In-Depth Clinical and Genetic Investigations of Branchial Arch Syndromes in a Consanguineous Population: Sporadic and Familial cases with Goldenhar and Möbius Syndromes

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INTRODUCTION

- Branchial arch syndromes encompass a group of congenital disorders, such as Goldenhar (GS) and Möbius syndromes (MBS), characterized by anomalies in the development of craniofacial structures derived from the branchial arches. The clinical presentation of patients affected by these syndromes is highly heterogeneous and not limited to craniofacial defects. Indeed, several associated anomalies have been reported including ocular, skeletal/ vertebral, renal, and heart defects.
- Both syndromes are marked by variable expressivity and the majority of patients remain without a conclusive genetic etiology.
- However, a genetic underlying cause is supported by the description of familial forms along with the identification of several variants of high impact in genes belonging to different pathways, mainly related to embryological development such as *MYT1*, *EYA3*, *ZIC3*, *ROBO1*, *GATA*, and *HOX* genes.
- Both syndromes share common clinical features, mostly craniofacial, ocular, and skeletal anomalies which are highly suggestive of a common genetic interplay during embryonic development.

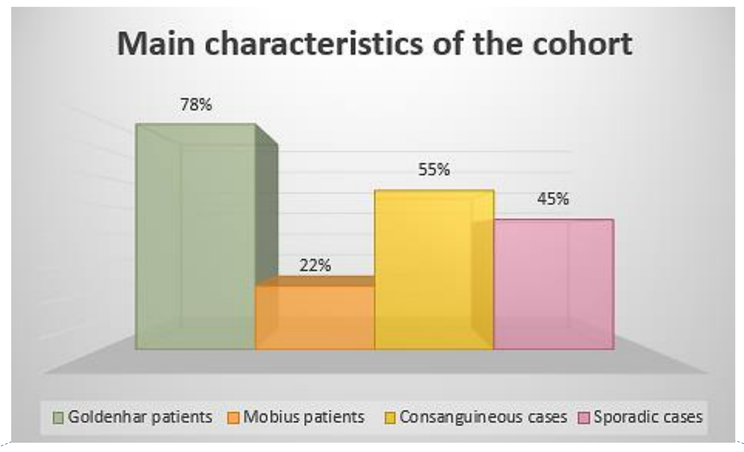
AIMS & OBJECTIVES

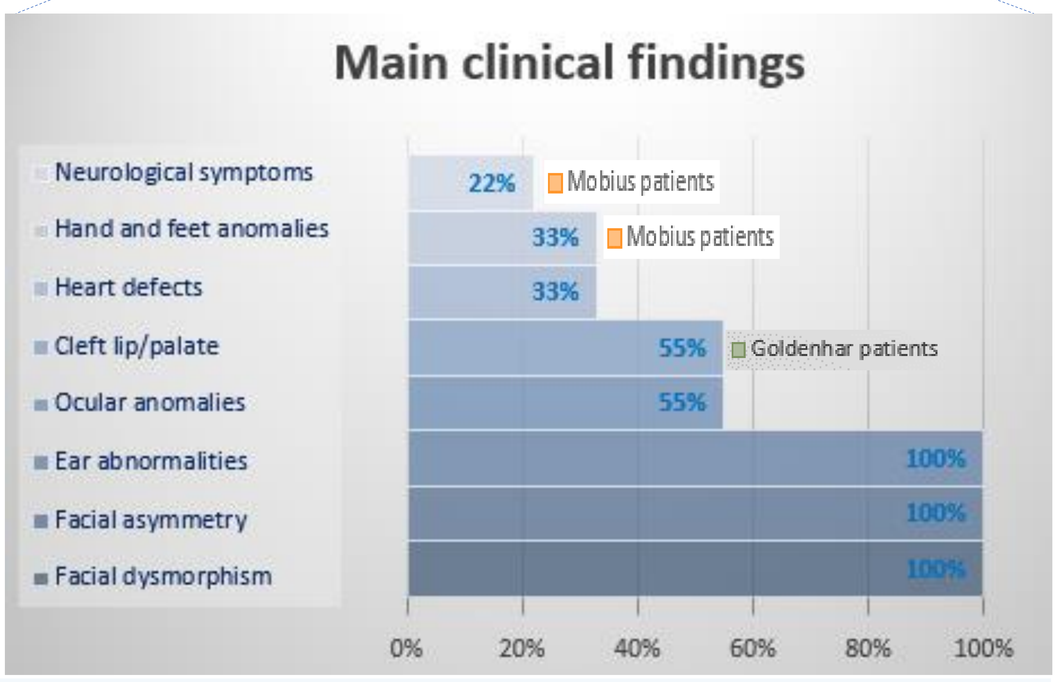
Despite extensive research efforts, the molecular etiology of GS and MBS remains elusive. In part, this can be explained by the limited availability of large cohorts or small cohorts with deep and consistent phenotyping. Thus, expanding the case-series by reporting novel patients from different ethnic backgrounds may help the identification of novel causative alleles and genes.

