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REVIEW ARTICLE

Glutaric aciduria type 1: a review of phenotypic and genetic characteristics

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ABSTRACT

Glutaric aciduria type I (GA1) is an inherited metabolic disorder in which excessive levels of the amino acids lysine, hydroxylysine, and tryptophan accumulate in the body as a result of defective glutaryl-CoA dehydrogenase (*GCDH*) enzyme activity. Excessive metabolites are toxic that can cause damage to the brain, particularly due to the occurrence of basal ganglia and intellectual disability. Missense, splicing, and other deletion mutations in *GCDH* gene lead to the deficiency of the enzyme activity and are known to cause GA1. The severity of GA1 along with its neurological manifestations and clinical outcome is dependent upon the age at onset and therefore, early definitive diagnosis of GA1 becomes essential. GA1 occurs in approximately 1 of every 30,000–40,000 individuals worldwide that may reach up to 1 in 300 newborn babies in the Amish and Canadian communities. Owing to very high consanguinity rates in Saudi Arabia, it is presumed to be much more common in the Kingdom and is one of the initial disorders that were included in the country's neonatal screening program. In the current study, we have reviewed clinical manifestations, diagnosis, updated management, and mutation spectrum in GA1 with an example of one of our patients with GA1, and highlighted the importance of multipara-metric strategy in the early diagnosis and management of the disease.

Keywords: Glutaric aciduria, *GCDH* gene, magnetic resonance imaging, carnitine, baclofen.

1. Introduction

Glutaric aciduria type I (GA1) is an autosomal recessive inherited metabolic disorder caused by mutations in the glutaryl-CoA dehydrogenase (*GCDH*) gene (OMIM #608801), which encodes an enzyme belonging to the acyl-CoA dehydrogenase family (1). The enzyme GCDH is active in mitochondria as a homotetramer and is involved in the metabolism of the amino acids L-lysine, L-hydroxylysine, and L-tryptophan, specifically catalyzing the dehydrogenation and subsequent decarboxylation of Glutaryl-CoA, a catabolite of amino acid metabolism, to glutaconyl-CoA and crotonyl-CoA, respectively (2). Deficiency of GCDH enzyme activity due to various mutations leads to the accumulation of toxic metabolites glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid in the blood, urine, and CSF and brain tissue thereby, resulting in the full clinical spectrum of GA1, including imbalances in neurotransmission and neurotoxic effect (3). Among GCDH related pathways are the super pathway of lysine, hydroxyl-lysine, and tryptophan utilization and metabolism (Figure 1). Flavin adenine dinucleotide binding and fatty-acyl-CoA binding are Gene Ontology annotations related to the *GCDH* gene and a number of interacting protein partners of GCDH are reported globally by different research groups (Figure 2). Clinically, neonates with GA1 may be asymptomatic but are usually presented with macrocephaly (4). Although the severity of GA1 varies considerably and the signs and symptoms in most cases occur in infancy, some patients present with milder clinical phenotype, while others have severe problems. The severity of the clinical outcome in GA1 and prevention of the progression to severe neurological and non-neurological manifestations (5) implies that early definitive diagnosis of GA1 is absolutely essential. To confirm the diagnosis promptly, urine organic acid analyses are performed and increased 3-hydroxyglutaric acid with or without increased glutaric acid will confirm GA1 (American College of Medical Genetics and Genomics, ACMG-based Newborn screening ACT sheets and algorithms, https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms). If urine organic acid analyses are unremarkable, it could be followed by urine glutarylcarnitine and blood and CSF 3-hydroxyglutaric

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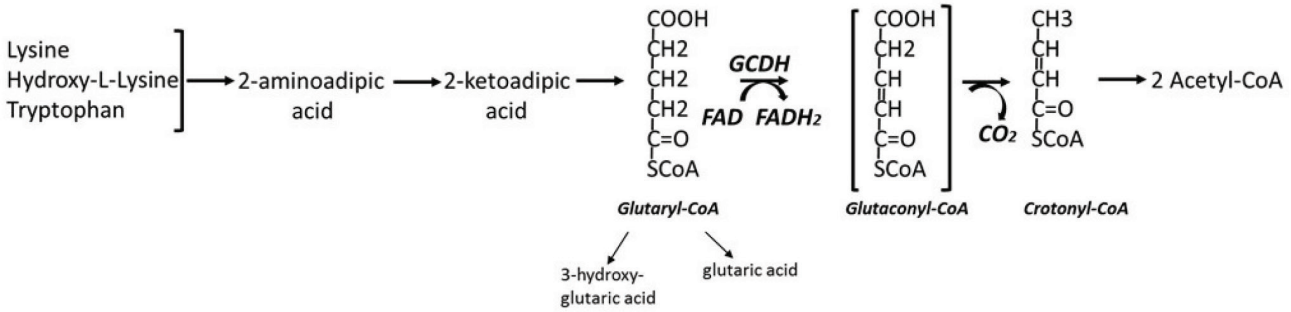

Figure 1. *Catabolism of lysine, hydroxyl-lysine and tryptophan through GCDH pathway.*

