UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Name: [redacted] **Sex:** M **CLIA-certified lab:** n/a
Date of birth: 10/15/2004 **Age:** 11 years
Specimen type: DNA **Date received:** 03/01/2010 **Date resulted:** 06/15/2016
Trait: Joubert syndrome
Trait Category: Affected Status, Genetic Syndromes

High Priority

Test Performed: Research targeted next generation sequencing
Performing laboratory: University of Washington Hindbrain Malformation Research Program

Test Result: ***AHI1*** **[OMIM: 608894]**
Mutation detected: NM_001134831.1: c.2172delA; p.Trp725Glyfs*fs5

Interpretation: This individual has a homozygous *AHI1* variant identified in a research laboratory that is predicted to be pathogenic.

The c.2172delA variant is predicted to result in a frameshift and prematurely terminate the protein. It is rare in controls, and predicted to be damaging. Based on the presumed autosomal recessive inheritance pattern of Joubert syndrome, the sequence variant identified is very likely to be disease-causing. It is important to remember that this research result has not been validated in a CLIA-certified lab. Therefore, confirmatory testing in the patient and parents is recommended. Although the variant is likely homozygous, a deletion of the other allele cannot be excluded by the methodology used, so parents should be tested for carrier status. If used for prenatal diagnosis, confirmation by prenatal imaging is also strongly recommended.

Guidance

- This Joubert syndrome research result should be interpreted in the context of clinical and family history information.
- This research result has not been CLIA-validated. In order for this result to be used in healthcare decision-making and management, confirmation in a CLIA-certified lab is required: http://www.ncbi.nlm.nih.gov/gtr/labs/?certificate=CLIA%20Certified&term=confirmation%20of%20research.
- Joubert syndrome is a rare genetic condition characterized by a cerebellar and brain stem malformation called the molar tooth sign, hypotonia, and developmental delays.
- This individual should be encouraged to share this research result with family members, as it may have important health implications for relatives.
- Genetic counseling is recommended for this person to help with understanding this research result, the associated health implications, management options, and health implications for family members.

Joubert Syndrome Research Program
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Seattle, WA 98195

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Supplemental Information

Clinical/epidemiologic characteristics: Joubert syndrome is a rare genetic condition characterized by a cerebellar and brain stem malformation called the molar tooth sign, hypotonia, and developmental delays. These findings are often accompanied by irregular breathing (tachypnea or apnea) and/or abnormal eye movements. Subsets of affected individuals have progressive retinal dystrophy, cystic kidney disease and liver fibrosis, and they require regular monitoring for these complications.

Genetic characteristics: Joubert syndrome due to mutations in the *NPHP1*, *AHI1*, *CEP290*, *RPGRIP1L*, *MKS3*, *CC2D2A*, *ARL13B*, *INPP5E*, *OFD1*, *TMEM216*, *CEP41*, *TMEM237*, *TCTN2*, *KIF7*, *TCTN1*, *TMEM138*, *MKS1*, *C5ORF42*, *TMEM231*, *TCTN3*, *CSPP1*, *PDE6D*, *IFT172*, *C2CD3*, *CEP120*, *B9D1*, *B9D2*, *NPHP4, KIAA0586, CEP104*, *KIAA0753*, *HYLS1,* and *KIAA0556* are inherited in an autosomal recessive pattern. Joubert syndrome due to mutations in the *OFD1* gene is inherited in an X-linked recessive pattern.

Population Prevalence: Unknown.

Test method: Targeted sequencing refers to sequencing the coding regions of all genes known to be associated with Joubert syndrome.

Test method limitations: Deleterious variants thought to be the cause of Joubert syndrome were identified in this sample. This result does not provide information about variants in other genes associated with Joubert syndrome. Rarely, a variant identified by research testing is not confirmed by clinical testing, or clinical testing reveals a different variant than the one identified by research testing. If the clinical test result differs than the research test result, then the research result is void. Typically, targeted next generation sequencing does not determine chromosomal phase of the identified variants/mutations. For further information about these analyses, please refer to “Information on Limitations.” Other sources of error include, but are not limited to, sample misidentification and sample contamination.

