Biochemical and Biophysical Research Communications xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

The adult polyglucosan body disease mutation *GBE1* c.1076A>C occurs at high frequency in persons of Ashkenazi Jewish background

Abrar Hussain [a], Joy Armistead [a], Lara Gushulak [a], Christa Kruck [a], Steven Pind [a], Barbara Triggs-Raine [a], Marvin R. Natowicz [b,*]

[a] Department of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, Canada
[b] Pathology and Laboratory Medicine Institutes and Genomic Medicine, Neurological and Pediatrics Institutes, Cleveland Clinic, Cleveland, OH 44195, USA

ARTICLE INFO

Article history:
Received 10 August 2012
Available online xxxx

Keywords:
Glycogen branching enzyme
Polyglucosan body disease
Ashkenazi Jewish

ABSTRACT

Mutations of the glycogen branching enzyme gene, *GBE1*, result in glycogen storage disease (GSD) type IV, an autosomal recessive disorder having multiple clinical forms. One mutant allele of this gene, *GBE1* c.1076A>C, has been reported in Ashkenazi Jewish cases of an adult-onset form of GSD type IV, adult polyglucosan body disease (APBD), but no epidemiological analyses of this mutation have been performed. We report here the first epidemiological study of this mutation in persons of Ashkenazi Jewish background and find that this mutation has a gene frequency of 1 in 34.5 (95% CI: 0.0512–0.0145), similar to the frequency of the common mutation causing Tay-Sachs disease among Ashkenazi Jews. This finding reveals APBD to be another monogenic disorder that occurs with increased frequency in persons of Ashkenazi Jewish ancestry.

© 2012 Published by Elsevier Inc.

1. Introduction

The glycogen biosynthetic enzyme gene *GBE1* encodes the glycogen branching enzyme (EC 2.4.1.15), an enzyme that catalyzes the transfer of alpha-1,4 linked glucosyl units from the outer end of a glycogen chain to an alpha-1,6 position on the same or nearby oligosaccharide chain. This enzyme activity results in the branching of high molecular weight glycogen molecules and thereby enables the packing of a large number of glycosyl units into a relatively soluble spherical molecule [1].

The absence or defective function of glycogen branching enzyme results in one of several clinical forms of glycogen storage disease type IV (GSD type IV; OMIM #232500) in humans and in mouse and other animal models [1–3]. Despite marked heterogeneity in age of onset and natural history, all clinical forms of GSD type IV are associated with an accumulation of structurally abnormal glycogen in tissues and diminished or absent glycogen branching enzyme activity. In most instances where mutation analysis has been carried out, two pathologic DNA sequence variants of the *GBE1* gene have been found, consistent with autosomal recessive inheritance.

GSD type IV is a panethnic disorder. One form of GSD type IV, an adult-onset form termed adult polyglucosan body disease (APBD; OMIM #263570), occurs in persons of diverse backgrounds but many of the reported cases are of Ashkenazi Jewish background [4]. It, like other forms of GSD type IV, is due to reduced glycogen branching enzyme activity [5].

The mutations of *GBE1* reported in persons having APBD are heterogeneous [6–9], although all persons of Ashkenazi Jewish background reported to date have at least one copy of the c.1076A>C mutation. This raises the question whether there is an increased frequency of c.1076A>C among individuals of Ashkenazi Jewish background. No population-based studies from which to make accurate epidemiologic assessments have yet been done.

The epidemiology of numerous monogenic and multifactorially determined conditions has been studied in detail in persons of Ashkenazi Jewish background, with some disorders and their associated mutations occurring at increased levels relative to many other populations [10,11]. We report here the first epidemiologic study of the mutation frequency of the ABPD-associated *GBE1* mutation c.1076A>C in a large Ashkenazi Jewish cohort.

2. Materials and methods

2.1. Clinical samples

The samples used in this study were de-identified leukocyte pellets previously used for clinical carrier screening for Tay-Sachs disease. All individuals had provided informed consent for carrier screening and had stated that all four grandparents were of Ashkenazi Jewish heritage. Genomic DNA was extracted from the leukocyte pellets by standard methods [12].

* Corresponding author. Address: Cleveland Clinic, LL-3, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Fax: +1 216 445 9212.
E-mail address: natowim@ccf.org (M.R. Natowicz).

