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Case Report

An Adult Goldenhar Syndrome Patient with a Mosaic Small Supernumerary Marker Chromosome (sSMC) Identified as Ring Chromosome 19

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Abstract: Goldenhar Syndrome (GS), also known as oculoauriculovertebral spectrum (OVAS), is a rare congenital condition characterized by impaired development of structures such as ears, eyes, nose, palate, lip, mandible, maxilla, and teeth. The etiopathogenesis is multifactorial and dependent on genetic and environmental factors, yet the syndrome has many unknowns. We report a case of a 31-year-old male diagnosed clinically with GS as an infant with an absent left ear, hearing loss, absent left lung lobe, reduced growth of left upper limb, decreased size of left face, absent left kidney, and a missing left thumb, who was seen in the genetic clinic for prenatal genetic counseling. A microarray comparative genome hybridization (aCGH) was performed for copy number abnormalities and targeted NGS panels were performed for hereditary hearing loss and limb/digital malformations. aCGH revealed a 471kb loss at 16p12.2 and a mosaic 7.3Mb gain at 19p12q12. Metaphase FISH confirmed the orientation of 19p12q12 gain as small supernumerary ring chromosome 19. NGS revealed multiple variants (*MYH14* c.4001C>T, *PDE1C* c.8C>T, *ADGRV1* c.15502A>G, *CDH23* c.8772C>A, *MYO3A* c.484G>A, *ADAMTS10* c.506G>A, *CHUK* c.1294C>T, *CSPP1* c.1972A>G, and *TCTN2* c.160G>A). Due to the heterogeneous clinical manifestation and genetic heterogeneity of GS, a comprehensive genetic testing strategy is needed for timely diagnosis and better patient care.

Keywords: Goldenhar Syndrome; small supernumerary marker chromosome (sSMC); mosaic ring chromosome 19; 16p12.2 deletions; chromosomal microarray; comparative genomic hybridization; genetic testing

1. Introduction

Goldenhar Syndrome (GS) – oculoauriculovertebral spectrum (OAVS)- is a rare condition that is present at birth. The occurrence ranges from 1 in 3500 to 1 in 5600, and there is a higher prevalence among males compared to females, with a ratio of 3 to 2 [1-4]. It is a unilateral, or bilateral deformity characterized most by impaired development of the eyes, ears, lip, tongue, palate, mandible, maxilla, and teeth [1]. This craniofacial syndrome is also known as 1st and 2nd Branchial Arch Syndrome as it is produced by neural crest migration disturbances resulting in abnormal development of the first and second branchial pouches and occlusion of placental vessels. [4, 5]. These patients have ocular symptoms, auricular symptoms, craniofacial deformities, skeletal abnormalities, and internal organ abnormalities [4, 6, 7, 8, 9]. Due to maxillary and/or mandibular hypoplasia, nearly all GS patients reveal some degree of hemifacial macrosomia (HFM). The majority of patients also suffer from some degree of hearing loss; hence GS patients require an audiological assessment [10]. Additionally, in children with GS, it is also possible to see speech disorders, autistic behaviors, short stature, and delayed psychomotor development [11].

The etiology and pathogenesis of the Goldenhar syndrome are influenced by a combination of genetic and environmental factors, although numerous aspects of the condition remain unexplored. In patients with phenotypic characteristics of GS, chromosomal anomalies support a genetic basis. Beleza-Meireles A, et al. published a review of the aCGH copy number variation loci reported in

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patients with GS and their associated phenotypes [10]. These anomalies include deletions, duplications, and chromosomal rearrangements. Deletion 5p15 (5p15.33-pter), deletions 22q11.2, X chromosome aneuploidies, duplication 14q23.1, mosaicism of trisomy 7, 9, 22 are some of many examples of published chromosomal anomalies in patients with phenotypic characteristics of GS [10]. Additionally, single nucleotide variants (SNVs) by NGS or WES have also been identified in Goldenhar patients. Tingaud-Sequeira A, et al. listed several genes frequently involved in the pathogenesis of GS [12], including *SF3B2*, *MYT1*, *VWA1*, *ZIC3*, *EYA3* and *ZYG11B*. Even though some common molecular markers have been identified, it is expected that the new variants may be identified in GS patients due to heterogenous clinical manifestation and multiple overlapping syndromes.

