SLC16A2 mutations in two Japanese patients with Allan–Herndon–Dudley syndrome

Toshiyuki Yamamoto1, Keiko Shimojima1, Ayako Umemura2, Mitsugu Uematsu3, Tojo Nakayama3 and Ken Inoue4

Allan–Herndon–Dudley syndrome (AHDS; MIM #300523) is recognized as a neurodevelopmental disorder that manifests in intellectual disability and motor developmental delay. Thyroid hormone transporter dysfunction due to SLC16A2 mutation is the underlying cause of this disorder. We identified a novel (P537del) and a recurrent (A150V) SLC16A2 mutation in Japanese AHDS patients from two different families. A150V co-segregated with S33P. Both patients showed similar clinical features including severe neurological features and delayed myelination. Thyroid function showed a common finding of elevated T3 levels. No clear genotype–phenotype correlation was observed in patients with SLC16A2 alterations.

Human Genome Variation (2014) 1, 14010; doi:10.1038/hgv.2014.10; published online 9 October 2014

1Tokyo Women’s Medical University Institute for Integrated Medical Sciences, Tokyo, Japan; 2Department of Pediatrics, Central Hospital, Aichi Human Service Center, Kasugai, Japan; 3Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan and 4National Institute of Neuroscience, National Center for Neurology and Psychiatry, Kodaira, Japan
Correspondence: T Yamamoto (yamamoto.toshiyuki@twmu.ac.jp)
Received 24 July 2014; revised 28 July 2014; accepted 31 July 2014

DATA REPORT

SLC16A2 mutations in two Japanese patients with Allan–Herndon–Dudley syndrome

Toshiyuki Yamamoto1, Keiko Shimojima1, Ayako Umemura2, Mitsugu Uematsu3, Tojo Nakayama3 and Ken Inoue4

Allan–Herndon–Dudley syndrome (AHDS; MIM #300523) is recognized as a neurodevelopmental disorder that manifests in intellectual disability and motor developmental delay. Thyroid hormone transporter dysfunction due to SLC16A2 mutation is the underlying cause of this disorder. We identified a novel (P537del) and a recurrent (A150V) SLC16A2 mutation in Japanese AHDS patients from two different families. A150V co-segregated with S33P. Both patients showed similar clinical features including severe neurological features and delayed myelination. Thyroid function showed a common finding of elevated T3 levels. No clear genotype–phenotype correlation was observed in patients with SLC16A2 alterations.

Human Genome Variation (2014) 1, 14010; doi:10.1038/hgv.2014.10; published online 9 October 2014

1Tokyo Women’s Medical University Institute for Integrated Medical Sciences, Tokyo, Japan; 2Department of Pediatrics, Central Hospital, Aichi Human Service Center, Kasugai, Japan; 3Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan and 4National Institute of Neuroscience, National Center for Neurology and Psychiatry, Kodaira, Japan
Correspondence: T Yamamoto (yamamoto.toshiyuki@twmu.ac.jp)
Received 24 July 2014; revised 28 July 2014; accepted 31 July 2014
In patient 1, a 3-bp deletion (c.1390_1392delCCC), leading to an in-frame amino-acid deletion (P464del), was identified in exon 5 (Figure 2a). This deletion has never been previously reported. Because his mother declined to be genotyped, we do not know whether this mutation is de novo or familial.

In patient 2, we identified two single-nucleotide variants (SNVs) that lead to amino-acid changes: c.97T > C in exon 1 (S33P) and c.449C > T in exon 2 (A150V) (Figure 2b,c). The SNVs were listed in dbSNP build 138 as rs6647476 and rs104894936, respectively. The damaging effect scores of the SNVs were calculated using PolyPhen-2 and SIFT; however, no difference was observed between the SNVs. The PolyPhen-2 scores were 0.898 (S33P) and 0.673 (A150V), indicating that they were benign. SIFT scores were 0.47 (S33P) and 0.25 (A150V), indicating that the SNVs were TOLERATED. The minor allele frequency (MAF) of S33P was 36.632%, indicating that it is a common SNP with ≥ 1% MAF. In comparison, the MAF of A150V is low, at < 1%, indicating that it is a flagged SNP. Based on these data, S33P was considered benign, whereas A150V was considered pathogenic. The mother of patient 2 was homozygous and heterozygous for S33P and A150V, respectively, showing that these variants co-segregated in the maternally derived allele.

