Molecular Genetics and Metabolism Reports 10 (2017) 81–82

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

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

Correspondence

Prevalence of adenylosuccinate lyase deficiency based on aggregated exome data

Keywords:
Adenylosuccinate lyase
Prevalence
Hardy-Weinberg equilibrium

We read with great interest the recent paper by Donti et al. [1] on the diagnosis of adenylosuccinate lyase deficiency via plasma metabolomics. In their Supplementary Table S3, the authors provide the allele frequency for previously reported *ADSL* mutations. Based on this data, and adding the allele frequency of other pathogenic variants, one can estimate the minimal prevalence of the disease. The prevalence of adenylosuccinase deficiency remains unknown, with almost 80 patients reported to date [2].

Other than the previously reported mutations provided by the authors, one can mine ExAC for *ADSL* variants classified as pathogenic according to current ACMG variant interpretation guidelines, meaning variants with very strong evidence of pathogenicity (nonsense, frameshift or canonical splice site), extremely rare, with in silico algorithms predicting a deleterious effect on the gene product [3]. The allele frequencies of these variants are provided in Table 1. The total allele frequency is thus 109/121,412. By assuming Hardy-Weinberg equilibrium, where the allele frequency corresponds to q and the carrier frequency to 2pq, one can then estimate the disease frequency (q^2). A similar approach has been recently used to calculate the frequency of other metabolic conditions, such as Smith-Lemli-Opitz syndrome [4], cerebrotendinous xanthomatosis [5], Niemann-Pick type C [6] and McArdle disease [7]. The prevalence of the adenylosuccinatase lyase deficiency is thus approximately 1 in 1,240,710, with a carrier frequency of 1 in 557. It should be noted that this carrier frequency is much higher than expected, as it was previously presumed to be around 1 in 10,000 [2].

This disease frequency of about 1 in 1.25 million corresponds in fact to a conservative estimate of its prevalence, as it is likely that other missense pathogenic mutations exist that have not yet been reported, and those were not taken into account for the calculation above.

Funding

Dr. Ferreira has no funding sources to declare related to the manuscript preparation.

References

[1] T.R. Donti, G. Cappuccio, L. Hubert, J. Neira, P.S. Atwal, M.J. Miller, A.L. Cardon, V.R. Sutton, B.E. Porter, F.M. Baumer, M.F. Wangler, Q. Sun, L.T. Emrick, S.H. Elsea, Diagnosis of adenylosuccinate lyase deficiency by metabolomic profiling in plasma reveals a phenotypic spectrum, Mol. Genet. Metab. Rep. 8 (2016) 61–66.
[2] A. Jurecka, M. Zikanova, S. Kmoch, A. Tylki-Szymańska, Adenylosuccinate lyase deficiency, J. Inherit. Metab. Dis. 38 (2015) 231–242.
[3] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W.W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H.L. Rehm, ACMG Laboratory Quality Assurance Committee, standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet. Med. Off. J. Am. Coll. Med. Genet. 17 (2015) 405–424.
[4] J.L. Cross, J. Iben, C.L. Simpson, A. Thurm, S. Swedo, E. Tierney, J.E. Bailey-Wilson, L.G. Biesecker, F.D. Porter, C.A. Wassif, Determination of the allelic frequency in Smith-

Table 1
ADSL truncating variants in ExAC with their respective allele frequencies.

Chrom	Position	Ref	Alt	Transcript change	Protein change	Consequence	Allele count	Allele number	CADD Phred
22	40749122	G	T	c.402 + 1G > T		Splice donor	1	121298	26.6
22	40754866	A	C	c.483 − 2A > C		Splice acceptor	1	121410	25.4
22	40755311	G	A	c.701 + 1G > A		Splice donor	1	121412	29.4
22	40757347	G	T	c.862 + 1G > T		Splice donor	1	121402	27.8
22	40758984	G	A	c.1011 − 1G > A		Splice acceptor	1	121408	26.6
22	40757290	T	TA	c.807dupA	p.Arg270Thrfs*14	Frameshift	1	121406	35
22	40760901	CAG	C	c.1212_1213delAG	p.Arg404Serfs*11	Frameshift	1	121410	36
22	40760367	C	T	c.1189C > T	p.Gln397*	Stop gained	1	115304	43
22	40760914	C	T	c.1222C > T	p.Gln408*	Stop gained	1	121412	43
22	40742635	G	T	c.73G > T	p.Glu25*	Stop gained	1	92518	38
22	40760935	AAG	A	c.1244_1245delAG	p.Lys415Thrfs*5	Frameshift	1	121410	35
22	40745835	GA	G	c.154delA	p.Thr52Hisfs*14	Frameshift	1	119038	24.2
22	40742697	G	A	c.135G > A	p.Trp45*	Stop gained	1	95974	37
22	40761059	AG	A	c.1368 + 1delG		Frameshift	2	121402	35

http://dx.doi.org/10.1016/j.ymgmr.2016.12.009

Lemli-Opitz syndrome by analysis of massively parallel sequencing data sets, Clin. Genet. 87 (2015) 570–575.
[5] V. Appadurai, A. DeBarber, P.-W. Chiang, S.B. Patel, R.D. Steiner, C. Tyler, P.E. Bonnen, Apparent underdiagnosis of cerebrotendinous xanthomatosis revealed by analysis of ~60,000 human exomes, Mol. Genet. Metab. 116 (2015) 298–304.
[6] C.A. Wassif, J.L. Cross, J. Iben, L. Sanchez-Pulido, A. Cougnoux, F.M. Platt, D.S. Ory, C.P. Ponting, J.E. Bailey-Wilson, L.G. Biesecker, F.D. Porter, High incidence of unrecognized visceral/neurological late-onset Niemann-Pick disease, type C1, predicted by analysis of massively parallel sequencing data sets, Genet. Med. Off. J. Am. Coll. Med. Genet. 18 (2016) 41–48.
[7] M. De Castro, J. Johnston, L. Biesecker, Determining the prevalence of McArdle disease from gene frequency by analysis of next-generation sequencing data, Genet. Med. Off. J. Am. Coll. Med. Genet. 17 (2015) 1002–1006.

Carlos R. Ferreira
National Human Genome Research Institute, National Institutes of Health, 10 Center Drive, Building 10, Room 9N248B, Bethesda, MD 20892-1851, United States
E-mail address: ferreiracr@mail.nih.gov.

30 December 2016