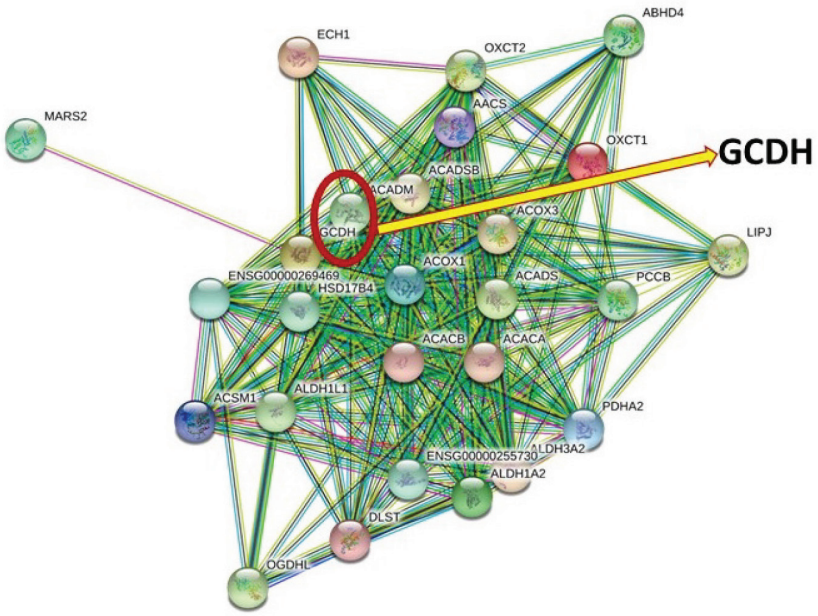

Figure 2. *STRING interaction network of GCDH showing its interaction with protein partners (GeneCards).*

acid analyses, and finally by enzyme assay in fibroblasts, and/or molecular analysis of the *GCDH* gene.

In Saudi Arabia, GA1 was among the first disorders included in the neonatal screening program (6) and therefore, can be appropriately managed once diagnosed early. The reason behind its inclusion in the program stems from the fact that 50%–60% of the marriages in Saudi Arabia are consanguineous that may even reach 80% in some tribal areas (7,8). Moreover, since the incidence of GA1 is high among heavily consanguineous communities, such as the Amish and the Indians in Canada (9,10), it was assumed and rightly so, that autosomal recessive disorders, such as GA1 may occur with a high incidence in Saudi Arabia as well. Despite its inclusion in the Newborn screening (NBS) program and a few literature reports on GA1 from Saudi Arabia, a combinatorial literature review that includes clinical and laboratory-based investigations, including genetics is lacking. This review aims to fill these gaps with data from Saudi GA1 patients in addition to compiling a comprehensive list of all the Human Gene Mutation Database (HGMD) reported mutations in GCDH that could act as a useful resource for future studies.

2. Clinical manifestations

There is variability in the clinical presentation of GA1 among patients, even between relatives, suggesting an interplay of genetics and environmental components. Macrocephaly at birth is the most common feature of GA1. Other clinical features in GA1 include progressive dystonic cerebral palsy, frontotemporal atrophy, acute infantile encephalopathy associated with an upper respiratory and/or gastrointestinal infection, dystonia affecting the upper and lower limbs, face, neck, and trunk, hyperkinetic disorder, basal ganglia degeneration, and sudden death (11–15). Some patients may develop bleeding in the brain and eyes (16). In 60%–70% of patients with GA1, no neurodegenerative disease occurs

if appropriate treatment is given. However, neurological manifestations may begin as early as 6 months of age or as late as 35 years or more even though the patients present with macrocephaly (17). Acute neurological symptoms are triggered either by fever with some degree of dehydration or sometimes without any trigger leading to hypotonia, head control loss, and abnormal movements similar to seizures (18). Some patients may require a nasogastric tube or a permanent gastrostomy tube/button for feeding due to dystonia and decreased coordination of swallowing. Infants with GA1 may also develop acute striatal lesions or chronic striatal atrophy, thereby leading to permanent disability (19). Our own experience with GA1 patients (20) revealed neurodegenerative symptoms with recurrent chest infections, ischemic brain injury, bilateral subdural collections, and atrophy (Figure 3). GA1 clinical manifestations such as cerebral atrophy, cyst-like dilatation of the Sylvian fissures with "batwing" or "box-like" fissures, and basal ganglia atrophy are accompanied by subdural hemorrhages as the disease progress as revealed by brain imaging (21–23).

3. GA1 in the Kingdom of Saudi Arabia

Due to the dearth of literature on GA1 from Saudi Arabia, the current review was able to retrieve only a limited number of publications using the PubMed database. The first study on GA1 by Coates et al. (24) included only three patients (one, a 7-month old male, second, a 20-month old female and third, a 12-month male), which were initially diagnosed as cases of postmeningitic or post-traumatic progressive encephalopathy. Although normal at birth with expected milestones, the authors state that children developed hypotonia, seizures, and neurological symptoms, and were diagnosed as GA1 based on computed tomography (CT) and brain imaging studies (24). The clinical phenotype at the presentation in all the three cases was variable. The first had normal tendon reflexes and no dystonia, the second case had a fever, gastroenteritis, dystonic posturing, choreoathetosis, and spastic quadriplegia, and the third case had fever, vomiting, diarrhea, focal seizure involving left side of the body, and face with positive Babinski sign (24). Mohamed et al. (25,26) described one Saudi GA1 patient who presented with developmental delay, choreoathetosis, and myoclonic seizures and the other with dystonia, misdiagnosed as cerebral palsy, and to have GA1. The authors suggest pediatricians consider GA1 as a differential diagnosis in patients with dystonic cerebral palsy to prevent neurological damage (26). Al-Essa et al. (27) have described a series of seven patients with GA2, who had the distinct clinical phenotype. Alfadhel et al. (28) have recently reported an expanded newborn screening program in Saudi Arabia, and they reported three cases of GA1. The authors of the current study also had recently reported an 11-month old Saudi GA1 case with developmental regression, hepatosplenomegaly, seizure disorder, oropharyngeal swallowing problems, and recurrent chest infections (20).

