The potential consequences of bidirectional promoter methylation on GLA and HNRNPH2 expression in Fabry disease phenotypes in a family of patients carrying a GLA deletion variant

MOHAMMED A. AL-OBAIDE, IBTISAM I. AL-OBAIDI and TETYANA L. VASYLYEVA

Department of Pediatrics, School of Medicine, Texas Tech University Health Sciences Center, Amarillo, TX 79106, USA

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Abstract. Fabry disease (FD) is a rare inherited disease characterized by a wide range of symptoms attributed to GLA mutations resulting in defective α-galactosidase A (α-Gal A) and accumulation of glycosphingolipids. The GLA locus is paired in a divergent manner with the heterogeneous nuclear ribonucleoprotein HNRNPH2 locus mapped in the RPL36A-HNRNPH2 readthrough locus. As a follow-up to our recent finding of the co-regulation of GLA and HNRNPH2 via a bidirectional promoter (BDP) in normal kidney and skin cells, the potential accumulative influence of BDP methylation and GLA mutation on the severity of FD in patients from the same family, two males and two females carrying a GLA deletion family, c.1033_1034delTC (p.Ser345Argfs) was addressed in the present study. The molecular analyses of the FD patients compared with the control revealed that the expression of GLA was significantly low (P<0.05), and HNRNPH2 showed a tendency of low expression (P<0.1) when BDP methylation was elevated in FD patients, compared with normal, with low BDP methylation and high GLA expression (P<0.05), and a high trend of HNRNPH2 expression in normal individuals. The accumulative effects of the mutation and BDP methylation with the severity of the disease were observed in three patients. One male FD patient, a member of the FD family diagnosed with progressive loss of kidney function, hypertension, and eventually a stroke, and the lowest level of α-Gal A enzyme activity showed the highest BDP DNA methylation level. It is concluded that the DNA methylation of GLA-HNRNPH2 BDP may serve a role in diagnosing and treating FD.

Introduction

Fabry disease (FD) is a rare familial sex X-linked disorder attributed to GLA mutations. The disease is a progressive severe genetic condition that worsens over time and is characterized by various symptoms (1,2). Genetic and Rare Diseases Information Center (GARD) reported 76 symptoms that patients with this disease may have (rarediseases.info.nih.gov). The FD symptoms may develop during childhood (classic type) or middle adulthood (atypical type); males tend to have more severe symptoms (1). The GLA mutations can cause total or partial decreased activity of α-galactosidase A (α-Gal A) and accumulation of glycosphingolipids, globotriaosylceramide (Gb3/GL-3), and globotriaosylsphingosine (lyso-Gb3) in various cells and organs including the skin, eyes, kidneys, heart, brain, and peripheral nervous system (3,4). The therapeutic approach for FD is enzyme replacement therapy (ERT); this treatment is used to substitute the missing or an altered partially functional α-Gal A (5-8). Additionally, pharmacological chaperone (PC) 1-deoxygalactonojirimycin is used for the treatment of amenable α-Gal A missense mutations (9-11). However, ERT and PC cannot treat all FD symptoms and may cause adverse side effects; thus, persistent symptoms in patients reduce their quality of life (12). Consequently, it is an open question whether FD clinical manifestations are solely the result of α-Gal A malfunction. The GLA gene is located at chrX: 101397791-101408013, mapped at the reverse strand of the RPL36A-HNRNPH2 readthrough locus (chrX: 101390890-101414140) that appears on the forward strand of the complete genomic region NC_000023.11. The RPL36A-HNRNPH2 readthrough locus is composed of RPL36A and HNRNPH2 genes mapped at chrX: 101390890-101396154 and chrX: 101408133-101414140, respectively. Ensembl (https://useast.ensembl.org/index.html) and ClinVar-NCBI (https://www.ncbi.nlm.nih.gov/clinvar/) databases showed that GLA, HNRNPH2, and RPL36A genes are mapped in the RPL36A-HNRNPH2 readthrough genomic region in humans and are likely involved in FD and other genetic conditions (Table S1).

In our prior research (12), human cells (adult epidermal keratinocytes, renal glomerular endothelial cells, renal epithelial cells, and 293 T cells) were used to show the function of the bidirectional promoter (BDP) in the expression of GLA and HNRNPH2 loci, which are paired in a divergent manner. One of the primary BDP features is the presence of a susceptible CpG Island (CGI) to DNA methylation (12). The promoters' methylation is associated with various diseases, and the level of CGI methylation is a further factor in the severity of the...
Participants. Of more invasive tissues, such as skin or kidney biopsy.

and GLA on the severity of the disease in FD patients and on the Genomics databases. GLA, Mainz Severity Score Index (FOS‑MSSI) (15). (MSSI) and the Fabry Outcome Survey adaptation of the data in scientific research. The blood samples were collected and FD participants agreed to the use of their samples and referred by primary care physicians and were not on any medi‑