In the present study, we diagnosed two patients with AHDS who showed severe developmental delay, especially with respect to motor development. Neither patient acquired head control. The results of the thyroid function examination showed elevated T3 levels in both patients despite variable TSH and T4 levels. This is the typical pattern for AHDS. Brain MRI showed severely delayed myelination in both patients. Additionally, the total brain volume was mildly reduced in both patients.

Molecular analysis identified a novel single-amino-acid deletion arising from a 3-bp nucleotide deletion in patient 1 (P464del). A missense mutation, P464L, affecting this residue had been previously reported.6 A150V identified in patient 2 has been recurrently reported,7–9 and functional analysis of this mutation confirmed that it results in a complete loss of specific T3 uptake8 and damaged T3 metabolism.10 To our knowledge, co-segregation of S33P and A150V was reported for the first time in the present study. Although we had no evidence of whether A150V was inherited in this family or occurred de novo, the relatively frequent occurrence of A150V in AHDS patients suggests that this region containing a "CGCG" repeat sequence may be a mutation hot spot.

In conclusion, we identified an in-frame/single-amino-acid deletion as well as a recurrent missense mutation in AHDS patients. Because both patients showed similar clinical manifestations, no clear genotype–phenotype correlation was observed for SLC16A2 alterations.
HGV DATABASE
The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.507, http://dx.doi.org/10.6084/m9.figshare.hgv.509 and http://dx.doi.org/10.6084/m9.figshare.hgv.511.

ACKNOWLEDGEMENTS
We would like to express our gratitude to the patients and their families for their cooperation. This work was partially supported by a Grant-in-Aid for Scientific Research from Health Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare, Japan (TY).

COMPETING INTERESTS
The authors declare no conflict of interest.

REFERENCES
1 Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff SA. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004; 74: 168–175.
2 Heuer H, Maier MK, Iden S, Mittag J, Friesema EC, Visser TJ et al. The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. Endocrinology 2005; 146: 1701–1706.
3 Vaurs-Barriere C, Deville M, Sarret C, Giraud G, Des Portes V, Prats-Vinas JM et al. Pelizaeus-Merzbacher-Like disease presentation of MCT8 mutated male subjects. Ann Neurol 2009; 65: 114–118.
4 Gika AD, Siddiqui A, Hulse AJ, Edward S, Fallon P, McEntagart ME et al. White matter abnormalities and dystonic motor disorder associated with mutations in the SLC16A2 gene. Dev Med Child Neurol 2010; 52: 475–482.
5 Friesema EC, Visser WE, Visser TJ. Genetics and phenomics of thyroid hormone transport by MCT8. Mol Cell Endocrinol 2010; 322: 107–113.
6 Papadimitriou A, Dumitrescu AM, Papavasiliou A, Fretzayas A, Nikolaidou P, Refetoff S. A novel monocarboxylate transporter 8 gene mutation as a cause of severe neonatal hypotonia and developmental delay. Pediatrics 2008; 121: e199–e202.
7 Friesema EC, Grueters A, Krude H, von Moers A, Reeser M et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet 2004; 364: 1435–1437.
8 Biebermann H, Ambrugger P, Tamow P, von Moers A, Schweizer U, Grueters A. Extended clinical phenotype, endocrine investigations and functional studies of a loss-of-function mutation A150V in the thyroid hormone specific transporter MCT8. Eur J Endocrinol 2005; 153: 359–366.
9 Jansen J, Friesema EC, Kester MH, Schwartz CE, Visser TJ. Genotype-phenotype relationship in patients with mutations in thyroid hormone transporter MCT8. Endocrinology 2008; 149: 2184–2190.
10 Jansen J, Friesema EC, Kester MH, Milici C, Reeser M, Grueters A et al. Functional analysis of monocarboxylate transporter 8 mutations identified in patients with X-linked psychomotor retardation and elevated serum triiodothyronine. J Clin Endocrinol Metab 2007; 92: 2378–2381.

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-sa/3.0/