4. Diagnosis

During the diagnostic workup for patients suspected with GA1, clinical examination is followed by brain imaging and laboratory investigations, including biochemical and molecular genetic testing. At the time of presentation, carnitine levels in plasma may be mildly or severely decreased. Other laboratory investigations may reveal hypoglycemia, ketonuria, and metabolic acidosis with decreased bicarbonate levels. The authors believe that the multi-parametric approach is the best option in GA1 work-up and some of the important assessments include:

4.1 Newborn screening

Although some patients may excrete normal levels of organic acids such as glutarylcarnitine (C5 dicarboxyliccarnitine: C5-DC), elevated levels can be identified by NBS or by more sensitive high-performance liquid chromatography/Tandem MS-based technologies. For a definitive diagnosis, abnormal NBS results may need to be subsequently confirmed first by biochemical testing followed by either enzyme assay in cultured fibroblasts and/or mutation analyses (29,30). NBS helps not only to achieve the diagnosis of GA1 earlier but also impacts long-term implications by allowing earlier treatment management before the onset of symptoms. It has been demonstrated (31) by statistical modeling that GA1 patients identified by NBS show improved motor development and neurological outcome than selective screening group (71% *vs*. 29%). In addition, the manifestation of a movement disorder was significantly reduced in the NBS compared with selective screening group (74% *vs*. 26%). Thus, long-term effects of NBS are clear with a major beneficial effect for neurological outcome parameters.

4.2 Biochemical studies

In the event of positive NBS result, the family of the patient must be immediately informed and confirmatory testing should be initiated as recommended by the pediatric metabolic specialist. Urine organic acid analysis by tandem mass spectroscopy (MS), MS/MS and gas chromatography (GC/MS) is the method of choice for all the diagnostic laboratories dealing with GA1. Increased glutarylcarnitine, glutaconic acid in some patients, and the high excretion of ketone bodies and lactic acid in the urine are indicative of GA1. If urine organic acid analyses are unremarkable, it could be followed by urine glutarylcarnitine and blood and CSF 3-hydroxyglutaric acid Glutarylcarnitine (C5-DC) levels in the blood as measured by Tandem MS, MS/MS analyses, and finally by enzyme assay in fibroblasts, and/or molecular analysis of the *GCDH* gene. The diagnostic workup of patients with suspected GA1 is shown [Figure 4, source American College of Medical Genetics (ACMG) ACT sheet and algorithm].

4.3 Medical imaging

In children with suspected GA1, magnetic resonance imaging (MRI) of the brain is the first choice. Cerebral

atrophy and cyst-like dilatation of the Sylvian fissures with "batwing" or "box-like" fissures are often early findings in GA1 (20,21). Cranial sonography and CT have demonstrated similar findings (32,33). Brain imaging is also used to reveal severe leukoencephalopathy, dilatation of the insular cisterns, regression of the temporal lobes, and hypodensity of the lenticular nuclei (34).

4.4 Molecular genetic analyses

GA1 is caused by mutations in the *GCDH* gene that map to chromosome 19p13.2 with 12 exons encoding 438 amino acid proteins (NM_000159.2; NP_000150.1). In fact, more than 200 different types of mutations that include missense/nonsense, splicing, small deletions,

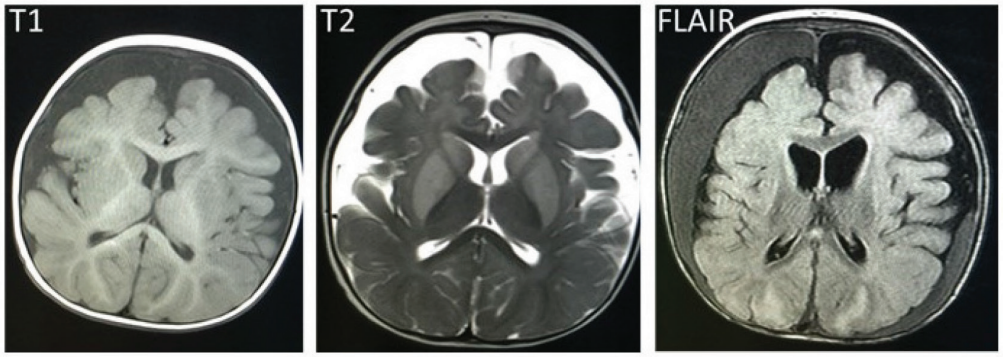

Figure 3. *Brain MRI images in a patient with GA1 showing bilateral subdural collections and atrophy.*

