], it has been noted that infants are mostly hypotonic and have difficulty in feeding and breathing during the first phase of their life. They are low birth in weight, short in stature, have slender hand - feet and other musculoskeletal deformities. In cardiac, the left ventricular function is decreased as their age increases and also often meet with other criteria of metabolic syndromes. The valvular and vascular defects are also observed. In ophthalmologic, children at the age of 7yrs are affected with nyctalopia (night blindness) and in young adults, abnormal retinal findings are observed. The most prominent ophthalmic conditions are myopia and retina dystrophy[15]. Prenatal microcephaly is found in the first phase of life and extends till their adulthood. The individuals also suffer from unique facial features such as hypotonic facies, thick eyebrows, eyelashes and hair, low hairline, prominent nasal root, maxillary hypoplasia, micrognathia, face gestalt etc[16,17]. In dentition, the airway seems to be difficult due to upper prominent incisors. During Middle Ages, bull's eye macula is observed in most of the patients. Inability in communicating verbally and seizures have been a neurologic condition in these people. Leukopenia, specifically neutropenia has been observed where the individuals are prone to bacterial infections with neutrophilic leukocytosis. Delayed puberty is also one of the factors and the patients might also have impaired glucose tolerance. Psychologically, they are known to be cheerful and friendly. The individual skills and socialization are less. It has been denoted that majority of the individual fall under moderate to acute range of intellectual disability. Autistic kind of behavior is also observed in the affected individuals. The NCSD has also denoted that the

children are observed to be underweight in childhood and overweight during their adulthood along with truncal obesity. The infants are noticed to have abnormal high pitched and weak cry. Apart from these, many other medical conditions are also observed.

Diagnosis of these conditions can be performed in various methods, whereas there is no particular diagnostic criteria found for chromosome 18q deletion syndrome. Some of the common diagnostic methods are followed for the detection[18]. During the pregnancy, it is considered to be a difficult task in identifying the chromosomal abnormalities. Ultrasound is considered as the safest diagnostic tool as it is a non-radiation technique. An ophthalmologic investigation and absolute neutrophil count (ANC) must be done. The diagnosis in infants is difficult but is easier in young children. In cases of mental retardation in young children, an MRI scan must be performed. Karyotyping along with FISH for sub-telomeric deletion is also recommended for people with Cohen syndrome. A differential white cell counts and electrodiagnostic tests are also considered. On the basis of molecular analysis, various approaches can be followed such as Single Gene Testing, Targeted Analysis and Multigene Panel[19]. Amniocentesis is another way of detection of the chromosome causing abnormality. It is conducted during the pregnancy where the amniotic fluids are removed and tested. These are some of the diagnoses that are recommended.

The individuals can be given treatment based on the particular symptom. A thorough check-up is must and the medications should be followed in a proper manner. The individuals must be given special care and attention. Individual with mental retardation is considered to be more sensitive and must be handled with care. Individuals with walking disability are tend to use wheelchairs and physiotherapy is also prescribed along with walking practice. Speech therapy is prescribed for patients with communication disability. Psychological assistance and counselling are recommended. In some cases, individuals with facial deformities along with cleft lip and palate tend to have surgeries for their appearance. They must undergo multiple surgeries as it cannot be fixed in a single surgery and is also a risk factor along with side effects. Individual affected with ophthalmologic conditions may be prescribe with eye glasses based on their symptoms and may also be recommended for surgeries if possible[20]. An extensive orthodontic and dental surgeries is considered in majority of the cases and some may require orthognathic surgery. A 24/7 medical attention is a must. These are treatments that can be provided to maintain their physical and mental stability.

FORENSIC ASPECTS DURING INVESTIGATION

Lip prints are one of the major types of evidence especially in sexual assault cases. They are recovered in various forms from different surfaces. These lip prints can be latent/patent/static/ half-static etc. The collection of the samples depends upon the form of lip prints and the surface type using various methods along with photography. Lip prints also used for DNA phenotyping. A morphometric analysis can also be performed but in patients affected by the syndrome, the result cannot be accurate as they may develop changes due to therapy and growth[21]. Individuals having cleft lip and palate have a distinctive lip phenotype when compared with the healthy individuals. It is also known that no two palates are identical but a new type of whorl pattern was

identified in children with cleft lip and palate whereas the number of grooves were higher in father's when compared with mother in the upper lip and is other way in lower lip. In this condition, Cheiloscopy is the best technique for the identification of individuals through lip prints and with the help of it the gender can also be identified. In some cases, the individuals also face mental retardation and it makes them ineligible in witnessing or providing statements until there is a presence of third person during the crime and in those situations medical examinations are the best method that is followed.

Palatoscopy helps in the determination of a person's identity whereas an interracial differentiation during palatoscopy can also be determined. Based on the various classifications of palatal rugae, comparison /observations are made for the identification process as they may not change due to growth of an individual. Instead, it may reappear due to any trauma or surgical removal. Palatal rugae, with the combination of measuring points of cleft produces changes in the anterior palate in the patients with cleft palate. It is also emphasized that palatoscopy can be considered as an additional method in cases of crimes and aircraft accidents. However, it is denoted as an adjunctive source of human identification in forensic investigations.

CONCLUSION

It is known that Cohen syndrome is also known as Chromosome 18q deletion syndrome that is caused due to the chromosomal mutation (deletion) by COH1 gene. It causes the various kinds of congenital abnormalities and Cleft lip and palate is one among them. Medical conditions that are caused apart from cleft lip and palate is also mentioned along with the diagnostic procedure and basic treatments. In forensic aspects, lip prints are one of the major types of evidence present in the court of law and are in various forms and surfaces. They play a significant role in human identification. Cheiloscopy and Palatoscopy helps in the study of lip prints and palate for the identification of an individual and with the help of lip prints. DNA phenotyping of lip prints can prove its authenticity in form of evidential value and help to nab the suspected.

CONFLICT OF INTEREST: NA

SOURCE OF FUNDING; NA

ETHICAL CONSENT; NA

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