Genetic and clinical predictors of hearing loss among patients with CHARGE syndrome: A retrospective chart review

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1. Background

CHARGE Syndrome: CHARGE syndrome (CS) affects approximately one in every 10,000 births. The acronym, CHARGE, describes the characteristic features: **c**oloboma, congenital **h**eart defects, **a**tresia of the choanae, **r**etardation of growth and development, **g**enital hypoplasia, and **e**ar abnormalities causing deafness. Recent studies suggest that CS represents a vast phenotypic spectrum. The discovery of *CHD7* gene variants as a cause for CS allows for use of molecular confirmation of a CS phenotype.

Hearing Loss: Most individuals with CS experience more than one structural ear abnormality. It is estimated that >90% of those with CS have hearing loss of some degree, as a result of sensorineural, conductive, or mixed types.

Study Purpose & Significance:

- We conducted this study to further understand the phenotypic spectrum, with an emphasis on audiologic presentations
- Given the unsatisfactory prediction and lack of studies, we assess if a patient's genotype and clinical features, such as temporal bone scan results and/or craniofacial abnormalities, can provide a personalized hearing loss risk assessment to families
- A personalized risk assessment could be used to guide decisions, enhance counseling, and optimize management

2. Methods

The study cohort was obtained through the Cincinnati Children's Hospital Medical Center (CCHMC) CHARGE Center.

Inclusion Criteria

- Molecular diagnosis of CS with a likely pathogenic or pathogenic *CHD7* variant identified

Data Collection

- Demographic and clinical information abstracted from EMRs
- Data managed using REDCap electronic data capture tools

Data Analysis

- Descriptive statistics to characterize cohort
- Comparative statistics using chi-square analysis ($\alpha < 0.05$) to:
  - Assess relationship between hearing loss type and *CHD7* variant type
  - Assess relationship between hearing loss degree and *CHD7* variant type

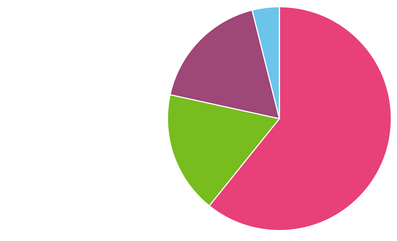
3. Cohort Characteristics

- 57 Total Individuals with *CHD7*+ CS
- Clinically and/or molecularly diagnosed with CS between birth and 14yrs 7mos
- Average age of diagnosis: 26mos

Summary of Hearing Loss Characteristics

	N	Frequency (%)
Presence of Hearing Loss	57	55 (96.5%)
Symmetric Hearing Loss	55	30 (54.6%)
Hearing Loss Severity - Worst Ear	54	
Slight		2 (3.7%)
Moderate		4 (7.4%)
Moderate-Severe		3 (5.6%)
Severe		17 (31.5%)
Profound		28 (51.9%)
Hearing Loss Type per Ear	106	
Sensorineural		59 (55.7%)
Conductive		24 (22.6%)
Mixed		23 (21.7%)
Hearing Loss Type per Individual	55	
Bilateral Sensorineural Hearing Loss		24 (43.6%)
Bilateral Conductive Hearing Loss		8 (14.6%)
Bilateral Mixed Hearing Loss		9 (16.4%)
Hearing Loss Management per Ear	106	
Hearing Aid		45 (42.5%)
Cochlear implant		14 (13.2%)
Bone conduction		26 (24.5%)
None		21 (19.8%)

Prevalence of CHD7 Variant Type (N=51)



Pathogenic and likely pathogenic variants in *CHD7* tend to be unique between unrelated patients.

Prevalence of Craniofacial Abnormalities (N=57)

Cleft Palate	22 (38.6%)
Facial Palsy	22 (38.6%)
Cleft Lip	16 (28.1%)
Microphthalmia	13 (22.8%)
Choanal Atresia	12 (21.1%)
Choanal Stenosis	9 (15.8%)
Midface Hypoplasia	4 (7.0%)

Prevalence of Temporal Bone Scan Findings (N=67)

	Ossicles	Oval Window	Vestibule	Semicircular Canals	Cochlea	Cochlear aperture	Facial Nerve	Cochlear Nerve
Normal	2	1	4	4	11	16	4	7
Dysplastic	55	0	61	4	54	33	53	0
Absent	0	31	0	59	0	7	0	7
Deficient	0	0	0	0	0	0	0	4
Unable to Determine	10	35	2	0	2	11	10	49

4. Hearing Loss and Molecular Findings

Type of hearing loss was correlated with *CHD7* variant type (p=0.01). We saw an increased risk of sensorineural hearing loss in cases with *CHD7* haploinsufficiency (nonsense/frameshift variants).

A geneotype – phenotype correlation was not observed between hearing loss severity and *CHD7* variant type.

Hearing Loss Type Compared to *CHD7* Variant Type (N=100)

p=0.01

5. Hearing Loss and Craniofacial Abnormalities

Number of Craniofacial Anomalies Among Patients with Severe or Profound Hearing Loss

# of Anomalies	Patients with # of Anomalies	Patients with # of Anomalies and Severe or Profound Hearing Loss
0	8	6 (75%)
1	16	9 (69.2%)
2	19	17 (89.5%)
3	8	7 (87.5%)
4	5	5 (100%)
Missing	1	–

No craniofacial anomaly was associated with a type or degree of hearing loss. Patients with severe or profound hearing loss were more likely to have multiple craniofacial anomalies identified, though this did not meet statistical significance.

6. Future Directions

- Include patients with clinically diagnosed CS and negative genetic testing and/or variants in other genes
- Collect data on audiologic intervention efficacy, to create tailored counseling for families regarding expectations and care goals
- Further characterize phenotypes associated with CS to increase knowledge and improve clinical care
- Assess barriers to care to better provide equitable access to the CCHMC CHARGE Center

7. Conclusion

- Regardless of the *CHD7* variant, patients are at risk for craniofacial and audiological abnormalities
- Our study shows the importance of early temporal bone scans despite a patient's *CHD7* genotype
- It is crucial to the CS population that we as providers are offering comprehensive and detailed screening to all CS patients given the variability in presentation
- Collecting both genotypic and phenotypic data regarding CS can expand our understanding and counseling

Acknowledgements

We would like to thank those individuals and families within the CHARGE Center at CCHMC whose sharing of stories and willingness to participate in research allow us as a community to further our understanding of CS.

Grant T73MC00032