Information resources for clinicians:

Bachmann-Gagescu R, Dempsey JC, Phelps IG, O'Roak BJ, Knutzen DM, Rue TC, Ishak GE, Isabella CR, Gorden N, Adkins J, Boyle EA, de Lacy N, O'Day D, Alswaid A, Ramadevi A R, Lingappa L, Lourenço C, Martorell L, Garcia-Cazorla À, Ozyürek H, Haliloğlu G, Tuysuz B, Topçu M, Chance P, Parisi MA, Glass IA, Shendure J, Doherty D. Joubert syndrome: a model for untangling recessive disorders with extreme genetic heterogeneity. J Med Genet. (2015) 52(8):514-22. PMID: 26092869.

Doherty, D. (2009). "Joubert syndrome: insights into brain development, cilium biology, and complex disease." *Seminars in Pediatric Neurology* 16(3): 143-154.

Parisi M, Glass I. (Updated 11 March 2013). Joubert Syndrome and Related Disorders. In: *GeneReviews* at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1325/. Accessed [04/26/2013].

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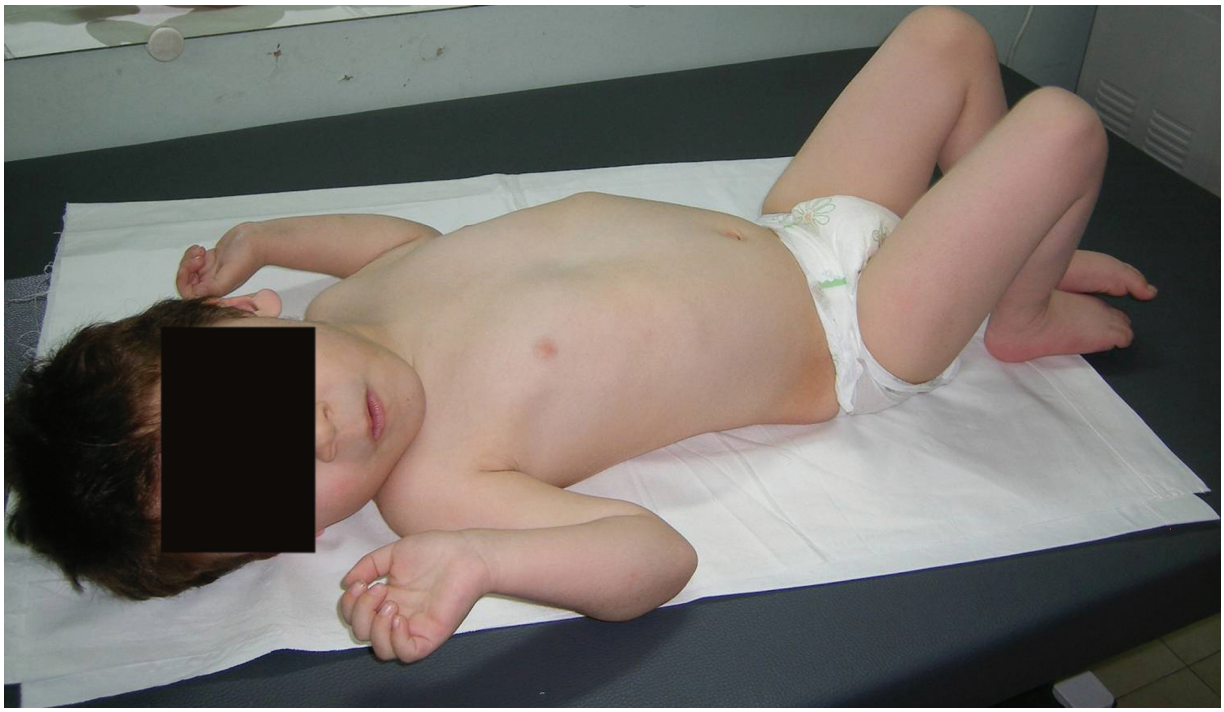

