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Literature review of human HDR syndrome with GATA3 Haplo insufficiency

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Abstract

This literature mining project is regarding mutations that cause hearing loss in patients with human hypo parathyroid, deafness, and renal dysplasia (HDR) syndrome caused by a mutation in the GATA3 gene. The disease is unique; not all diagnosed individuals present with all symptoms of the triad. Van Esh et al. found that the haploinsufficiency of the GATA3 is found on chromosome 10p14-p15 (ref.1). The focus of this work is to condense the literature on GATA3 haploinsufficiency correlating to human HDR syndrome. Due to the lack of global healthcare access, it can be assumed that many cases remain undiagnosed; 180 have been identified (2).

Background

The anatomical ear is subdivided into three parts: outer, middle, and inner. The outer ear consists of the fleshy portion visibly seen, and the narrow opening is referred to as the ear canal. A series of waves collect in the outer ear, move through the ear canal, and result in vibration of the eardrum. The eardrum also called the tympanic membrane, distinguishes the outer ear from the middle ear. The inner ear comprises the cochlea and vestibular system. The inner ear transforms mechanical vibrations into signals capable of being recognized by the brain. Tiny hair cells methodically lining the fluid-filled cochlea of the inner ear move based on the shift of the tiny bones in the middle ear. In the snail-shaped chamber, hair cells act as sensory receptors that send transmissions along the auditory nerve. The auditory system consists of two types of sensory cells, inner hair cells (IHC) and outer hair cells (OHC). From there, the signals from each ear combine along the brainstem in several stages.

The noise of modern-day life results in a growing public health concern as hearing loss is the third-highest chronic health conditioned recorded in the United States (3). Hearing loss is common, impacting dimensions of daily living, but with appropriate intervention, the standard of living improves. Sensorineural hearing loss is most common, defined by the loss of inner ear hair cells or auditory nerve fibers. Loss of hair cells prevents sounds waves from being signaled to the brain. Sensorineural hearing loss is considered a permanent condition, as hair cells cannot be regenerated once lost. Medical treatments cannot currently reverse most sensorineural hearing loss. Cochlear plants work well for some; others present with poor outcomes. Young individuals' acquisition of spoken language processing and robust speech recognition is developmentally essential to form neurocognitive pathways allowing for communication.

Human hypoparathyroidism, renal dysplasia, and hearing loss (HDR) syndrome is a rare disease that is inherited dominantly (4). HDR patients are consistently diagnosed with various degrees of sensorineural deafness and varying degrees of hypoparathyroidism and renal abnormalities. The phenotype developed from a distinct mutation in each patient requires personalized treatment plans that address symptoms. HDR syndrome indications in an infant presenting with a defect in 10p or pre-natal ultrasounds findings of congenital kidney and urinary anomaly should have genetic GATA3 testing done. Genetic testing done on family members shows a 50% chance affected parent can pass on the gene. Genetic counseling is the front line of the treatment, with the management of present symptoms following.

GATA3 is a transcription factor critical for fetal development. It is generally expressed in the breasts, parathyroid gland, urinary bladder, rectum, inner ear, and kidneys. Possessing two zinc finger domains, ZnF1acts to stabilize DNA binding affinity, and ZnF2 is essential for DNA binding. GATA3 haploinsufficiency is related to HDR syndrome, and there is a correlation between mutation locations and symptoms that present during embryonic development as a dominant genetic disorder; only one copy of the gene is needed to cause abnormalities in development.

Analyzing case study literature of patients who have GATA3 haploinsufficiency and human HDR syndrome will further progress advances in genetic treatments options. Results will verify the mutation and severity of hearing loss in published patient studies.