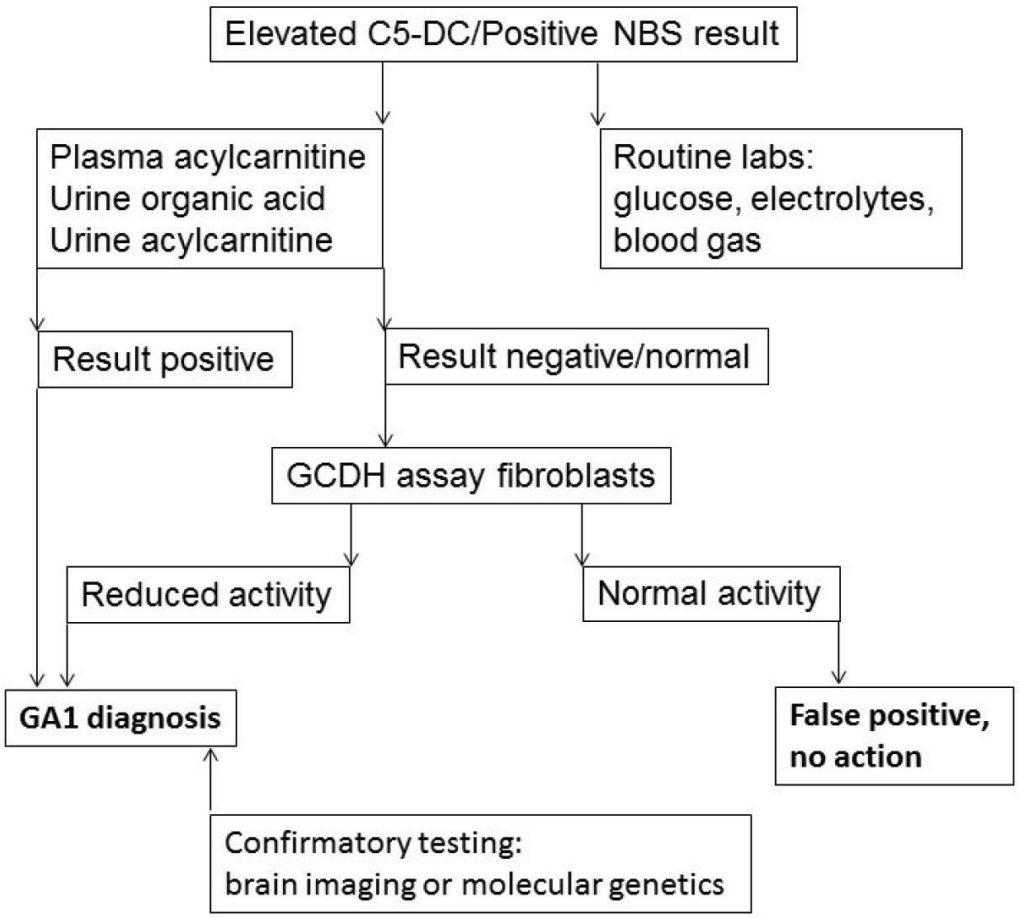

Figure 4. *Algorithm in the diagnostic work-up of GA1 (source ACMG).*

Table 1. *GCDH mutations reported in the literature (HGMD source with references).*

GCDH Missense Mutations					
Variant (nucleotide change)	**Variant (amino acid change)**	**Literature reference**	**Variant (nucleotide change)**	**Variant (amino acid change)**	**Literature reference**
c.227A>C	p.Q76P	*Abdul Wahab (2016) Biomed Res Int 2016, 4074365*	c.1A>G	p.M1?	*Boy (2018) Ann Neurol 83, 970*
c.392A>T	p.E131V		c.148T>G	p.W50G	
c.892G>A	p.A298T		c.240G>C	p.M80I	
c.1168G>T	p.G390W		c.238A>C	p.M80L	
c.278A>G	p.H93R	*Alfadhel (2016) Orphanet J Rare Dis 11, 126*	c.299T>C	p.M100T	
c.242C>T	p.P81L	*Al-Shamsi (2014) Sultan Qaboos Univ Med J 14, e42*	c.380C>T	p.A127V	
c.427G>A	p.V143I		**c.481C>T**	**p.R161W**	
c.301G>A	p.G101R	*Anikster (1996) Am J Hum Genet 59, 1012*	c.510G>C	p.K170N	
c.848T>C	p.L283P		c.511G>T	p.G171W	
c.914C>T	p.S305L		c.538A>G	p.T180A	
c.1168G>C	p.G390R		c.553G>A	p.G185R	
c.1247C>T	p.T416I		c.561C>A	p.D187E	
c.883T>C	p.Y295H	*Biery (1992) Am J Hum Genet 51S A165*	c.641C>T	p.T214M	
c.262C>T	p.R88C		c.682T>C	p.C228R	
c.532G>A	p.G178R		c.764C>G	p.S255W	
c.680G>C	p.R227P		c.881G>A	p.R294Q	
c.877G>A	p.A293T		c.967G>T	p.G323C	
c.1093G>A	p.E365K		c.1127G>A	p.G376E	
c.1156C>T	p.R386*		c.1133C>T	p.A378V	
c.1198G>A	p.V400M		c.1153G>A	p.A385T	
c.1204C>T	p.R402W		c.1163T>C	p.M388T	
c.1240G>A	p.E414K		c.1189G>A	p.E397K	
c.1262C>T	p.A421V		c.1225G>A	p.A409T	
c.727C>G	p.R243G	*Bijarnia (2008) J Inherit Metab Dis 31, 503 c.1239C*	c.1239C>G	p.Y413*	
c.733C>T	p.L245F		c.1243G>A	p.G415S	
c.1274G>T	p.G425V		c.1249C>T	p.H417Y	
c.394C>G	p.R132G	*Boy (2017) Orphanet J Rare Dis 12, 77*	c.1253A>T	p.D418V	
c.1169G>T	p.G390V	*Busquets (2000) Mol Genet Metab 71, 535*	c.467G>T	p.G156V	*Chalmers (2006) Mol Genet Metab 88, 29*
c.1317A>G	p.*439W		c.148T>C	p.W50R	*Chen (2011) Zhonghua Yi Xue Yi Chuan Xue Za Zhi 28, 374*
c.212T>C	p.F71S		c.263G>A	p.R88H	

