



Baby Badger Network ECHO Series



# Navigating the Genetic Test Report

*Friday Sept 20, 2024 11:30 am*

*Sara Zoran MS, CGC*



gDD, microcephaly, hypotonia, preaxial polydactyly, SNHL, FTT, delayed myelination, dysmorphic facial features, abn ear morphology

## Summary

PRIMARY FINDINGS: **Heterozygous for a Variant of Uncertain Significance in *GLS*; ~3.10 Mb Copy Gain (Likely Pathogenic)**

SECONDARY FINDINGS: **None Detected**

INDICATION FOR TESTING: Global developmental delay, microcephaly, hypotonia, preaxial hand polydactyly (right), sensorineural hearing impairment (right), feeding difficulties, dysphagia, failure to thrive, abnormal bronchus morphology (absence of right middle lobe), delayed myelination, decreased circulating acth level, frontal bossing, prominent forehead, depressed nasal bridge, telecanthus, epicanthus (mild), upslanted palpebral fissure (mild), abnormal ear morphology (right, unusual contoured antitragus and overfolded superior pinna)

Variants in genes known to be associated with phenotype:

Copy Number Variant(s):

Genomic Coordinates	Type	Size	Inheritance	Zygoty	Interpretation
chr14q11.2(20000424-23103770)x4	Copy Gain	~3.10 Mb	Not Determined	See text	LIKELY PATHOGENIC

COPY NUMBER VARIANT INFORMATION:  
 This patient harbors an ~3.10 Mb copy gain corresponding to a minimum boundary via NGS sequencing data of chr14:20,000,424-23,103,770(GRCh37/hg19). Previous chromosome analysis undertaken by an outside laboratory indicated that this copy gain is a supernumerary pseudoisodicentric chromosome 14 which results in tetrasomy of 14q11.2. This region encompasses many genes, including the following OMIM morbid disease genes: *TTC5* (OMIM #619244); *OSGEP* (OMIM #617729); *PNP* (OMIM #613179); *ANG* (OMIM #611895); *RPGRIP1* (OMIM #608194 and #613826); *SUPT16H* (OMIM #619480); *CHD8* (OMIM #615032); *SALL2* (OMIM #216820); and *TRAC* (OMIM #615387). Similar overlapping duplications have been reported in patients with intellectual disability, developmental delays, and/or microcephaly with facial dysmorphisms (see, for example, Monfort et al. 2007).

Medically actionable variants in guideline recommended genes\*: None detected

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Pg. 1

Karyotype: supernumerary pseudoisodicentric chr resulting in tetrasomy WES (proband only)

- a/w the reported phenotype
- possibly a/w phenotype
- prelim evidence of a/w pheno



# Primary Results (pg 1)

## Variant(s) a/w the phenotype

Variants in genes known to be associated with phenotype:

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**Factors influencing classification**

**Inheritance**

**Phenotype association**

**Size and gene content**

**Population Data**

**Penetrance**

Proband only  
(inheritance not reported)



# Variant(s) in genes possibly a/w the phenotype (pg.2)



Variants in genes possibly associated with the phenotype:

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
GLS, NM_014905.4	AD, AR, 138280	c.107G>T, p.Arg36Leu, Heterozygous	Not listed in ClinVar	0.0067% European (Non-Finnish)	Conflicting	UNCERTAIN

## GLS VARIANT INFORMATION:

This patient is heterozygous in the *GLS* gene for a sequence variant defined as c.107G>T, which is predicted to result in the amino acid substitution p.Arg36Leu. To our knowledge, this variant has not been reported in the literature. This variant is reported in 0.0067% of alleles in individuals of European (Non-Finnish) descent in gnomAD (<http://gnomad.broadinstitute.org/variant/2-191745917-G-T>). At this time, the clinical significance of this variant is uncertain due to the absence of conclusive functional and genetic evidence.

Pathogenic variants in *GLS* have been associated with autosomal dominant infantile cataract, skin abnormalities, glutamate excess, and impaired intellectual development (OMIM #618339), autosomal recessive early infantile epileptic encephalopathy 71 (OMIM #618328), and autosomal recessive global developmental delay, progressive ataxia, and elevated glutamine (OMIM #618412). A family study of affected and unaffected individuals may help clarify the clinical significance of this variant.