Methods

The goal of this literature mining project is to collect data from published studies on human HDR patients. Publications on embryotic development of GATA3 haploinsufficiency in human HDR patients were collected methodically. Due to the variability in cases a plethora of symptoms can present, condensing embryonic development of GATA3 haploinsufficiency literature aids scientists in advances in genetic treatments for sensorineural hearing loss. Table 1 compiles mutation type, exon location, DNA, protein, sex, the projected impact of ZnF1 & ZnF2, and level of deafness for each individual. With human HDR syndrome, few conclusions have been drawn; the compilation of the genetic data in this paper aims to hypothesize gene location and severity of deafness. In cases of mutation variants that demonstrate different symptoms ascribing cause is complex. It was hypothesized that literature analysis would display a direct relationship within the genic presentation to sensorineural hearing loss. As human HDR syndrome leads to loss of hair cells, furthering understanding of the mechanism of action provides insights to possible sensorineural hearing loss restoration.

Results

Symbol Key	
B	Bilateral
R	Right ear
L	Left ear
NM	Not mentioned
NE	Not examined
ABR	Auditory brainstem response
NO	No existence of deafness
SNM	Severity not mentioned
*	Indicates stop codon
Mild	26-40
Moderate	41-55
Moderately severe	56-70
Severe	71-90

TABLE 1

Type	Exon	DNA	Protein	Sex	Deafness	Zinc Finger Projected Result	Reference
Nonsense	1	c.192C>A	p. Tyr64Term	Male	B SNM	NM	Goodwin, Gregory, Hawley, Pamela P, & Miller, David T. (2016). A Case of HDR Syndrome and Ichthyosis: Dual Diagnosis by Whole-Genome Sequencing of Novel Mutations in GATA3 and STS Genes. The Journal of Clinical Endocrinology and Metabolism, 101(3), 837-840.
Nonsense	2	c. 64C>T	p.Gln22*	Female	B SNM	ZnF1 & ZnF2 lost	Ali A, Christie PT, Grigorieva IV, Harding B, Van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: Insight into mechanisms of DNA binding by the GATA3 transcription factor. *Hum Mol Genet.* 2007;16:265–75. doi: 10.1093/hmg/ddl454. [PubMed]
				Son Male	B SNM		
Frame shift Intragenic deletions	2	c. 149delT	p.Phe51Leufs*144	Mother female	B mild to moderate	ZnF1 & ZnF2 lost	Lin YH, Wu CC, Hsu TY, Chiu WY, Hsu CJ, Chen PL. Identification of a novel GATA3 mutation in a deaf Taiwanese family by massively parallel sequencing. *Mutat Res.* 2015;771:1–5. doi: 10.1016/j.mrfmmm.2014.11.001. [PubMed]
				Daughter female	B mild to moderate		
Nonsense	2	c. 515C>A	p.S172*	Father male	B severe	ZnF1 & ZnF2 lost	Zhu ZY, Zhou QL, Ni SN, Gu W. GATA3 mutation in a family with hypoparathyroidism, deafness and renal dysplasia syndrome. *World J Pediatr.* 2014;10:278–80. doi: 10.1007/s12519-014-0505-x. [PubMed]
				Son male	B severe		
Frame Shift Intragenic deletions	3	c. 708delC	p.Ser237Alafs*29	Mother female	L>R SNM	ZnF1 & ZnF2 lost	Ali A, Christie PT, Grigorieva IV, Harding B, Van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: Insight into mechanisms of DNA binding by the GATA3 transcription factor. *Hum Mol Genet.* 2007;16:265–75. doi: 10.1093/hmg/ddl454. [PubMed]
				Daughter female	B SNM		
				Son male	B SNM		
	3	c. 404-405insC	p.Ala136Glyfs*168	Father male	B SNM	NM	Ali A, Christie PT, Grigorieva IV, Harding B, Van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: Insight into mechanisms of DNA binding by the GATA3 transcription factor. *Hum Mol Genet.* 2007;16:265–75. doi: 10.1093/hmg/ddl454. [PubMed]