Small supernumerary marker chromosomes (sSMCs) are structural anomalies whose origins cannot be determined through conventional cytogenetics alone, necessitating molecular approaches. Notably, 70% of sSMCs are of de novo origin, 20% are inherited maternally, and 10% are inherited paternally [13, 14]. The phenotypes associated with sSMCs are extremely variable, from normal to severely abnormal depending on its origin and nature [15]. Approximately 70% of individuals carrying small supernumerary marker chromosomes (sSMCs) exhibit no phenotypic abnormalities. Conversely, the remaining 30% manifest developmental delays, intellectual disabilities, mixed gonadal dysgenesis (MGS), or infertility, with the specific outcome contingent upon the origin of the sSMC [13]. Many of these sSMCs have been reported before the era of DNA microarray technology and thus the nature of these sSMCs were not fully identified.

Our detailed literature review suggests that no GS patient with either 16p12.2 deletion or mosaic ring 19 chromosome has been reported yet. Multiple congenital anomalies and overlapping phenotypes make it difficult for clinicians and healthcare providers to diagnose these patients appropriately without the knowledge of the relationship between phenotype and genotype. It is recommended that the analysis of chromosomal rearrangements using chromosomal microarrays, molecular cytogenetic, and molecular testing should be performed in order to comprehend the complexity of the phenotypes in known syndromes, followed by genetic counseling of the patients and families.

2. Case study and Methods

The proband, a 31-year-old single male from non-consanguineous parents of Italian descent consulted a private ambulatory clinic in Strong Memorial Hospital. He was interested in having children in the future and wished to speak to a geneticist regarding risk to future children.

2.1. Case Presentation

Proband was born after a pregnancy of 34 weeks. The mother experienced excessive bleeding and skull fusion issues during labor and has a history of 4 miscarriages during early pregnancy. He was diagnosed with Goldenhar syndrome as an infant with an absent left ear, absent lung lobe on the left side, reduced growth of left upper limb, decreased size of left face, absent left kidney, and a missing left thumb. His active problem list includes acute gastric volvulus, Goldenhar Syndrome, thrombocytopenia, splenomegaly, testicular cancer, systemic lupus erythematosus, cough, anxiety, long-term use of Plaquenil, latent hypermetropia of both eyes, amblyopia in the left eye, long term use of immunosuppressant medication. He had multiple surgical interventions, such as abdominal surgery, hand surgery, exploration of undescended testis, inguinal hernia repair x2, vesicoureteroreflux surgery, and tonsillectomy. He had no reported history of fine/gross motor delay or learning disability. Facial asymmetry was observed on clinical examination with the right being more dominant than the left, down slanting palpebral fissures and microtia on the left side, and surgically repaired cleft palate. In his upper limb, he was noted to have a left radial anomaly with a short forearm and absent thumb. Cardiac issues include bicuspid aortic valve, premature ventricular contractions, left bundle branch block, and history of pericarditis associated with Lupus. Due to the complex clinical picture, the patient was referred for genetic testing.

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2.2. Methods

DNA was isolated manually using QIAamp DNA Blood mini kit (Qiagen-51106), followed by array comparative genome hybridization to rule out any chromosomal gains and losses. DNA from the patient and normal male reference DNA was digested and labeled with an Agilent DNA labeling kit. Patient DNA was labeled with Cy5 and reference DNA with Cy3. Both DNA were then co-hybridized on SurePrint G3 ISCA Human CGH+SNP Microarray 4x180k arrays (Agilent- G4890A) for 40 hours at 64-68^{0}C in a rotating oven. Array slides were then washed and scanned on SureScan Dx Microarray Scanner (Agilent-G5761A). Array data was extracted using feature extraction software (Agilent, V12.1) and analysis was performed on CytoGenomics software (Agilent, V5.3.014). Genomic copy number changes were identified with the assistance of the Aberration Detection Method 2 algorithm with the sensitivity threshold set at 6.0 and minimum size of 250kb for deletion and duplication. Copy number changes identified in the samples were evaluated by using the UCSC Genome Browser website (http://genome.ucsc.edu) and the Database of Genomic Variants (http://projects.tcag.ca/variation). The array data was analyzed using the annotation GRCh37/hg19. The DECIPHER (http://decipher.sanger.ac.uk/) database was used to support genotype-phenotype correlation.