Health Sciences Center (Amarillo). The healthy subjects were study from the outpatient clinic of the Texas Tech University subjects, two males and two females were recruited for the study. The healthy participants age ranges were 28‑45 and 18‑39 years respectively. The mean age of the healthy and FD participants was 34.3±7.5 and 31.5±9.3 years respectively. The inclusion criteria for participants were written informed consent, collection of venous blood, understanding and agreeing to comply with the planned study procedures, and for FD patients they had to be part of the family being studied and had to be diagnosed with FD. The females could not be or trying to get pregnant during the duration of the study. Exclusion criteria included being unable or unwilling to provide consent to participate in this study. The healthy subjects, two males and two females were recruited for the study from the outpatient clinic of the Texas Tech University Health Sciences Center (Amarillo). The healthy subjects were referred by primary care physicians and were not on any medications and had no significant medical problems. The healthy and FD participants agreed to the use of their samples and data in scientific research. The blood samples were collected between May 2016‑May 2018. The severity of FD in the four patients was measured using the Mainz Severity Score Index (MSSI) and the Fabry Outcome Survey adaptation of the Mainz Severity Score Index (FOS‑MSSI) (15).

Genomics databases. The sequences of the GLA, HNRNP2H, and RPL36A and the predicted sequence of the BDP for the divergently paired genes GLA and HNRNP2H were searched in NCBI‑Gene (https://www.ncbi.nlm.nih.gov/gene/), UCSC genome browser (https://genome.ucsc.edu/), and the Ensembl genomics databases (https://useast.ensembl.org/index.html). Genomic tools in the databases were used to retrieve the sequences and identify the forward and reverse strands. The BLAT tool (https://genome.ucsc.edu/cgi‑bin/hgBlat?command=start) was used to verify map position on a Tandem Mass Spectrometry to verify abnormal serum GLA‑HNRNPH2 deletion mutation was performed by Duke University Health System/BGL‑Genzyme Fabry Testing (Durham). The patient's genomic DNA from peripheral blood was amplified by PCR, followed by Sanger DNA sequencing of the coding region of the GLA gene and flanking intronic sequences, with a minimum of 20 bp of the GLA gene.

Detection of the GLA deletion variant. The genetic analysis to identify the GLA mutation was performed by Duke University Health System/BGL‑Genzyme Fabry Testing (Durham). The patient's genomic DNA from peripheral blood was amplified by PCR, followed by Sanger DNA sequencing of the coding region of the GLA gene and flanking intronic sequences, with a minimum of 20 bp of the GLA gene.

a‑GAL test. The a‑GAL test was performed by Quest diagnostics (Amarillo, TX, USA) using Flow Injection Analysis on a Tandem Mass Spectrometry to verify abnormal serum a‑GAL results in male patients with a clinical presentation suggestive of FD (testdirectory.questdiagnostics.com/test/test‑detail/37621/alpha‑galactosidase‑leukocytes?cc=MASTER).

Statistical analysis. Microsoft Excel 365 (Microsoft Corporation) was used for sorting the data and for analysis. Data are presented as the mean ± SD. GraphPad Prism version 7.01 (GraphPad Software, Inc.) was used for statistical analysis of the various parameters reported in this study. A Student's
**Results**

**Case presentation.** Four members of the same family were diagnosed with FD (Table I); two males and two females were recruited for the study from the outpatient clinic of the Texas Tech University Health Sciences Center. The four patients showed variable MSSI and FOS-MSSI severity scores (Table SII). The FD family history is shown in the pedigree diagram (Fig. 1). Among the male members of the family, one, FD4 (Table I, Fig. 1) was diagnosed based on a very low level of the α-GAL enzyme (<1%), the test was performed by Quest Diagnostics after presenting to our clinic with progressive loss of kidney function, depression, stroke, angiokeratomas, and hypertension. Additionally, FD3 was diagnosed with the typical distribution of angiokeratomas and peripheral neuropathy. Two female patients, who were sisters (FD1 and FD2) had arrhythmias, bradycardia, and peripheral neuropathy with no renal involvement. BGL-G enzyme Fabrazyme (agalsidase β), an enzyme replacement therapy, was used to treat FD patients, which, although prevented the development of renal involvement in the male who was diagnosed early, did not lead to the resolution of all symptoms in the observed patients; the patients were followed-up for 5 years. Considering our previous finding (12), the potential

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**Table I. List of the FD patients and their clinicopathological criteria.**

| Patients | Sex/age, years | Symptoms | Family history | ERT | RRT | Notes |
|----------|----------------|----------|----------------|-----|-----|-------|
| FD1      | F/35           | Arrhythmia/Bradycardia, Peripheral Neuropathy | Yes | Yes | No  | ERT stopped |
| FD2      | F/34           | Arrhythmia/Bradycardia, Peripheral Neuropathy | Yes | Yes | No  | ERT stopped |
| FD3      | M/18           | Multiple angiokeratomas, Peripheral Neuropathy | Yes | Yes | No  | Died of an unrelated cause |
| FD4      | M/39           | Progressive loss of kidney function, ESRD Hypertension, Depression, stroke, angiokeratomas | Yes | Yes | Yes | Died of a from stroke |

M, male; F, female; ERT, enzyme replacement therapy; RRT, renal replacement therapy; FD, Fabry disease; ESRD, end-stage renal disease.