				Daughter female	B SNM		
				Sister female	B SNM		
Nonsense	3	c. 682G> T	p.Gln228*	Mother female	B SNM	ZnF1 deletion	Nesbit MA, Bowl MR, Harding B, Ali A, Ayala A, Crowe C, et al. Characterization of GATA3 mutations in the hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome. *J Biol Chem.* 2004;279:22624–34. doi: 10.1074/jbc.M401797200. [PubMed]
				Son male	B SNM		
Frame Shift	3	c. 736del GinsAT	p.G246Mfs57*	Mother female	NM SNM	loss of DNA binding potential because of lack ZnF2	Higuchi Y, Hasegawa K, Yamashita M, Fujii Y, Tanaka H, Tsukahara H. HDR syndrome in a Japanese girl with biliary atresia: A case report. *BMC Pediatr.* 2016;16:14. doi: 10.1186/s12887-016-0550-9. [PMC free article] [PubMed]
				Daughter female	L mild		
Missense	4	c. 823T> A	p.W275R	Mother female	NM Moderately severe	ZF1 domain mutation leading to ZF2 loss	Muroya K, Hasegawa T, Ito Y, Nagai T, Isotani H, Iwata Y, et al. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. *J Med Genet.* 2001;38:374–80. doi: 10.1136/jmg.38.6.374. [PMC free article] [PubMed]
				Daughter female	NM		
Non conservative amino acid substitution		c. 827C> G	p.R276P	Mother female	B	ZnF1 residue mutation leading to loss of ZnF1	Zahirieh A, Nesbit MA, Ali A, Wang K, He N, Stangou M, et al. Functional analysis of a novel GATA3 mutation in a family with the hypoparathyroidism, deafness, and renal dysplasia syndrome. *J Clin Endocrinol Metab.* 2005;90:2445–50. doi: 10.1210/jc.2004-1969. [PubMed]
				Daughter female	B high frequency		
				Daughter female	B high frequency		

		c. 826C> T	p.R276*	Mother and Son	NM	ZnF1 & ZnF2 lost	Van Esch H, Groenen P, Nesbit MA, Schuffenhauer S, Lichtner P, Vanderlinden G, et al. GATA3 haplo-insufficiency causes human HDR syndrome. *Nature.* 2000;406:419–22. doi: 10.1038/35019088. [PubMed]
				Grandmother female	B severe		Li Wang Qiong-Fen Lin Hong-Yang Wang Jing Guan Lan Lan Lin-Yi Xie Lan Yu Ju Yang Cui Zhao Jin-Long Liang Han-Lin Zhou Huan-Ming Yang Wen-Ping Xiong Qiu-Jing Zhang Da-Yong Wang Qiu-Ju Wang. (2017). Clinical Auditory Phenotypes Associated with GATA3 Gene Mutations in Familial Hypoparathyroidism-deafness-renal Dysplasia Syndrome. Chinese Medical Journal, 130(6), 703-709.
				Mother female	B moderate		
				Son male	B moderately severe		
Missense	4	c.827G >A	p.R276Q	Male	mild	ZnF1 mutation location	Yeşiltepe Mutlu, Gül, Kırmızıbekmez, Heves, Nakamura, Akie, Fukami, Maki, & Hatun, Şükrü. (2015). A Novel De Novo GATA Binding Protein 3 Mutation in a Turkish Boy with Hypoparathyroidism, Deafness, and Renal Dysplasia Syndrome. Journal of Clinical Research in Pediatric Endocrinology, 7(4), 344-348.
		c. 856A> G	p.N276D	Father male	B SNM		Belge H, Dahan K, Cambier JF, Benoit V, Morelle J, Bloch J, et al. Clinical and mutational spectrum of hypoparathyroidism, deafness and renal dysplasia syndrome. *Nephrol Dial Transplant.* 2016 pii: gfw271. doi: 10.1093/ndt/gfw271. [PubMed]
				Daughter female	B SNM		
				Daughter female	B SNM		
Missense		c. 883-886del AACG	p.Asn295Aspfs*60	Mother female	B SNM	Truncated protein with loss of ZnF1 and ZnF2	Ali A, Christie PT, Grigorieva IV, Harding B, Van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: Insight into mechanisms of DNA binding by the GATA3 transcription factor. *Hum Mol Genet.* 2007;16:265–75. doi: 10.1093/hmg/ddl454. [PubMed]
				Daughter female	B SNM		
				Son male	B SNM		
Missense	4	CGG > CAG	p.R299Q / Arg-299	Mother female	B R<L moderate	Spatial mutation changing confirmation	Okawa T, Yoshida M, Usui T, Kudou T, Iwasaki Y, Fukuoka K, et al. A novel loss-of-function mutation of GATA3 (p.R299Q) in a Japanese family with Hypoparathyroidism, Deafness, and Renal Dysplasia (HDR) syndrome. *BMC Endocr Disord.* 2015;15:66. doi: 10.1186/s12902-015-0065-7. [PMC free article]