Peripheral blood samples were cultured using standard cytogenetic methods for 72 h with phytohemagglutinin (PHA) stimulation to yield metaphases. Fluorescence in situ hybridization (FISH) was performed with standard techniques using RP11-141O15 BAC probe (Spectrum Red, Empire Genomics, NY) at 16p12.2 and TelVysion 16p (Spectrum Green, Abbott Laboratories, Des Plaines, IL) at 16PTEL05 (control) confirming the deletion of 16p12.2. BAC probe RP11-359H18 (Spectrum Red, Empire Genomics, NY) at 19p12 and BAC probe RP11-714C4 (Spectrum Green, Empire Genomics, NY) at 19q11 were used to confirm the structural variation, ring chromosome 19.

Targeted next generation sequencing (NGS) was performed at Invitae and Prevention Genetics Reference labs for below panels;

1. Prevention Genetics Hereditary Hearing Loss and Deafness Panel: https://www.preventiongenetics.com/testInfo?val=Hereditary-Hearing-Loss-and-Deafness-Panel

   Invitae Limb and Digital Malformations Panel: https://www.invitae.com/us/providers/test-catalog/test-55010

3. Results

Microarray CGH analysis revealed a 471 kilobase loss at 16p12.2 from 21959891 to 22430592 base pairs encompassing the UQCRC2 gene (Figure 1) and a mosaic 7.3 megabase gain at 19p12-q12 from 22470583 to 29795821 base pairs, likely indicating mosaicism for a small supernumerary ring chromosome 19 (Figure 2).

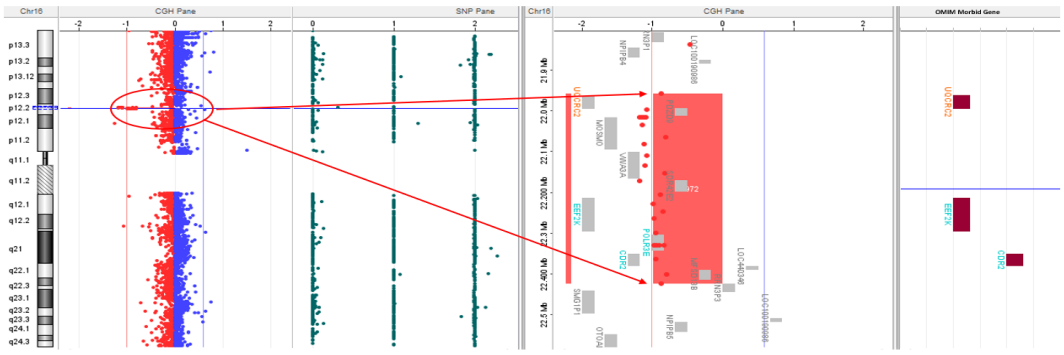

Figure 1. aCGH showing 471 kb deletion in the short arm of chromosome 16 at p12.2 region (21959891-22430592). The deleted region is zoomed in on the right showing *EEF2K*, *POLR3E*, *UQCRC2*, and *CDR* genes.