0006-291X/$ - see front matter © 2012 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.bbrc.2012.08.089

Please cite this article in press as: A. Hussain et al., The adult polyglucosan body disease mutation *GBE1* c.1076A>C occurs at high frequency in persons of Ashkenazi Jewish background, Biochem. Biophys. Res. Commun. (2012), http://dx.doi.org/10.1016/j.bbrc.2012.08.089

UNCORRECTED PROOF

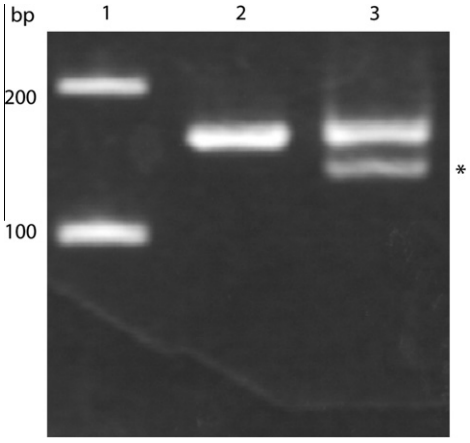

Fig. 1. Detection strategy for *GBE1* c.1076A>C. DNA was amplified with primers that create an HnfI site only in the presence of the c.1076A>C mutation. PCR products were digested with HnfI and separated on a 2% agarose gel. Lanes: 1-Molecular Weight Marker, 2-Control PCR Product, 3-Carrier PCR Product. An asterisk indicates the new 123 bp DNA fragment created only in the presence of the mutation. The 19 bp fragment is run off the bottom of the gel.

2.2. Detection of the GBE1 c.1076A>C mutation

The region harboring the *GBE1* c.1076A>C mutation (NM_000158) was PCR-amplified with forward primer 5′-tgggatagcagattgtttgact-3′ and reverse primer 5′-taagaacattaagtaccagtga-3′ using an annealing temperature of 55 °C. All other PCR conditions are as described previously [13]. A site-directed C to A substitution in the forward primer (underlined), resulted in an Hnf1 restriction enzyme site that created a 123 bp fragment only in the presence of the 1076A>C mutation. The 142 bp PCR product and 123/19 bp restriction products were separated on a 2% agarose gel or an 8% acrylamide gel and visualized by ethidium bromide staining (Fig. 1).

2.3. Detection of the HEXA c.1278insTATC mutation

For the detection of the c.1278insTATC mutation in exon 11 of *HEXA*, a 387 bp PCR-product was generated with forward primer 5′-tcccatgttgcctgtgtatg-3′ and reverse primer 5′-cctcaccccagctaagttgt-3′. The mutation was detected by the presence of an additional elution peak using denaturing high performance liquid chromatography (dHPLC). Samples were separated on a Transgenomics Wave® 3500 system using a manufacturer supplied DNASep® column and Wave optimized buffers (Transition Technologies, Inc., Toronto). Separations were performed at an oven temperature of 58.4 °C using a gradient of 56.8–65.8% buffer B. Samples with an additional peak by dHPLC analysis were confirmed to have the c.1278insTATC mutation by heteroduplex analysis as described previously [14].

3. Results and discussion

DNA was successfully analyzed for the presence/absence of *GBE1* c.1076A>C in samples from 380 persons who reported that all four grandparents were of Ashkenazi Jewish background. Eleven samples had this mutation (Fig. 1), resulting in a heterozygote frequency of 1 in 34.5 persons (95% CI: 0.0512–0.0145), an unexpectedly high carrier frequency that approximates the carrier frequencies of the most common deleterious mutations for several disorders that more commonly occur in persons of Ashkenazi Jewish background [10,11].

A possible explanation for the high heterozygote frequency of c.1076A>C in *GBE1* noted above is a biased or otherwise unusual representation of persons of Ashkenazi Jewish background in the cohort studied here. In consideration of this possibility, we then assessed the frequency of the most common recessive mutation for Tay-Sachs disease in persons of Jewish background, the *HEXA* c.1278insTATC mutation, in the same cohort. DNA was successfully analyzed for the presence/absence of the *HEXA* c.1278insTATC allele in 402 samples. Fourteen samples had this mutation, resulting in a heterozygote frequency of 1 in 28.7 (95% CI: 0.0577–0.0192), similar to the heterozygote frequency of *HEXA* c.1278insTATC reported for American Ashkenazi Jews as well as Ashkenazi Jews in other countries [15–20]. This result, in turn, makes it unlikely that the high frequency of *GBE1* c.1076A>C observed in this study is due to a sampling bias.