						linker of ZnF1 & ZnF2 locations	
				Daughter female	B R>L Moderately severe		
Missense mutation	5	c. 942T> A /CAG to CTG	p.C318S	Father male	B moderate	Mutation located adjacent to ZnF2	Nakamura A, Fujiwara F, Hasegawa Y, Ishizu K, Mabe A, Nakagawa H, et al. Molecular analysis of the GATA3 gene in five Japanese patients with HDR syndrome. *Endocr J.* 2011;58:123–30. doi: 10.1507/endocrj.K10E-246.
				Son male	B moderate		
				Daughter female	B moderate		
Missense	6	c. 1514C A>C	p.Asn320Lys	Mother female	B	Disruption of ZnF2	Nesbit MA, Bowl MR, Harding B, Ali A, Ayala A, Crowe C, et al. Characterization of GATA3 mutations in the hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome. *J Biol Chem.* 2004;279:22624–34. doi: 10.1074/jbc.M401797200. [PubMed]
				Daughter female	B		
Missense	6	c. 1059A >T	p.R353S	Mother female	B SNM	Disruption of ZnF1 & ZnF2	Chiu WY, Chen HW, Chao HW, Yann LT, Tsai KS. Identification of three novel mutations in the GATA3 gene responsible for familial hypoparathyroidism and deafness in the Chinese population. *J Clin Endocrinol Metab.* 2006;91:4587–92.doi: 10.1210/jc.2006-0864. [PubMed]
				Daughter female	B SNM		
				Son male	B SNM		

Nonsense	6	c. 1099C >T	p.R367*	Mother female Normal on ARB	NM NE	ZnF1 lost	ea K, Hasegawa T, Ito Y, Nagai T, Isotani H, Iwata Y, et al. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. *J Med Genet.* 2001;38:374–80. doi: 10.1136/jmg.38.6.374. [PMC free article] [PubMed]
				Daughter female NE	NM NE		
Missense		c. TGC>T GG	p.C288W	Male	SNM	ZnF1 impacted due to condon encoding cysteine residue	Kamezaki, Michitsugu, Kusaba, Tetsuro, Adachi, Takaomi, Yamashita, Noriyuki, Nakata, Mayumi, Ota, Noriyoshi, . . . Tamagaki, Keiichi. (2017). Unusual Proliferative Glomerulonephritis in a Patient Diagnosed to Have Hypoparathyroidism, Sensorineural Deafness, and Renal Dysplasia (HDR) Syndrome with a Novel Mutation in the GATA3 Gene. Internal Medicine (Tokyo, 1992), 56(11), 1393-1397.
	NM	c.1099 C > T	p.Arg367*	Mother female	B severe		
				Daughter female	B severe		
Frame shift / premature stop codons	3	c. 431del G	p.Gly144Alafs*5 1	Mother female	B moderate	ZnF1 & ZnF2 lost OR just ZnF2	Hernández AM, Villamar M, Roselló L, Moreno-Pelayo MA, Moreno F, Del Castillo I. Novel mutation in the gene encoding the GATA3 transcription factor in a Spanish familial case of hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome with female genital tract malformations. *Am J Med Genet A.* 2007;143A:757–62. doi: 10.1002/ajmg.a.31617. [PubMed]
				Daughter female	B moderate		
Donor splicing truncated	4	c. 478del G	p.Asp160Thrfs*3 5	Father male	B SNM	Disruption of ZnF1 & ZnF2	Chiu WY, Chen HW, Chao HW, Yann LT, Tsai KS. Identification of three novel mutations in the GATA3 gene responsible for familial hypoparathyroidism and deafness in the Chinese population. *J Clin Endocrinol Metab.* 2006;91:4587–92.doi: 10.1210/jc.2006-0864. [PubMed]
				Son male	B SNM		
				Son male	B SNM		
Missense mutation Truncated	3	c.228 GAG> TAG		Mother female	B SNM	Lack both ZnF1 & ZnF2	Nesbit MA, Bowl MR, Harding B, Ali A, Ayala A, Crowe C, et al. Characterization of GATA3 mutations in the hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome. *J Biol Chem.* 2004;279:22624–34. doi: 10.1074/jbc.M401797200. [PubMed]