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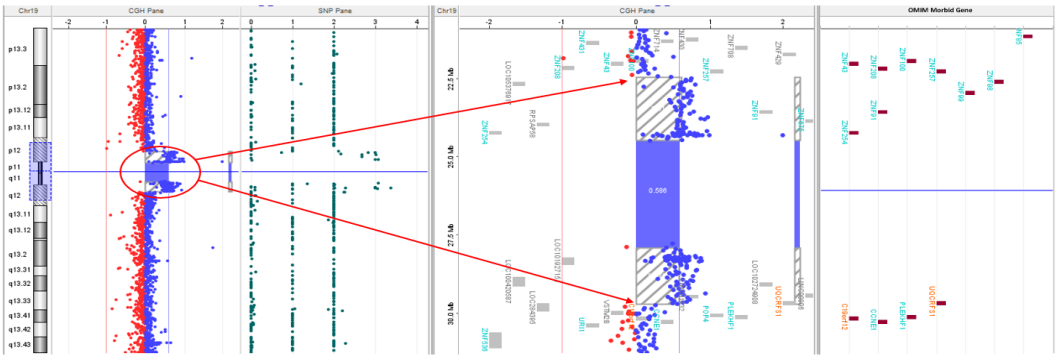

Figure 2. aCGH showing 7.3 Mb duplication extending from 19p12-19q12 (22470583-29795821). The duplicated region is zoomed in on the right showing multiple *ZNF* genes and *UQCRFS1* gene.

Interphase and metaphase FISH confirmed the deletion 16p12.2 (Figure 3) and the duplication 19p12q12 (Figure 4a). In addition, metaphase FISH also confirmed the 19p12q12 duplication was the result of sSRC19 (Figure 4b). The level of mosaicism is approximately 90% on metaphases/reverse DAPI.

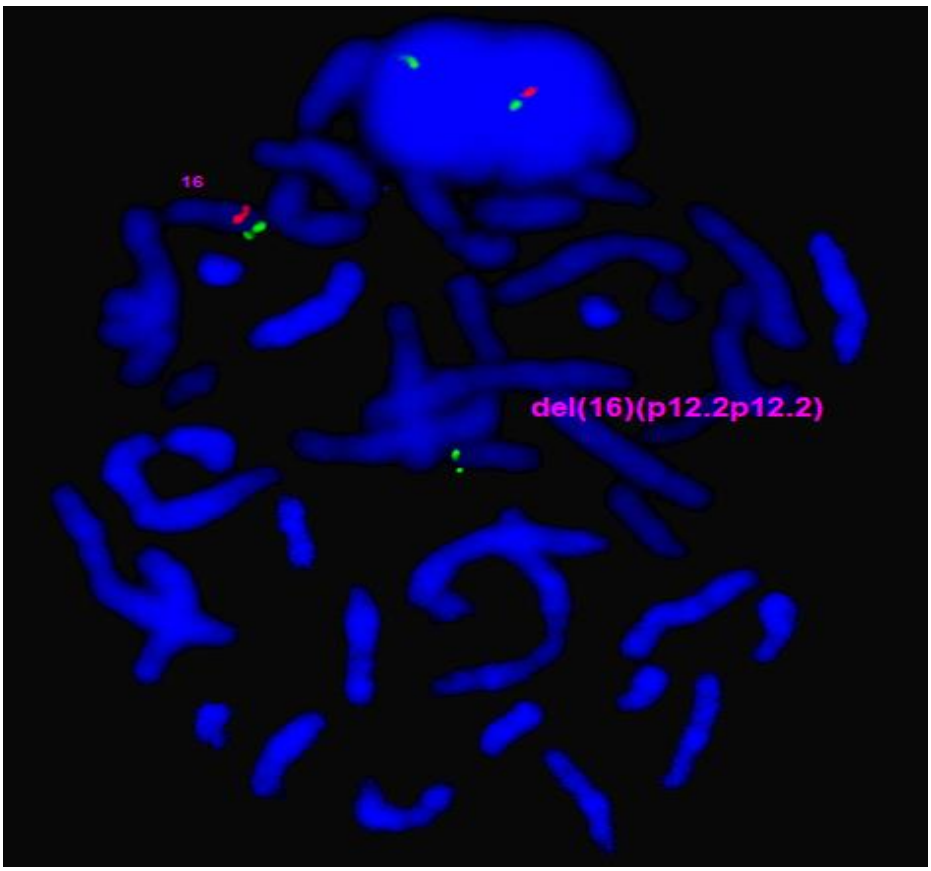

Figure 3. FISH analysis using BAC probe RP11-141O15 (16p12.2p12.2)-spectrum red and TelVysion 16p-spectrum green shows one normal chromosome 16 (one red signal and one green signal) and a deletion of 16p12.2 chromosome (only one green signal) in proband's metaphase.