- Aim 1: To characterize the genetic landscape of GS and MBS through detailed clinical phenotyping and genetic investigations. This involves identifying causative genetic variants and patterns of inheritance within the patient cohort.
- Aim 2: To identify novel candidate genes associated with GS and MBS by analyzing the genetic data and conducting in-depth phenotyping.
- Aim 3: Investigating the association between genetic variants and cardiovascular pathways, particularly in relation to the cardiac defects observed in some GS and MBS patients. This involves screening specific genes, such as *ZIC3* and *HOX* genes, to assess their implication in cardiac anomalies.

THE COHORT

- So far, our cohort contains six MBS cases and seven GS cases, five of them were born to first-degree consanguineous parents. The total number of samples is 14 including one trio (GS), and one MBS family (4 members). The DNA of other patients will be collected in the next months.
- Prenatal and family histories were gathered for all the patients to check familial recurrence and exposure to teratogenic substances during pregnancies. The mean age at diagnosis is 1 year and 10 months (range 2 months-6 years).





- Hand and foot anomalies observed in our cohort are Club foot, clinodactyly, oligodactyly, syndactyly, and toe agenesis (Figures 1 and 2).
- Heart defects found in our Möbius cases are tetralogy of Fallot, atrial septal defect, and mitral regurgitation.
- Ocular findings identified in our cohort are ptosis, strabismus, microphthalmia, anophtalmia, bilateral cataract, and iridal coloboma.
- Neurological disorders detected in our Möbius cases are central hypotonia and ventriculomegaly.

HAND AND FOOT ABNORMALITIES IN MÖBIUS PATIENTS

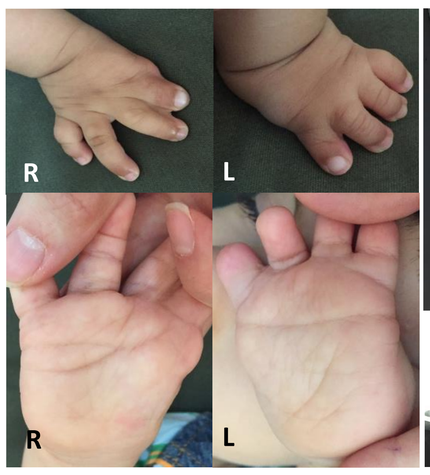


Figure 1: Oligodactyly, Bilateral thumb agenesis; Fingers Syndactyly (right hand); Brachydactyly; Bilateral single transverse palmar creases