				Daughter female	B SNM		
Deletion	3	c. 709ins C	p.Ser273Glnfs*67	Mother female	B SNM	ZnF1 & ZnF2 both lost	Mino Y, Kuwahara T, Mannami T, Shioji K, Ono K, Iwai N. Identification of a novel insertion mutation in GATA3 with HDR syndrome. *Clin Exp Nephrol*. 2005;9:58–61. doi: 10.1007/s10157-004-0327-6. [PubMed]
				Daughter female	L SNM		
Premature stop codon	4	c. 901del CinsA ACCC T	p.Leu301Asn*57	Father male	B moderate	ZnF2 lost	Muroya K, Hasegawa T, Ito Y, Nagai T, Isotani H, Iwata Y, et al. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. *J Med Genet.* 2001;38:374–80. doi: 10.1136/jmg.38.6.374. [PMC free article] [PubMed]
				Daughter male	B Severe (R), profound (L)		
				Daughter male	ABR normal		
Small insert	2	c. 255_25 6insGT GC		Father male	SNM	NM	Shim YS, Choi W, Hwang IT, Yang S. Hypoparathyroidism, sensorineural deafness, and renal dysgenesis syndrome with a GATA3 mutation. *Ann Pediatr Endocrinol Metab.* 2015;20:59–63. doi: 10.6065/apem.2015.20.1.59. [PMC free article] [PubMed]
				Son male	B R>L		
	3	c. 523-528dup	p.Gln178Profs*19	3 generations 5 people	B		
Splicing	Intron 4	IVS4+2 T>GCT TACTT CCC		Mother female	B L>R moderate	ZnF1 & ZnF2 both lost	Chiu WY, Chen HW, Chao HW, Yann LT, Tsai KS. Identification of three novel mutations in the GATA3 gene responsible for familial hypoparathyroidism and deafness in the Chinese population. *J Clin Endocrinol Metab*. 2006;91:4587–92.doi: 10.1210/jc.2006-0864. [PubMed]