The finding of a high frequency of a disease-associated allele is not unique in this population. Much work has been done on the population genetics of persons of Jewish background, especially Ashkenazi Jews [21–23]. Among the mutant alleles for serious disorders that occur at high frequencies in persons of Ashkenazi Jewish background, only specific mutant alleles for Gaucher disease (*GBA* p.409S), Tay-Sachs disease (*HEXA* c.1278insTATC) and familial dysautonomia (*IKBKAP* c.2204+6T>C) occur at similar or higher frequencies than the *GBE1* c.1076A>C heterozygote frequency reported here [10,11]. The determination of the origin and subsequent population history of the *GBE1* c.1076A>C mutation and how this relates to its high prevalence in persons of Ashkenazi Jewish background is an important question that arises from this work.

Sequencing of all exons and intron/exon junctions typically reveals two allelic mutations of the *GBE1* locus in Ashkenazi Jews with ABPD, usually homozygosity of c.1076A>C. There are, however, several instances of clinically, neuroradiologically and biopsy-proven APBD in Ashkenazi Jewish individuals where mutation analysis revealed only a single copy of that mutant allele and an apparent absence of another allelic mutation ([24], M. Natowicz, personal observations), as well as a report of a non-Jewish individual with clinically-definite APBD and only a single detected mutant *GBE1* mutation [9]. These cases, in turn, raise several interesting possibilities: (1) that a small percentage of individuals with APBD are manifesting heterozygotes of a single mutation of *GBE1*; (2) that there is an undetected mutation of the other allele of *GBE1* in these individuals, such as a promoter mutation in trans to the detected mutant allele; or (3) that these individuals harbor a mutation of another gene that acts synergistically with the single mutated allele. Thus far, only coding region or splice junction mutations have been reported for the *GBE1* gene. Synergistic heterozygosity as the basis for a subset of cases of APBD is without precedent and, if present, would add to our understanding of the complexity of glycogen metabolism. Two instances of possible synergistic heterozygosity related to heterozygosity for myophosphorylase, another enzyme of glycogen metabolism, have been reported [25].

APBD now appears to be another genetic condition prevalent in individuals of Ashkenazi Jewish background. Insofar as APBD is clinically heterogeneous in its initial presentation and natural history, it is often difficult to diagnose and the correct diagnosis can be delayed for many years; affected individuals are often misdiagnosed as having multiple sclerosis or prostatic hyperplasia [4]. The findings of this study have particular relevance for persons of Ashkenazi Jewish background for whom APBD might be a clinical consideration. This work also raises interesting questions regarding the population history of this mutation and its impacts on glycogen metabolism.

Acknowledgments

We are grateful to the Louis and Susan Coddon Family Foundation for support of this work.

UNCORRECTED PROOF

Please cite this article in press as: A. Hussain et al., The adult polyglucosan body disease mutation *GBE1* c.1076A>C occurs at high frequency in persons of Ashkenazi Jewish background, Biochem. Biophys. Res. Commun. (2012), http://dx.doi.org/10.1016/j.bbrc.2012.08.089

References

[1] P.S. Kishnani, D. Koeberl, Y.-T. Chen, Glycogen storage diseases, in: D. Valle, A.L. Beaudet, B. Vogelstein, K.W. Kinzler, S.E. Antonarakis, A. Ballabio (Eds.), Scriver's Online Metabolic and Molecular Basis of Inherited Disease, McGraw-Hill, New York, 2009 (Chapter 71).

[2] Y.-C. Lee, C.-J. Chang, D. Bali, et al., Glycogen-branching enzyme deficiency leads to abnormal cardiac development: novel insights into glycogen storage disease IV, Hum. Mol. Genet. 20 (2011) 455–465.

[3] H.O. Akman, T. Sheiko, S.K.H. Tay, et al., Generation of a novel mouse model that recapitulates early and adult onset glycogenosis type IV, Hum. Mol. Genet. 20 (2011) 4430–4439.

[4] C.J. Klein, Adult polyglucosan body disease, in: R.A. Pagon, T.D. Bird, C.R. Dolan, et al. (Eds.), GeneReviews™ [Internet], Seattle, WA, 2009.

[5] A. Lossos, V. Barash, D. Soffer, et al., Hereditary branching enzyme dysfunction in adult polyglucosan body disease: a possible metabolic cause in two patients, Annu. Neurol. 30 (1991) 655–661.

[6] A. Lossos, Z. Meiner, V. Barash, et al., Adult polyglucosan body disease in Ashkenazi Jewish patients carrying the $Tyr^{329}Ser$ mutation in the glycogen-branching enzyme gene, Annu. Neurol. 44 (1998) 867–872.