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**Figure 1. The pedigree of the FD family.** Circle, female; square, male; white, not examined subjects or individuals who showed no symptoms; black diagonal line, FD deceased family member; red diagonal line, carrier; arrow, the first patient diagnosed in the study. FD1-FD4: patients participated in the study. FD, Fabry disease.
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link between CGI methylation levels of the BDP and the expression of GLA and HNRNPH2 was investigated in the FD family members with variable clinical manifestations and FD severity.

The genomic setting of TC deletion in the GLA locus. The GLA locus is mapped to the reverse strand of the RPL36A-HNRNPH2 readthrough locus that appears on the forward strand of the complete genomic region NC_000023.11 (Fig. 2A). The c.1033_1034delTC deletion mutation is in GLA exon seven of the translated region (Fig. 2B and 3A). The position of the TC dinucleotide deletion is c.1033_1034delTC in the coding sequence at the last TC dinucleotide of the TC tri-dinucleotide repeat, TCTCTC, underlined in Fig. 3B. The consequence of TC deletion is a shift in the DNA sequence and the generation of a distorted reading frame of the coding sequence and the formation of three premature nonsense codons indicated by the circled portion of the sequence in Fig. 3C, compared with one natural termination codon, TAA in the normal GLA sequence (Fig. 3B). The deletion mutation results in an amino acid serine (S) (Fig. 4A), encoded by the triplet TCA (Fig. 3B), along the α-Gal A polypeptide sequence, being altered to a new sequence starting with arginine (R) (Fig. 4B), encoded by the triplet AGG (Fig. 3C). The new amino acid sequence is terminated by a premature nonsense codon, TAA (END) (Fig. 3C and 4B). In addition to the NCBI-ClinVar database (Table II), peer-reviewed studies (18-23) have also reported the deletion variant, c.1033_1034delTC, in FD patients previously.

Methylation analysis of the GLA- HNRNPH2 BDP. The GLA and HNRNPH2 loci are located within the readthrough locus RPL36A-HNRNPH2, the GLA locus is at the reverse strand, whereas the HNRNPH2 locus appears at the forward strand (Fig. 2A). Our previous study showed one of three identified BDP CpG islands, CGI-2 composed of 323 bp and mapped along the BDP sequence, was methylated in four normal human cell types (12). Using the same Methylation-Specific PCR (MSP) protocol and the same primers reported in our previous study (12), the methylation status of the BDP CGI-2 at position 241-563 (Fig. S1) in DNA isolated from blood samples of FD patients compared with normal individuals was evaluated. The DNA methylation analysis showed variable levels of methylation in BDP in the tested blood samples; DNA methylation was elevated in both the male and female patients compared with methylation in the normal group (Fig. 5A-1 and B-1, P<0.05).

Expression of GLA and HNRNPH2 in Fabry patients and healthy individuals. The molecular events regulating the expression of the GLA and HNRNPH2 transcripts are not well established. As a follow-up to our previous finding of GLA-HNRNPH2 BDP and the observed methylation levels in normal kidney and skin cells (12), in this study, the potential impact of BDP methylation on GLA and HNRNPH2 expression in four FD patients carrying the deletion mutation c.1033_1034delTC (p.Ser345Argfs) was determined. As shown in Fig. 5, the expression of GLA is significantly lower (P<0.05) and HNRNPH2 showed a tendency of low expression (P=0.1) in the FD patients when the levels of BDP methylation were high compared with high GLA expression when BDP methylation was low in normal individuals (P<0.05). The results showed potential accumulative effects of the GLA mutation c.1033_1034delTC and BDP methylation with the severity of disease in FD patients as discussed below. This association was
clearly demonstrated in male patient FD4, a family member who was diagnosed with progressive loss of kidney function, depression, stroke, angiokeratomas, and hypertension. He had the highest BDP DNA methylation and lowest GLA and HNRNPH2 expression levels (Fig. S2, Table SIII).