				Daughter female	B		
Small deletion Incorrect splicing and exon skipping	Exon Intron 4 junction	C.924+4_924+19del		Mother female	B L>R Moderate	NM	Belge H, Dahan K, Cambier JF, Benoit V, Morelle J, Bloch J, et al. Clinical and mutational spectrum of hypoparathyroidism, deafness and renal dysplasia syndrome. *Nephrol Dial Transplant.* 2016 pii: gfw271. doi: 10.1093/ndt/gfw271. [PubMed]
				Son male	B SNM		
Splice donor site Error	Intron 5	IVS5+1 G>C		Son male	B moderate	Untranslated in ZnF2 domain of GATA3	Fukami M, Muroya K, Miyake T, Iso M, Kato F, Yokoi H, et al. GATA3 abnormalities in six patients with HDR syndrome. *Endocr J.* 2011;58:117–21. doi: 10.1507/endocrj.K10E-234. [PubMed]
				Father male	Not examined		
				Grandmother	Not Examined		
Gene deletions	D10S1779	250 kb deletion	Deletion of one allele	Uncle male	B SNM	No impact	Van Esch H, Groenen P, Nesbit MA, Schuffenhauer S, Lichtner P, Vanderlinden G, et al. GATA3 haplo-insufficiency causes human HDR syndrome. *Nature.* 2000;406:419–22. doi: 10.1038/35019088.
				Brother male	B SNM		
				Niece female	B SNM		
				Niece female	B SNM		
	6	c.1201_1202delAT	p.Met401Valfs*106	Male	B severe	ZnF1 & ZnF2 are present because they are located down stream	Yang, Aram, Kim, Jinsup, Ki, Chang-Seok, Hong, Sung Hwa, Cho, Sung Yoon, & Jin, Dong-Kyu. (2017). HDR syndrome with a novel mutation in GATA3 mimicking a congenital X-linked stapes gusher: A case report. BMC Medical Genetics, 18(1), 121.

Single Deletion premature stop codon	6	c.1063delC	p.L355X	Female	B moderately severe	NM	Nakamura A, Fujiwara F, Hasegawa Y, Ishizu K, Mabe A, Nakagawa H, et al. Molecular analysis of the GATA3 gene in five Japanese patients with HDR syndrome. *Endocr J.* 2011;58:123–30. doi: 10.1507/endocrj.K10E-246.
Novel frame shift	3	c.649_653delinsAAA	p.His217Lysfs*86	Male	B Moderate	Zinc finger domain disrupted	Kusakawa M, Sato T, Hosoda A, Araki E, Matsuzaki Y, Yamashita Y, Ishihara J, Inagaki Y, Uchida N, Ishii T, Hasegawa T. A neonatal case of HDR syndrome and a vascular ring with a novel *GATA3* mutation. Hum Genome Var. 2019 Dec 23;6:55. doi: 10.1038/s41439-019-0087-1. PMID: 31885872; PMCID: PMC6928020.

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Discussion

The literature review concerned published journals with affected patients presenting with HDR syndrome; analysis failed to display a direct relationship within the genetic presentation to sensorineural hearing loss. 96.7% of reviewed HDR syndrome patients consistently present with nerve deafness. Bilateral deafness occurred at the highest frequency. Collected work highlights sporadic variability in expression of HDR; it can be assumed that the syndrome is more common than data suggests due to unreported cases. Definition of nerve deafness, phenotypically described as "D," identified differencing components resulting in lack of continuity with diagnoses. Audiometry tests provide insight into the degree of hearing loss; these highlights should be provided in HDR literature.

In the reviewed literature, a heterozygous GATA3 nonsense mutation c.826C>T (p.R276*) was determined in family 12/99 by Van Esch et al. and a Chinese family by Wang et al.(1,6). A novel de novo mutation in a Turkish boy identified heterozygous missense mutation c.827G>A (p.R276Q) by Multu et al. (4). Zahirieh et al. found in their study a family with a novel mutation in p.R276. The p.276 variant is located on the first zinc finger motif, resulting in loss of ZnF 1 & ZnF2. The two zinc finger domains are essential for the GATA3 protein binding. Disruption of GATA3 expression has been found to disrupt cochlear structural patter and postsynaptic distinction of the inner ear (6,29,30). Reoccurrence of the variant further infers the proteins' pathogenic role in human HDR syndrome.

GATA3 expression in the inner ear provides insights into inner ear development. Understanding the mechanics of sensorineural hair cell loss in genetic disorders now clues to development and eventually restoration. Novel mutation and the dissimilarity of clinical manifestations broaden the phenotypic and genotypic range of human HDR syndrome. From the collected data, it is evident that no relationship between the genotype and phenotype exists.

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