[7] F. Ziemssen, E. Sindern, J.M. Schroder, et al., Novel missense mutations in the glycogen-branching enzyme gene in adult polyglucosan body disease, Annu. Neurol. 47 (2000) 536–540.

[8] E. Sindern, F. Ziemssen, T. Ziemssen, et al., Adult polyglucosan body disease: a postmortem correlation study, Neurology 61 (2003) 263–265.

[9] R. Massa, C. Bruno, A. Martorana, et al., Adult polyglucosan body disease: proton magnetic resonance spectroscopy of the brain and novel mutation in the *GBE1* gene, Muscle Nerve 37 (2008) 530–536.

[10] J. Charrow, Ashkenazi Jewish genetic disorders, Fam. Cancer 3 (2004) 201–206.

[11] S.J. Gross, B.A. Pletcher, K.G. Monaghan, Carrier screening in individuals of Ashkenazi Jewish descent, Genet. Med. 10 (2008) 54–56.

[12] S. Pind, E. Slominski, J. Mauthe, et al., V490M, a common mutation in 3-phosphoglycerate dehydrogenase deficiency, causes enzyme deficiency by decreasing the yield of mature enzyme, J. Biol. Chem. 277 (2002) 7136–7143.

[13] J. Armistead, S. Kharker, B. Meyer, et al., Mutation of a gene essential for ribosome biogenesis, *EMG1*, causes Bowen–Conradi syndrome, Am. J. Hum. Genet. 84 (2009) 728–739.

[14] B.L. Triggs-Raine, R.A. Gravel, Diagnostic heteroduplexes: simple detection of carriers of a 4-bp insertion mutation in Tay-Sachs disease, Am. J. Hum. Genet. 46 (1990) 183–184.

[15] M. Kaback, J. Lim-Steele, D. Dabholkar, et al., Tay-Sachs disease – carrier screening, prenatal diagnosis, and the molecular era: an international perspective, 1970–1993, JAMA 270 (1993) 2307–2315.

[16] J.M. DeMarchi, C.T. Caskey, C.S. Richards, Population-specific screening by mutation analysis for diseases frequent in Ashkenazi Jews, Hum. Mutat. 8 (1996) 116–125.

[17] G. Bach, J. Tomczak, N. Risch, J. Eckstein, Tay-Sachs screening in the Jewish Ashkenazi populations: DNA testing is the preferred procedure, Am J. Med. Genet. 99 (2001) 70–75.

[18] R. Rozenberg, L. da Veiga Periera, The frequency of Tay-Sachs disease causing mutations in the Brazilian Jewish population justifies a carrier screening program, Sao Paulo Med. J. 119 (2001) 146–149.

[19] S.A. Scott, L. Edelman, L. Liu, et al., Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases, Hum. Mutat. 31 (2010) 1240–1250.

[20] R. Lew, L. Burnett, A. Proos, Tay-Sachs disease preconception screening in Australia: self-knowledge of being an Ashkenazi Jew predicts carrier state better than does ancestral origin, although there is an increased risk for c.1421+1G>C mutation in individuals with South African heritage, J. Commun. Genet. 2 (2011) 201–209.

[21] G. Atzmon, L. Hao, I. Pe'er, et al., Abraham's children in the genome era: major Jewish diaspora populations comprise distinct genetic clusters with shared Middle Eastern ancestry, Am. J. Hum. Genet. 86 (2010) 850–859.

[22] D.M. Behar, B. Yunusbayev, M. Metspalu, et al., The genome-wide structure of the Jewish people, Nature 466 (2010) 238–243.

[23] S. Guha, J.A. Rosenfeld, A.K. Malhotra, et al., Implications for health and disease in the genetic signature of the Ashkenazi Jewish population, Genome Biol. 13 (2012) R2.

[24] E.E. Ubogu, S.T.K. Hong, H.O. Akman, et al., Adult polyglucosan body disease: a case report of a manifesting heterozygote, Muscle Nerve 32 (2005) 675–681.

[25] J. Vockley, P. Rinaldo, M.J. Bennett, et al., Synergistic heterozygosity: disease resulting from multiple partial defects in one or more metabolic pathways, Mol. Genet. Metab. 71 (2000) 10–18.

UNCORRECTED PROOF

Please cite this article in press as: A. Hussain et al., The adult polyglucosan body disease mutation *GBE1* c.1076A>C occurs at high frequency in persons of Ashkenazi Jewish background, Biochem. Biophys. Res. Commun. (2012), http://dx.doi.org/10.1016/j.bbrc.2012.08.089