Continued

GCDH Missense Mutations					
Variant (nucleotide change)	Variant (amino acid change)	Literature reference	Variant (nucleotide change)	Variant (amino acid change)	Literature reference
c.268G>A	p.E90K		c.371G>A	p.G124E	
c.356C>T	p.S119L		c.1169G>A	p.G390E	
c.382C>T	p.R128*		c.658G>A	p.D220N	*Couce (2013) Eur J Paediatr Neurol 17, 383*
c.463T>C	p.Y155H		c.1193A>G	p.Y398C	
c.541G>A	p.E181K		c.542A>G	p.E181G	*Crombez (2008) Mol Genet Metab 94, 132*
c.764C>T	p.S255L		c.683G>T	p.C228F	
c.910G>A	p.A304T		c.192G>T	p.E64D	*Georgiou (2014) Clin Biochem 47, 1300*
c.947C>A	p.A316D		c.803G>T	p.G268V	
c.1115G>A	p.R372K		c.478C>T	p.Q160*	*Park (2010) J Korean Med Sci 25, 957*
c.1298C>T	p.A433V		c.658G>T	p.D220Y	
c.344G>A	p.C115Y	*Goodman (1998) Hum Mutat 12, 141*	c.1147C>A	p.R383S	*Shadmehri (2018) J Cell Biochem*
c.365C>T	p.A122V		c.281G>A	p.R94Q	*Gupta (2015) JIMD Rep 21, 45*
c.382C>G	p.R128G		c.401A>G	p.D134G	
c.412A>G	p.R138G		c.662T>C	p.L221P	
c.416C>T	p.S139L		c.881G>C	p.R294P	
c.536T>G	p.L179R		c.1238A>G	p.Y413C	
c.706T>C	p.F236L		c.1241A>C	p.E414A	
c.796A>G	p.M266V		c.373C>T	p.L125F	*Han (2017) Zhonghua Er Ke Za Zhi 55, 539*
c.923G>C	p.C308S		c.493C>A	p.L165M	
c.926T>G	p.L309W		c.767T>C	p.L256P	
c.937C>T	p.R313W		c.479A>G	p.Q160R	*Höliner (2010) Klin Padiatr 222, 35*
c.997C>G	p.Q333E		c.1015A>G	p.M339V	*Ikeda (1998) Am J Med Genet 80, 327*
c.1060G>C	p.G354R		c.728G>A	p.R243Q	*Jin (2017) Nat Genet 49, 1593*
c.1063C>T	p.R355C		c.922T>C	p.C308R	*Kim (2014) Ann Clin Lab Sci 44, 213*
c.1123T>C	p.C375R		c.245G>C	p.R82P	*Lin (2018) Zhonghua Yi Xue Yi Chuan Xue Za Zhi 35: 39*
c.1144G>A	p.A382T		c.798G>T	p.M266I	*Madruga-Garrido (2007) Rev Neurol 45, 127*
c.1147C>T	p.R383C		c.1021A>C	p.T341P	*Korman (2007) Eur J Paediatr Neurol 11, 81*
c.1148G>A	p.R383H		c.1175A>G	p.N392S	
c.1157G>A	p.R386Q		c.1213A>G	p.M405V	