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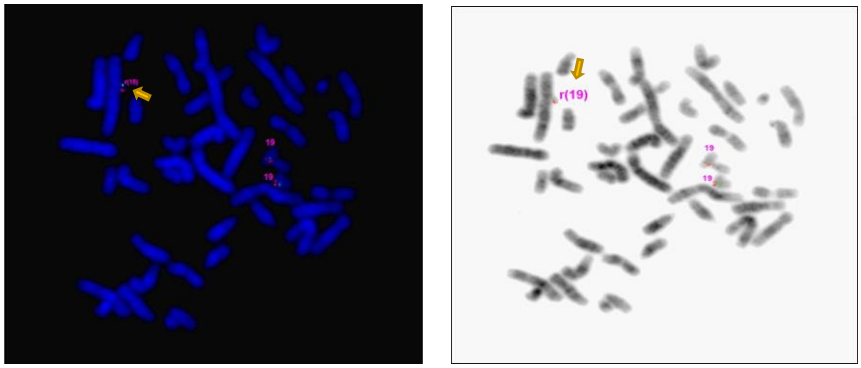

(**a**) (**b**)

Figure 4. FISH analysis using BAC probe RP11-359H18 (19p12)-spectrum red and RP11-714C4 (19q12)- spectrum green show two normal chromosomes 19. (a) Two red and two green signals) and an arrow pointing to ring chromosome 19 (r19) with extra red and green signals in proband's metaphase. (b) Ring chromosome confirmed on inverted DAPI.

Variants identified by targeted NGS reported at the reference lab are listed in Table 1.

Table 1. Variants identified by targeted Next Generation Sequencing (NGS) Panels. a) Hereditary Hearing Loss and Deafness Panel. b) Limb and Digital Malformation Panel:.

Gene Transcript	**Mode of Inheritance, OMIM ID**	**DNA variants, Predicted effects, Zygosity**	**Highest Allele Frequency in a gnomAD Population**
MYH14, NM_001145809.1	Autosomal Dominant, 608568	c.4001C>T, p.Ala1334Val, Heterozygous	0.0071% East Asian
PDE1C, NM_001322059.1	Autosomal Dominant, 602987	c.8C>T, p.Ser3Leu, Heterozygous	0.026% European (Non-Finnish)
ADGRV1, NM_032119.3	Autosomal Recessive, 602851	c.15502A>G, p.Thr5168Ala, Heterozygous	Not present
CDH23, NM_022124.5	Autosomal Recessive, 605516	c.8772C>A, p.Ser2924Arg, Apparently Mosaic	0.00089% European (Non-Finnish)
MYO3A, NM_017433.4	Autosomal Recessive, 606808	c.484G>A, p.Gly162Ser, Heterozygous	Not present
Gene Transcript	**Mode of Inheritance, OMIM ID**	**DNA variants, Predicted effects, Zygosity**	**Highest Allele Frequency in a gnomAD Population**
ADAMTS10, NM_030957.3	Autosomal Recessive, 608990	c.506G>A, p.Thr5168Ala, Heterozygous	Not present
CHUK, NM_001278.4	Autosomal Recessive, 600664	c.1294C>T, p.Ala1334Val,	0.0017% European (Non-Finnish)

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CSPP1, NM_024790.6	Autosomal Recessive, 611654	Heterozygous c.1972A>G, p.Arg658Gly, Heterozygous	0.092% (Admixed American)
TCTN2, NM_024809.4	Autosomal Recessive, 613846	c.160G>A, p.Val54Met, Heterozygous	0.0061% (African/African-American)

Segregation analysis on proband's parents was not performed due to unavailability of parents.