Factors influencing SNV classification

Population Data  
Computational/Predictive Data

Functional Data  
Familial Data

Allelic Data  
Penetrance



## Secondary Findings

**PRIMARY FINDINGS: Heterozygous for a Variant of Uncertain Significance in *GLS*; ~3.10 Mb Copy Gain (Likely Pathogenic)**

**SECONDARY FINDINGS: None Detected**



**INDICATION FOR TESTING:** Global developmental delay, microcephaly, hypotonia, preaxial hand polydactyly (right), sensorineural hearing impairment (right), feeding difficulties, dysphagia, failure to thrive, abnormal bronchus morphology (absence of right middle lobe), delayed myelination, decreased circulating acth level, frontal bossing, prominent forehead, depressed nasal bridge, telecanthus, epicanthus (mild), upslanted palpebral fissure (mild), abnormal ear morphology (right, unusual contoured antitragus and overfolded superior pinna)

**Variants in genes known to be associated with phenotype:**

**Copy Number Variant(s):**

Genomic Coordinates	Type	Size	Inheritance	Zygoty	Interpretation
chr14q11.2(20000424-23103770)x4	Copy Gain	~3.10 Mb	Not Determined	See text	LIKELY PATHOGENIC

**COPY NUMBER VARIANT INFORMATION:**

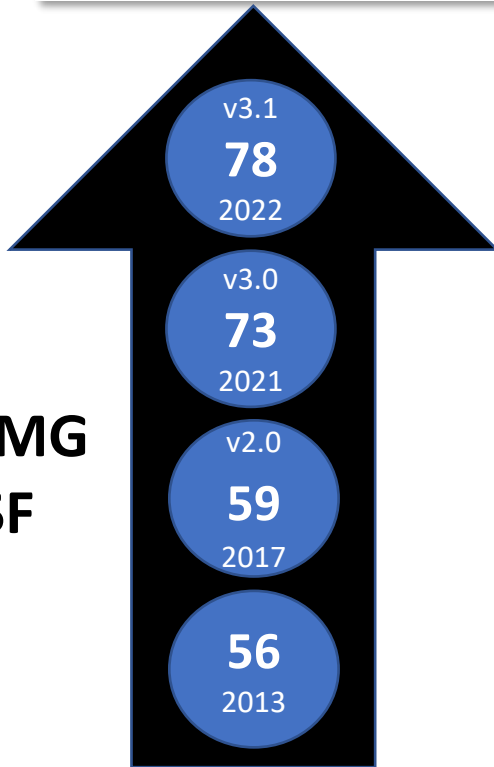
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# ACMG Secondary Finding (SF) Genes: An option to provide medical benefit

American College of Medical Genetics and Genomics (ACMG) Recommendation:  
When performing ES/GS, report Primary and Secondary Findings in the “ACMG SF” genes.

ACMG  
SF

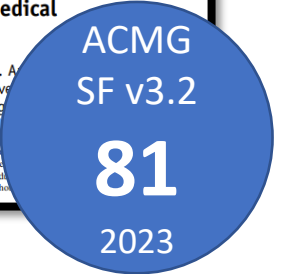
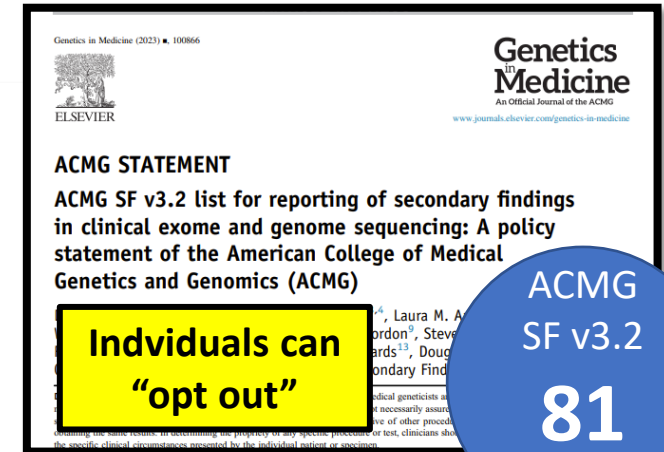


Genes associated with

- Variety of specific conditions
- Definable set of clinical features
- Possibility of early diagnosis
- Reliable clinical genetic test
- Effective intervention or treatment.

Goal

To provide medical benefit by preventing or better managing health conditions.





## Other results

- Not a/w pheno but variant results in a Mendelian disorder
- Rare variants in a candidate gene for which there is limited evidence of pheno association
- Carrier status (some labs will report, if requested)
- Regions of Homozygosity (ROH) were detected



## Other Info, Limitations & Methodology (pg 3-6)

- Reanalysis of sequence data at a later date (>1 year) may yield additional new diagnoses
- Targeted testing of first degree family members (at no charge) may be helpful
- Sample was not sufficient for CNV analysis
- Poor coverage of a specific region
- The ability to detect low level mosaicism of variants is limited
- Balanced translocations or inversions are only rarely detected



## Rapid ES/GS preliminary (verbal) results: Variant and Classification



Variants in genes known to be associated with phenotype:

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variations, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
ZEB2, NM_014795.3	✘	c.1349_1350del, p.Phe450Serfs*5, Heterozygous	Not listed in ClinVar ✘	Not present ✘	Not detectable ✘	LIKELY PATHOGENIC

Classification can change after provisional results are delivered

Document prelim results in the EMR  
Gene name, c., p. and classification