Continued

GCDH Missense Mutations					
Variant (nucleoti de change)	Variant (amino acid change)	Literature reference	Variant (nucleoti de change)	Variant (amino acid change)	Literature reference
c.1169G>C	p.G390A		c.713T>C	p.L238P	*Lin (2002) Prenat Diagn 22, 725*
c.1174A>G	p.N392D		c.533G>A	p.G178E	
c.1205G>A	p.R402Q		c.1054C>T	p.Q352*	*Martinez Granero (2005) Neurologia 20, 255*
c.1208A>G	p.H403R		c.148T>A	p.W50R	*Mosaeilhy (2017) Metab Brain Dis 32, 1417*
c.1218C>G	p.N406K		c.158C>A	p.P53Q	
c.1220T>C	p.L407P		c.1189G>T	p.E397*	
c.1261G>A	p.A421T		c.1284C>G	p.I428M	
c.508A>G	p.K170E	*Wen (2012) Zhonghua Yi Xue Yi Chuan Xue Za Zhi 29,*	c.797T>C	p.M266T	*Wen (2012) Zhonghua Yi Xue Yi Chuan Xue Za Zhi 29, 642*
c.655G>A	p.A219T	*Tang (2000) Hum Mutat 16, 446*	c.873C>A	p.N291K	*Tsai (2017) J Chin Med Assoc 80, 253*
c.1156C>G	p.R386G		c.176A>C	p.Q59P	*van der Watt (2010) Mol Genet Metab 101, 178*
c.215G>T	p.R72L	*Mushimoto (2011) Mol Genet Metab 102, 343*	IVS1 ds G-T +5	c.91+5G>T	*Greenberg (1995) Hum Mol Genet 4, 493*
c.464A>G	p.Y155C		IVS2 as A-T -2	c.128-2A>T	*Zschocke (2000) J Med Genet 37, 177*
c.556A>T	p.S186C		IVS3 ds G-A +1	c.271+1G>A	*Tang (2000) Hum Mutat 16, 446*
c.730G>A	p.G244S		IVS4 ds G-T -1	c.334G>T	*Zhang (2016) Clin Chim Acta 453, 75*
c.1061G>C	p.G354A		IVS4 ds T-C +2	c.334+2T>C	*Mushimoto (2011) Mol Genet Metab 102, 343*
c.1081A>G	p.K361E		IVS4 ds G-A +5	c.334+5G>A	*Goodman (1998) Hum Mutat 12, 141*
c.1237T>G	p.Y413D		IVS5 ds G-A +1	c.505+1G>A	*Xiong (2015) Science 347*
c.1219C>G	p.L407V	*Pierson (2015) Neurogenetics 16, 325*	IVS6 as G-A -1	c.636-1G>A	*Xiong (2015) Science 347*
c.730G>T	p.G244C	*Pirzadeh (2017) Iran J Child Neurol 11, 58*	IVS7 as A-G -2	c.853-2A>G	*Alfadhel (2016) Orphanet J Rare Dis 11, 126*
c.1118A>G	p.N373S		IVS7 ds G-A +5	c.852+5G>A	*Bijarnia (2008) J Inherit Metab Dis 31, 503*
c.674G>A	p.W225*	*Radha Rama Devi (2016) Brain Dev 38, 54*	IVS10 as A-G -11	c.1244-11A>G	*Abdul Wahab (2016) Biomed Res Int 2016*

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GCDH Missense Mutations					
Variant (nucleoti de change)	Variant (amino acid change)	Literature reference	Variant (nucleoti de change)	Variant (amino acid change)	Literature reference
c.856C>T	p.P286S		IVS10 as A-C -2	c.1244-2A>C	*Chen (2018) Zhonghua Yi Xue Yi Chuan Xue Za*
c.1228G>A	p.V410M		IVS10 as A-G -2	c.1244-2A>G	*Fraidakis (2015) JIMD Rep 18, 85*
c.397G>T	p.V133L	*Schillaci (2016) Mol Genet Metab 119, 50*	IVS10 ds G-C +1	c.1243+1G>C	*Schwartz (1998) Hum Genet 102, 452*
c.521T>C	p.L174P		**GCDH Small Deletion Mutations**		
c.997C>T	p.Q333*		c.11delG	p.(Arg4Lysfs*8)	*Crombez (2008) Mol Genet Metab 94, 132*
c.281G>T	p.R94L	*Schwartz (1998) Hum Genet 102, 452*	c.90delC	p.(Glu31Argfs*30)	*Mushimoto (2011) Mol Genet Metab 102, 343*
c.442G>A	p.V148I		c.109_110delCA	p.(Gln37Glufs*5)	*Tsai (2017) J Chin Med Assoc 80, 253*
c.482G>A	p.R161Q		c.146_149delACTG	p.(Asp49Glyfs*11)	*Wen (2012) Zhonghua Yi Xue Yi Chuan Xue Za*
c.572T>C	p.M191T		c.158delC	p.(Pro53Argfs*8)	*Goodman (1998) Hum Mutat 12, 141*
c.583G>A	p.A195T		c.219delC	p.(Tyr74Thrfs*68)	*Boy (2017) Orphanet J Rare Dis 12: 77*
c.770G>A	p.R257Q		c.387_388delGC	p.(Glu129Aspfs*58)	*Busquets (2000) Pediatr Res 48, 315*
c.769C>T	p.R257W		c.420_429del10	p.(Met141Serfs*80)	*Wen (2012) Zhonghua Yi Xue Yi Chuan Xue Za*
c.832C>T	p.P278S		c.485delA	p.(Gln162Argfs*62)	*Radha Rama Devi (2016) Brain Dev 38, 54*
c.880C>T	p.R294W		c.553_570del18	p.(Gly185_Ser190de	*Bross (2012) J Inherit Metab Dis 35, 787*
c.1045G>A	p.A349T		c.636-3_639delCAGG	p.(?)	*Shu (2003) J Formos Med Assoc 102, 729*
c.1060G>A	p.G354S		c.636-4_639delCCAG	p.(?)	*Wen (2012) Zhonghua Yi Xue Yi Chuan Xue Za*
c.1064G>A	p.R355H		c.848delT	p.(Leu283Argfs*8)	*Pierson (2015) Neurogenetics 16: 325*
c.1286C>T	p.T429M		c.873delC	p.(Asn291Lysfs*41)	*Wang (2014) Brain Dev 36, 813*
c.1298C>A	p.A433E		c.877delG	p.(Ala293Profs*39)	*Chen (2011) Zhonghua Yi Xue Yi Chuan Xue Za*
c.787A>G	p.M263V	*Muhlhausen (2003) J Inherit Metab Dis 26, 713*	c.1144_1145delGC	p.(Ala382Profs*14)	*Mushimoto (2011) Mol Genet Metab 102, 343*
c.431A>C	p.Q144P	*Tp (2017) J Pediatr Genet 6, 142*	c.1161_1174del14	p.(Asp387Glufs*5)	*Schwartz (1998) Hum Genet 102, 452*
c.456C>G	p.I152M		c.1173delG	p.(Asn392Metfs*9)	*Anikster (1996) Am J Hum Genet 59, 1012*