4. Discussion

Although GS usually occurs sporadically with no family history, genetic predisposition has been proposed based on growing evidence from the literature [16-19]. Familial case reports of autosomal dominant or autosomal recessive inheritance, as well as evidence of a genetic association in two families and the presence of features of GS in patients with multiple chromosomal aberrations and gene imbalances, all of which suggest that GS has a genetic basis in some instances [10]. Segregation analysis performed in 311 members of the families of 74 probands with GS provided evidence for an autosomal dominant mode of inheritance with reduced penetrance [20]. Kaye et al. hypothesized that OAVS may represent one end of a phenotypic continuum produced by the segregation of a single gene [20]. In their research, Rollnick et al. analyzed pedigree data on 97 cases, 44 of whom had a family history of the same or similar anomaly [21]. The authors have reported that first-degree relatives were most often affected (35/433, 8%). Of 176 sibs tabulated, 11 (6%) were considered affected. The pattern of occurrence in many families suggested multifactorial determination, although other interpretations are possible [22]. Moreover, the authors observe a broad phenotypic spectrum within families, which has also been observed by others. They suggest that familial inheritance is more prevalent than originally thought. Phenotypes observed in familial OAVS cases do not differ from those in sporadic ones [10, 21, 22].

The presence of chromosomal anomalies in individuals exhibiting phenotypic characteristics within the GS provides additional evidence supporting a genetic basis for this syndrome. Some examples of published chromosomal anomalies in patients with phenotypic characteristics of GS includes the deletion at 5p15, documented in multiple patients displaying features of GS [23-25]. Microduplications on 14q23.1 were detected in two families exhibiting autosomal dominant Oculo-Auriculo-Vertebral Spectrum (OAVS) [26, 27]. Within one of these families, two first-degree relatives manifested clinical features of both OAVS and Branchio-oto-renal syndrome. This suggests that the 14q23.1 region could potentially contain candidate genes not only for OAVS but also for additional developmental disorders related to the first and second pharyngeal arch [26, 27]. Some patients with features of GS have been found to exhibit deletions in the 12p13.33 region, specifically involving the *WNT5B* gene; however, it's noteworthy that not all individuals with GS characteristics display these deletions [28, 29]. Aberrations in the 22q region also have been frequently reported in individuals diagnosed with Goldenhar Syndrome [30-35]. Mosaicism for trisomy 22q has been also documented, suggesting that this genomic region could be a good candidate for certain cases of Goldenhar Syndrome [36].

In the study of Melis et al. (2011), cytogenetics revealed a female karyotype with the presence of de-novo small supernumerary chromosome rings in 100% of cells examined in a 15-year-old female with selective cognitive impairment and tall stature due to chromosome 19 supernumerary ring [37]. In 2020, Li et al. performed Next Generation Sequencing to identify the chromosomal origins of sSMCs and correlate certain sSMCs with a clinical picture in 75 patients. This study underlines the importance of setting of an economical and efficient methods for clinical small supernumerary marker chromosome diagnosis in terms of identifying genotype-phenotype correlations and integrating genomic data into clinical care [13]. The phenotype linked to partial trisomy 19q is marked by facial dysmorphism, growth and mental retardation, macrocephaly, as well as heart malformation,

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along with anomalies affecting the genitourinary and gastrointestinal tracts. On the other hand, the phenotype associated with partial trisomy 19p is characterized by dysmorphic features, severe mental retardation, abnormalities in brain morphology, and anomalies affecting the fingers [38-40].