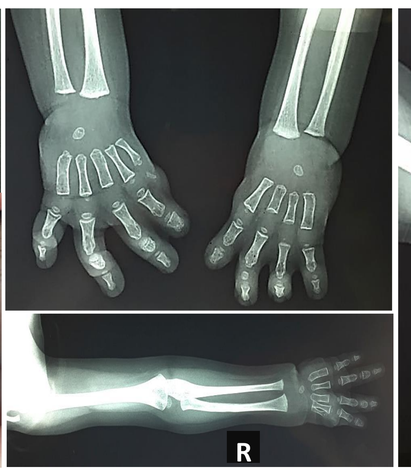
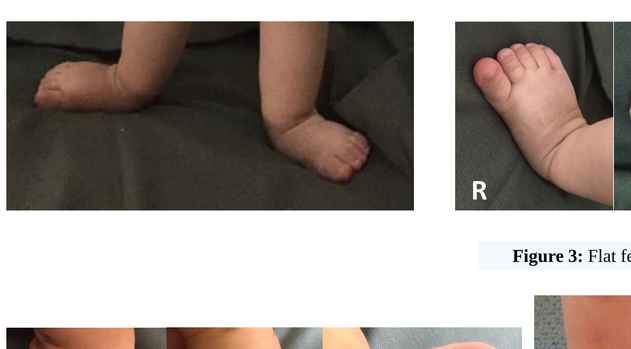
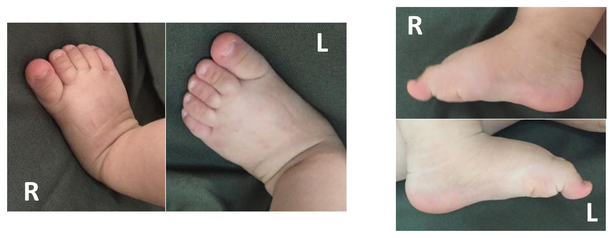


Figure 2: No visualization of the capitatum (both sides); Inequality of metacarpal length
Right side: Absence of the first right ray phalanges and absence of P3 of the 2nd and 5th rays.
Left side: Absence of the first left ray bones and absence of P3 in the 2nd, 4th, and 5th rays





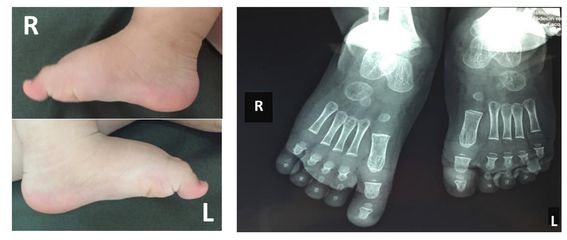
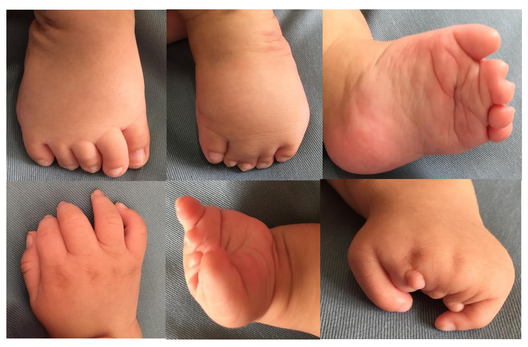
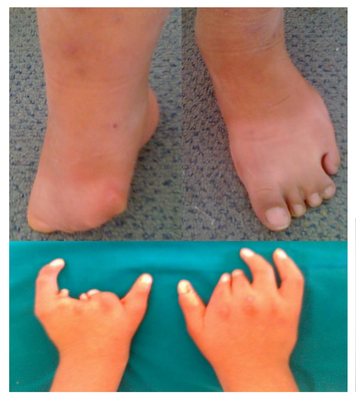
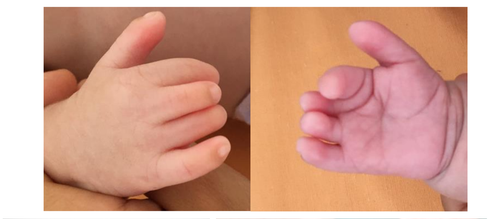