Continued

GCDH Missense Mutations					
Variant (nucleoti de change)	Variant (amino acid change)	Literature reference	Variant (nucleoti de change)	Variant (amino acid change)	Literature reference
c.1240G>T	p.E414*				
c.157C>T	p.P53S	*Viau (2012) Mol Genet Metab 106, 430*	c.578_579insTCA		*Korman (2007) Eur J Paediatr Neurol 11, 81*
c.437C>A	p.S146Y		c.646_649dupTCGC		*Moseilhy (2017) Metab Brain Dis 32, 35*
c.640A>G	p.T214A		c.1172_1173insT		*Wang (2014) Brain Dev 36, 813*
c.833C>G	p.P278R		c.1173dupG		*Gupta (2015) JIMD Rep 21, 45*
c.905T>C	p.L302P		**GCDH Indel Mutations**		
c.1022C>T	p.T341I		c.588_589delCTinsTCCA		Boy (2018) Ann Neurol 83, 970
c.150G>C	p.W50C	*Zschocke (2000) J Med Genet 37, 177*	**GCDH Missense Mutations**		
c.226C>T	p.Q76*		c.406G>T	p.G136C	*Wang (2014) Brain Dev 36, 813*
c.337T>C	p.Y113H		c.411C>G	p.Y137*	
c.383G>A	p.R128Q		c.416C>G	p.S139W	
c.395G>A	p.R132Q		c.901G>A	p.V301M	
c.397G>A	p.V133M		c.979G>A	p.A327T	
c.413G>A	p.R138K		c.1207C>T	p.H403Y	
c.526T>C	p.C176R		c.628A>G	p.K210E	
c.541G>C	p.E181Q		c.700C>T	p.R234W	
c.554G>C	p.G185A		c.731G>T	p.G244V	
c.650C>T	p.P217L		c.963G>C	p.Q321H	
c.743C>T	p.P248L		c.1031C>T	p.T344I	
c.775T>C	p.S259P		c.1109T>C	p.L370P	
c.938G>A	p.R313Q		c.1239C>A	p.Y413*	*Zschocke (2000) J Med Genet 37, 177*
c.1154C>T	p.A385V				

Various mutations in GCDH are categorized based on the nature of change (deletion, insertion, etc.) and/or structural effect on protein amino acid (missense, nonsense, splicing, etc.). Mutation nomenclature is based on the recommendations by HGVS (http://www.HGVS.org/mutnomen).

small insertions, indels, and intronic variants are known in GCDH1 (Table 1) (35). Consequently, molecular genetic testing plays a confirmatory role in the diagnosis of GA1. The most common mutation occurring in *the GCDH* gene is R402W in exon 10 that accounts for less than 20% of mutations and the mutation retains only about 3% enzyme activity (1). The current study authors have previously reported mutation c.482G > A; p.R161Q in one of the patients with GA1 (20). While polymerase chain reaction and Sanger sequencing-based techniques could identify targeted mutations in the *GCDH* gene, next-generation sequencing-based methods that include whole exome sequencing is increasingly being utilized (36–39) for disorders with allelic heterogeneity and could potentially be used as a discovery tool in GA1 for identifying novel allelic variants.

5.Management

5.1 Dietary and emergency management

Clinically GA1 could be kept symptom-free when treated and managed during the neonatal period (40). In contrast, delayed diagnosis and the appearance of neurologic manifestations may lead to poor clinical and therapeutic outcome although neurologic deterioration

Table 2. *Treatment protocol in patients with GA1 (based on guidelines by Koeller et al. (2011).*

Inpatient emergency management protocol (birth up to 6 years)	
1. Intravenous infusion IV	
Age group (years)	Glucose
0–1	12–15
1–3	10–12
3–6	8–10
Intravenous infusion IV	Insulin
If hyperglycemia	
Above 150–180 mg/dl (>8–10 mmol/l)	0.025–0.05
or glucosuira developed	
2. Protein intake	
Natural protein	Discontinue for 24 hours
	Introduce again for 2–3 days
3. Medication	
L-carnitine	100 mg/kg per day IV
Antipyretic above 38.5°C (ibuprofen or paracetamol)	10–15 mg/kg/dose three to four times per day
Sodium bicarbonate	
4. Monitoring	
Clinical	Vital signs
	Input-output chart
	Neurological assessment -Glasgow Coma Scale
Laboratory	Blood glucose, blood count, blood culture (if infection)
	Blood gases., Electrolytes
	Creatinine level
	Amino acids, carnitine, creatinine, C-reactive protein
	Urine ketone bodies and pH
Outpatient emergency management protocol (beyond 6 years)	
1. Maintenance Management	
Dietary management up to 6 years	Low lysine diet (calculated daily requirement)
	Tryptophan-reduced amino acid mixtures
	Combined with creatinine supplementation
Dietary management above 6 years	Controlled protein intake using natural protein
	Low lysine content and avoiding food with a high content of lysine
2. Medication	
Carnitine supplement	Reduce risk for striatal injury
Riboflavin	No clear evidence or standardized protocol
Baclofen	Treatment of movement disorders
Benzodiazepines-diazepam and clonazepam	Positive effects in the majority of symptomatic patients
Anticholinergic drugs-Trihexyphenidyl	For dystonia