Discussion

The detailed genetic presentation has not yet been fully elucidated in FD, which is a clinically heterogeneous, slow, and progressive disease that can show >70 symptoms (rarediseases.info.nih.gov). Although FD is a life-threatening, multisystemic condition, and patients exhibit a wide range of clinical symptoms, the primary cause of the disease is attributed to pathogenic GLA mutations (1-5). The present study highlights the association of additional genetic factors in addition to GLA with FD and shows an indicator of suspicion that FD is caused solely by GLA mutations. Our previous study (12) and the current study show the potential of including study of HNRNPH2 and the GLA-HNRNPH2 BDP methylation status in the diagnosis, therapy, and development of the disease.

Although few studies have dealt with the role of methylation in FD, for a review see Di Risi et al (24); the present study provided further evidence on the potential role of DNA methylation involvement in the clinical manifestation of FD. The GLA mutations can cause total or partial decreased activity of α-Gal A and accumulation of glycosphingolipids (3,4). Intriguingly, the potential source of GLA-HNRNPH2 BDP
methylolation is likely sphingolipids. Aside from their prominent roles as structural lipids, sphingolipids and their metabolizing enzymes are found in the nucleus and linked to chromatin remodeling and epigenetic regulation of gene expression (25). Furthermore, additional species of sphingolipids serve different functions, such as functioning as signaling molecules and can control gene expression via DNA methylation (26). A further point is that the FD patients in the present study were carriers of a TC deletion caused by c.1033_1034delTC in the GLA exon 7 near the 3'-UTR region, and such a deletion may influence the regulatory function of the 3'-UTR sequence. For example, methylation of the N(6) position of adenosine m(6)A is a posttranscriptional modification of RNA. It was found that m(6)A sites are enriched near stop codons and in 3' UTRs, and there is an association between m(6)A residues and microRNA-binding sites within 3' UTRs (27).

The majority of patients with FD may experience chronic or episodic pain, known as FD crises or acroparaesthesiae (12,28-30). The development of pain in FD is hypothesized to be primarily neuropathic; the suggested cause is serum and tissue accumulation of Gb3 and its influence on the peripheral nervous system, which may lead to cell swelling (31-34). Furthermore, a question has been raised on whether the HNRNPH2 and the BDP methylation may play a role in diagnosing and treating chronic pain in FD patients and other related FD clinical symptoms. Earlier studies have demonstrated the association between alternative RNA splicing and pain (35,36). The products of HNRNP genes, including HNRNPH2, are RNA binding proteins that are associated with the mRNA splicing process (12). HNRNPH1 and HNRNPF are post-transcriptional regulators of opioid receptor expression (37), and similar protein structures are produced by HNRNPH2 and HNRNPF (38). This may suggest HNRNPH2 involvement in the pain experienced by FD patients. BDP methylation may cause abnormalities in HNRNPH2 expression and defects in mRNA splicing. A previous study suggested that DNA methylation not only affects gene expression but also regulates alternative splicing (39).
At present, little is known regarding the role of RPL36A in FD. The knockdown of RPL36A, the first gene in the RPL36A-HNRNP2 readthrough region, using a targeting siRNA showed a significant decrease not only in RPL36A expression but also in GLA expression (40). The RPL36A gene, also known as MIG6, encodes the ribosomal protein L36a, and over-expression of this protein is associated with cellular proliferation in hepatocellular carcinoma (41,42).

In the present study, we also sought to explain the heterozygous status of GLA variant c.1033_1034delTC, p.Ser345Argfs, in the FD female patients. The inheritance of several X-linked conditions is not visibly dominant or recessive (43). In females, one altered copy of the gene usually leads to less severe health problems than those in affected males, or it may have no warning signs. In females a high FD penetrance was observed; at least 70% of females showed the clinical manifestations of the disease (44). Thus, it is suggested that when referring to females with FD, the term carrier should be avoided and replaced by the term heterozygotes (45).

Finally, although the results of the present study showed further evidence of the potential involvement of BDP methylation, in addition to the GLA gene and the HNRNP2 gene in FD severity, the precise mechanism that regulates the bidirectional transcription of GLA and HNRNP2 is yet to be fully understood. Additional studies using novel experimental and bioinformatics-based methods, including high-throughput approaches and data analysis by developing machine learning models for computational estimation of methylation profiling (46,47) are required for a better understanding of the architecture, cis-regulatory elements of GLA and HNRNP2 and the cumulative effects of GLA mutations and the GLA-HNRNP2 BDP methylation in FD.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions
TLV analyzed and interpreted the clinical patient data. MAAO and IIAO performed and interpreted the molecular analyses. TLV and MAAO confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate
The present study was approved by the Institutional Review Board of the Texas Tech University Health Science Center (Amarillo, USA).

Patient consent for publication
Written informed consent was obtained from the healthy individuals and patients, whom all agreed to the use of their blood samples for scientific research and for the publication of the anonymized data.

Competing interests
The authors declare that they have no competing interests.

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