The duplicated region in our case mainly contains Zinc Finger (ZNF) genes *ZNF98, ZNF99, ZNF91, and ZNF254* and *UQCRFS1* gene. ZNF genes have important role both in tissue homeostasis and disease. With an estimated 500-600 members, zinc finger (ZNF) genes are one of the largest gene families in the human genome [41-43]. Several studies have demonstrated their crucial role in cell and developmental differentiation by encoding transcriptional regulators. They consist of zinc finger domains that can bind selectively to certain DNA or RNA and associate with proteins, thus being able to regulate gene expression at both the transcriptional and translational levels [44]. Biallelic variations in the *UQCRFS1* gene are correlated with Mitochondrial Complex III Deficiency, Cardiomyopathy, and Alopecia Totalis [45]. Our case has bicuspid aortic valve, premature ventricular contractions, left bundle branch block, and history of pericarditis associated with Lupus as cardiovascular diseases, which may be associated with *UQCRFS1* gene overexpression.

The 16p12.2 deletion (previously termed as 16p12.1 deletion) observed in our case encompasses the *EEF2K, POLR3E, UQCRC2*, and *CDR* genes, this is a recurrent heterozygous deletion associated with variable phenotype and reduced penetrance. In most patients (~95.0%) this deletion is inherited from a parent, who may or may not have clinical traits linked to 16p12.2 recurrent deletion [46]. Although the clinical features of 16p12.2 deletion do not constitute a recognizable syndrome due to its varied expressivity and incomplete penetrance, it is associated with developmental delays, speech delays, cognitive impairment, mild dysmorphic facial features without a consistent pattern, sleep disturbance, epilepsy, cardiac/skeletal malformations, and a psychiatric and/or behavioral disorder commonly observed in probands. Based on the large study of 11873 cases, Girirajan et al**.** proposed 'two-hit' model to explain the severity and variability of 16p12.2/16p12.1 phenotypes [47]. Our case also supports the 'two hit' CNV model and is associated with severe phenotype due to the presence of large 7.3 Mb CNV on 19p12q12. It should be noted that most individuals with recurrent 16p12.2 deletions are identified by Chromosomal Microarray Analysis (CMA) performed in the context of evaluation for developmental delay, cognitive impairment, and/or autism spectrum disorder [46].

Targeted gene sequencing approach has been used in many studies to identify the candidate genes for GS [12,48]. Targeted NGS panels in our patient revealed multiple SNVs reported in patients with neurological, ocular, facial, sensorineural/ear, cardiac, skeletal and urogenital anomalies. Variants in *MYH14, PDE1C, ADGRV1, CDH23*, and *MYO3A* genes have been reported in both syndromic and non-syndromic patients with mild to complete hearing loss [49-56], which can be associated with hearing loss and ear anomalies present in our proband. Mutations in *ADGRV1* and *CDH23* are also reported in patients with ocular anomalies/ Vision loss [53, 57, 58]. Pulmonary, cardiac, and skeletal abnormalities in our case such as absent lung lobe, bicuspid aortic valve, facial asymmetry, and missing left thumb can be associated with *ADAMTS10* variants [59-61]. In the studies of Khandelwal et al**.** [62] and Cadieux-Dion [63], *CHUK* gene variants have been associated with severe skin and orofacial phenotypes such as ankyloblepharon, ectodermal dysplasia, cleft lip/palate, ectrodactyly, syndactyly, hypogammaglobulinemia, and growth delay, most of these features are present in proband. *CSPP1* and *TCTN2* variants have been reported in Joubert/Meckel syndrome like phenotypes involving CNS, urogenital, skeletal and pulmonary systems [64-67]. Based on the genotype/phenotype correlation and literature review, it is highly anticipated that these SNVs contribute to the patient's complex clinical manifestation as a result of multiple gene hits. Phenotypic/Genotypic correlation has been summarized in Table-2.

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Table 2. Phenotypic variation among the typical Goldenhar Syndrome, Proband, 16p12.2 deletion, sSRC19 and variants identified by targeted NGS.