may be overcome in some patients (41–43). When NBS result is positive or GA1 is suspected during the clinical examination after urine analyses, for example, treatment is recommended immediately to prevent metabolic crisis or neurological squall. Initiation of early treatment during the newborn period prevents symptoms in the majority of the patients (~90%). During a metabolic crisis, appropriate emergency management includes a low-lysine diet with carnitine supplementation to allow for the normal growth (44). Patients who follow maintenance therapy management recommendations rarely develop dystonia, and patients who are noncompliant to maintenance or emergency treatment develop dystonia to about 44% or 100%, respectively (45). Revised recommendations for the diagnosis and management of GA1 have been published by Boy et al. (46). In case of no alarming clinical crisis, such as consciousness, vomiting, and dystonia, home management for up to 12 hours and reassessment after every 2 hours is recommended followed by maintenance treatment. Maintenance treatment may involve dietary management to reduce lysine intake or medication. In order to avoid the less prominent clinical effect, the daily requirement of lysine should be calculated accurately (47). Strict adherence to the protocol has shown favorable neurological outcome in most studies (48–51). Maltodextrin solutions or comparable carbohydrate supplementations can be given orally or through NGT as appropriate.

GA1 patients presenting with encephalopathic crises require aggressive emergency management protocol since maintenance treatment by itself is not sufficient to overcome the metabolic crisis, and delayed treatment initiation may lead to striatal injury and dystonia. It is, therefore, recommended to start the emergency protocol as soon as possible with minimal clinical suspicion and intensified according to the need (52–54). The objective of this aggressive protocol is to reverse the metabolic crises, decrease neurotoxic metabolite production, and enhance physiological detoxification mechanisms. Since the acute crisis is significantly reduced beyond 6 years of age and subclinical cerebral insult cannot be excluded, the threshold to start emergency treatment should be low in this age group. The emergency management protocol (in-patient and out-patient) guidelines in practice (46) are summarized (Table 2), and the differences in the protocol depend upon the clinical status of the patient. The use of antipyretics is recommended when the body temperature is above 38.5°C. In the case of movement disorder and dystonia phenotype, appropriate medications are recommended (55) (Table 2).

5.2 Neurological complications management

Dystonia and epilepsy are the two major neurological complications in patients with GA1. A number of dystonia rating scales, such as the Bary-Albright, the Burke-Fahn-Marsden, and the gross motor function classification system have been proposed to assess the severity of neurological conditions (56,57). Despite the challenges in treating GA1-dystonia, drug therapy using specific drugs such as Baclofen together with Benzodiazepines (Diazepam and Clonazepam), Zopiclone, Anticholinergic drugs Trihexyphenidyl, and Botulinum toxin type A have been effectively used (55). The use of antiepileptic drugs in patients with GA1 should be based on individual assessment. Although the outcome has been poor, neurosurgery (pallidotomy) and deep brain stimulation remain an option for improvement of dystonia (58).

5.3 Long-term management

For long-term management of patients with GA1 to ensure the effectiveness of treatment, compliance, prevention of neurological complications and possibly early death, clinical monitoring, and transitional care concept must be adopted. Clinical monitoring may involve but is not restricted to, dietary components, neurological evaluation, psychological tests, and developmental milestones. On the other hand, transition care could involve an interdisciplinary team of experts consisting of metabolic experts, nutritionists, psychologists, neurologists, pediatricians, and social workers (59).

6. Animal Model of GA1

A knock-out mouse model of GA1 (GCDH −/− mice) was developed by Koeller et al. (60) via the GCDH gene targeting technology in embryonic stem cells. Although the biochemical phenotype and pathology of the GCDH −/− mice were similar to that seen in patients however, the knock-out mice failed to show any neurological phenotype observed in GA1 patients. The authors attribute this effect to intrinsic differences between the striata of mice and humans. When the GCDH −/− mouse was exposed to high protein or lysine diet, it resulted in vasogenic edema, neuronal loss, hemorrhage, paralysis, seizures, and death within days resembling human GA1 (61). GCDH −/− mouse was susceptible to encephalopathy and brain injury after exposure to dietary protein (62). These studies demonstrated the involvement of mitochondrial disruption in age-dependent brain injury of GA1.

7. Conclusion

In conclusion, GA1 as a disease is not well studied in Saudi Arabia from a research perspective. Since neurological manifestations can be permanent and devastating, future studies in Saudi Arabia are needed to investigate the prevention and targeting strategies, long-term outcome, and treatment monitoring. The establishment of GA1 focus-research groups that should aim to combine basic science with clinical research using modern high-throughput technologies, such as whole genome and/or whole exome approaches, is the way forward.

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This study is approved by the King Fahad Medical City Institutional Review Board (Ref. No.16-053).

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