Figure 3: Flat feet and inequality of metatarsal length







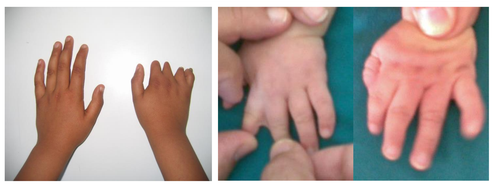
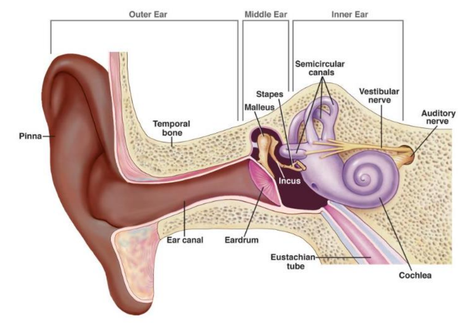


Figure 4: Fingers and toes agenesis

EAR ABNORMALITIES IN GOLDENHAR PATIENTS



Source: NIH/NIDCD

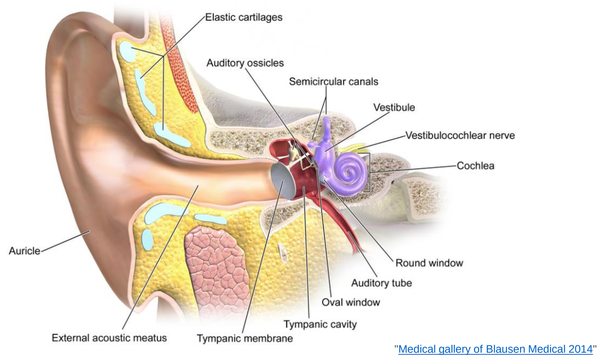


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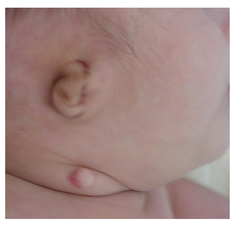
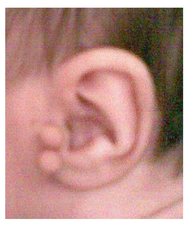
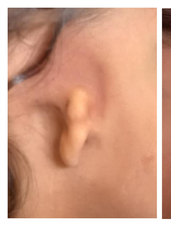
Figure 5: Anatomy of the ear



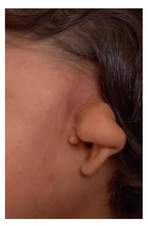
Case GS1



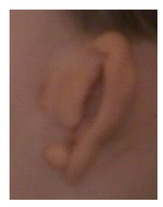
Case GS2



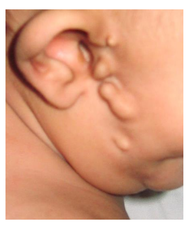
Case GS3



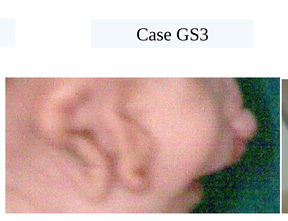
Case GS4



Case GS5



Case GS6



Case GS7; Ear anomalies, lip and cleft palate

The main ear abnormalities noted in our GS patients: Microtia, absence of the external auditory canal, absence of the tympanic cavity, bilateral auricular hypoplasia, and stenosis of the external auditory canal.

Ongoing genetic investigations

- All the cases have a normal karyotype. The 22q11.2 deletion syndrome has been excluded for all the patients by FISH.
- Whole exome sequencing will be performed for all the cases in order to identify missense and PTV variants within known genes such as *TUBB3*, *ZIC3*, *SOX*, and *HOX* genes and to prioritize novel candidate genes.
- CNV detection from exome data will be performed using: ExomeDepth, Control-FREEC, Cobalt, and Manta.
- Cellular and animal models will be generated to study the functional impact of the prioritized variants within novel candidate genes.

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