Goldenhar Syndrome Phenotypes and their Prevalence [4,10]	Proband Phenotypes	16p12.2 Deletion Phenotypes [46,47]	sSRC19 Phenotype [37]	Possible Variant association and Genes
Head and Face Anomalies/Hemifacial microsomia (~83.5%)	+	-	+	+ (*CHUK, TCTN2*)
Ocular Anomalies (23%)	+	-	-	+ (*ADGRV1, CDH23, ADAMTS10, CHUK, CSPP1*)
Ear Anomalies/Sensorineural defects/Deafness (~55%)	+	+	-	+ (*MYH14, PDE1C, ADGRV1, CDH23, MYO3A*)
Cardiac Anomalies & Congenital Heart Defects (~20.16%)	+	+	+	+ (*ADAMST10*)
Skeletal Anomalies (~27%)	+	+	+	+ (*ADAMTS10, CHUK, TCTN2*)
Urogenital Anomalies (~11.5%)	+	+	-	+ (*CHUK, TCTN2*)
Pulmonary Anomalies (~8%)	+	-	-	+ (*CSPP1, ADAMTS10*)
Gastrointestinal Anomalies (~7%)	+	-	-	-
Psychiatric & Behavioral Anomalies	+	+	-	+ (*CSPP1, TCTN2*)
Intellectual Disability	-	+	+	+ (*CSPP1, TCTN2*)
Developmental Delay (~11.5%)	-	+	+	+ (*CSPP1, TCTN2*)

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Central Nervous System Anomalies (~10%)	-	-	+	+ (CHUK, CSPP1, TCTN2)

*: Bogusiak et al. *World J Pediatr*. 2017;13(5):405-415 [4]. †: Beleza-Meireles A, et al. 2014 [10]. **: Girirajan S, et al. 2015 [46,47]. ***: Melis et al. *Clin Dysmorphol*. 2012;21(1):27-32 [37].

Due to complex and overlapping heterogeneous phenotypes of GS patients, clinicians diagnose these patients based on the principal anomalies, and many of the patients are not assessed for additional phenotypes. CMA and Exome Sequencing (ES) are recommended as the first-tier test by American College of Medical Genetics and Genomics (ACMG) for patients with neurodevelopmental disorders and/or multiple congenital anomalies [68,69]. The utilization of CMA has emerged as a pivotal diagnostic tool for the identification of genetic anomalies associated with additional or variable phenotypes in many syndromic patients. CMA at early ages can help in the proper diagnosis and management of patients. Additional Whole Exome Sequencing (WES) could identify pathogenic variants associated with the patient's additional phenotypes. Genetic counseling also plays an important role in such cases by providing the support required to address the uncertainties families face, guidance for future pregnancies, and medical intervention as well.

5. Conclusions

In this case, we report 16p12.2 deletion, ring chromosome 19 mosaicism and multiple single nucleotide variants in an adult patient who was diagnosed with Goldenhar Syndrome in infancy. The phenotypes associated with sSMC are extremely variable, from normal to severely abnormal depending on its origin and nature. The correlation of specific sSMC with distinct clinical phenotype has been reported for the isochromosome 18p syndrome (OMIM: 614290), isochromosome 12p (Pallister-Killian) syndrome (OMIM: 601803), and derivative 22 chromosomes (cat-eye) syndromes (OMIM: 115470). The patient in this study visited the genetic clinic to ascertain risks for future pregnancies. In general, the risk for an abnormal phenotype in prenatally ascertained de novo cases with any sSMC are given as approximately 13%, 7% for sSMC from chromosomes 13, 14, 21 or 22 and 28% for non-acrocentric chromosomes. Because the carrier shows an abnormal phenotype, as in our case, there is a high risk for an abnormal phenotype associated with mosaic ring chromosome 19 in prenatal outcome.

Author Contributions: Conceptualization, M.A.I and B.D.D.; methodology, S.A., B.D.D.; software, S.A., B.D.D.; formal analysis S.A., B.D.D.; resources, M.A.I.; Data curation, S.A., B.D.D.; writing—original draft preparation, B.D.D.; writing—review and editing, B.D.D., S.A., M.A.I, B.Z.; supervision, M.A.I, B.Z. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The authors declare that all data supporting the findings of this study are available within the article and its supplementary information files or from the authors upon request.

Conflicts of Interest: The authors declare no conflict of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The use of trademarks is for identification purposes only and does not imply endorsement by the U.S. Department of Health and Human Services.

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