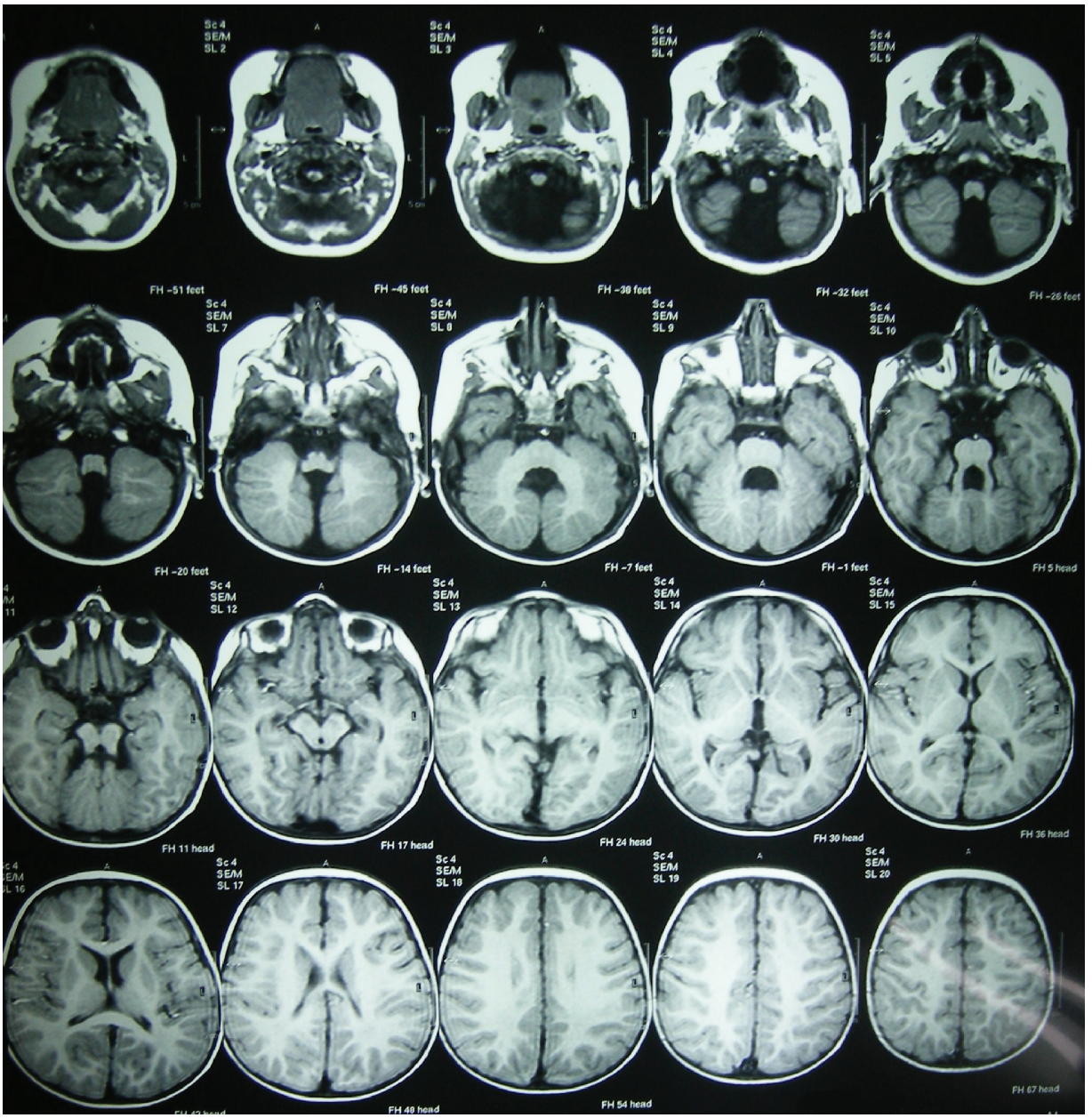

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Name: [redacted] **Sex:** M **CLIA-certified lab:** n/a
Date of birth: 01/30/2007 **Age:** 9 years
Specimen type: DNA **Date received:** 03/01/2010 **Date resulted:** 06/15/2016
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Trait Category: Affected Status, Genetic Syndromes

High Priority

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