their detailed functions in the central nervous system are unknown. Patient 1 has shown long-term survival without physical or mental deterioration despite the fact that the majority of patients with lissencephaly die early in childhood (de Rijk-van Andel et al., 1990). In contrast, MDS patients with a large telomeric deletion of 17p13.3 present with a severe phenotype, including lissencephaly; significant facial dysmorphism; and occasionally other congenital visceral anomalies such as gastrointestinal and cardiac defects; and furthermore, the severity of lissencephaly in MDS patients is severer than that seen in cases of isolated lissencephaly (Cardoso et al., 2003; Dobyns et al., 1991).

Mei et al. (2008) analyzed 45 patients with isolated lissencephaly; 44% of the patients (20/45) showed *LIS1* mutations, and small deletions/duplications were identified in 76% of the patients without *LIS1* mutations (19/25). One of the 19 patients lacking *LIS1* mutations exhibited duplication of three *LIS1* exons. Haverfield et al. (2009) analyzed 52 patients with lissencephaly, and intragenic duplication of *LIS1* was identified in 6 patients. These microduplications will disrupt *LIS1* structures and result in loss of function of the *LIS1* product. On the other hand, two recent reports described microduplications encompassing the entire *LIS1* region 11,13 (Bi et al., 2009; Roos et al., 2009). Using transgenic mice, Bi et al. (2009) confirmed that LIS1/PAFAH1B1 overexpression derived from genomic copy number gain was responsible for abnormal neurodevelopment. They also reported a patient with *LIS1* triplication (Subject 6) (Bi et al., 2009). Similarly, we identified a triplication of *LIS1* in patient 2, whose MRI demonstrated normal gyrus formation but a reduced cerebral volume. Patient 2 exhibited infantile spasms; whereas, the patient with *LIS1* triplication (Subject 6) reported by Bi et al. (2009) lacked seizure activity. This difference may have resulted from the size difference between them, as the triplication size of patient 2 was much larger than that of the patient (Subject 6) reported by Bi et al. (2009). Accordingly, genomic copy number aberrations at 17p13.3 including *LIS1* can lead to neurodevelopmental delay and epilepsy regardless of whether the aberration reflects a gain or loss of copy number.

In this study, patient 3 had a complete terminal deletion of 17p, and he demonstrated the dysmorphic facial features and growth retardation associated with mental retardation. This was compatible with a report by Sreenath Nagamani et al. (2009) in which haploinsufficiency of *YWHAE* and *CRK* was suggested to be responsible for facial dysmorphism and growth deficiency, respectively. However, in our present study, patient 3 had intractable epilepsy. Among the previously reported patients with a terminal deletion of 17p that did not include *LIS1*, only 1 patient with der(17)t(5;17)(p13.1;p13.3) was reported to have seizure episodes (Mutchinick et al., 1999).

In conclusion, it was suggested that the identified gain or loss of genomic copy number within 17p13.3 result in epileptogenesis and that triplication of *LIS1* can cause symptomatic West syndrome.

Conflict of interest

None of the authors has any conflict of interest to disclosure.

Acknowledgements

This work was supported by the International Research and Educational Institute for Integrated Medical Sciences and the Tokyo Women's Medical University, which is supported by the Program for Promoting the Establishment of Strategic Research Centers; Special Coordination Funds for Promoting Science and Technology; and Ministry of Education, Culture, Sports, Science and Technology (Japan).

References

Bi, W., Sapir, T., Shchelochkov, O.A., Zhang, F., Withers, M.A., Hunter, J.V., Levy, T., Shinder, V., Peiffer, D.A., Gunderson, K.L., Nezarati, M.M., Shotts, V.A., Amato, S.S., Savage, S.K., Harris, D.J., Day-Salvatore, D.L., Horner, M., Lu, X.Y., Sahoo, T., Yanagawa, Y., Beaudet, A.L., Cheung, S.W., Martinez, S., Lupski, J.R., Reiner, O., 2009. Increased LIS1 expression affects human and mouse brain development. Nat. Genet. 41, 168–177.

Cardoso, C., Leventer, R.J., Matsumoto, N., Kuc, J.A., Ramocki, M.B., Mewborn, S.K., Dudlicek, L.L., May, L.F., Mills, P.L., Das, S., Pilz, D.T., Dobyns, W.B., Ledbetter, D.H., 2000. The location and type of mutation predict malformation severity in isolated lissencephaly caused by abnormalities within the LIS1 gene. Hum. Mol. Genet. 9, 3019–3028.

Cardoso, C., Leventer, R.J., Ward, H.L., Toyo-Oka, K., Chung, J., Gross, A., Martin, C.L., Allanson, J., Pilz, D.T., Olney, A.H., Mutchinick, O.M., Hirotsune, S., Wynshaw-Boris, A., Dobyns, W.B., Ledbetter, D.H., 2003. Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. Am. J. Hum. Genet. 72, 918–930.

de Rijk-van Andel, J.F., Arts, W.F., Barth, P.G., Loonen, M.C., 1990. Diagnostic features and clinical signs of 21 patients with lissencephaly type 1. Dev. Med. Child Neurol. 32, 707–717.

Dobyns, W.B., Curry, C.J., Hoyme, H.E., Turlington, L., Ledbetter, D.H., 1991. Clinical and molecular diagnosis of Miller-Dieker syndrome. Am. J. Hum. Genet. 48, 584–594.

Dobyns, W.B., Reiner, O., Carrozzo, R., Ledbetter, D.H., 1993. Lissencephaly. A human brain malformation associated with deletion of the LIS1 gene located at chromosome 17p13. JAMA 270, 2838–2842.

Emanuel, B.S., Saitta, S.C., 2007. From microscopes to microarrays: dissecting recurrent chromosomal rearrangements. Nat. Rev. Genet. 8, 869–883.

Haverfield, E.V., Whited, A.J., Petras, K.S., Dobyns, W.B., Das, S., 2009. Intragenic deletions and duplications of the LIS1 and DCX genes: a major disease-causing mechanism in lissencephaly and subcortical band heterotopia. Eur. J. Hum. Genet. 17, 911–918.

Izumi, K., Kuratsuji, G., Ikeda, K., Takahashi, T., Kosaki, K., 2007. Partial deletion of LIS1: a pitfall in molecular diagnosis of Miller-Dieker syndrome. Pediatr. Neurol. 36, 258–260.

Kato, M., Dobyns, W.B., 2003. Lissencephaly and the molecular basis of neuronal migration. Hum. Mol. Genet., 12 Spec No. 1, R89-96.

Lee, J.A., Lupski, J.R., 2006. Genomic rearrangements and gene copy-number alterations as a cause of nervous system disorders. Neuron 52, 103–121.

Mei, D., Lewis, R., Parrini, E., Lazarou, L.P., Marini, C., Pilz, D.T., Guerrini, R., 2008. High frequency of genomic deletions—and a duplication—in the LIS1 gene in lissencephaly: implications for molecular diagnosis. J. Med. Genet. 45, 355–361.

Mignon-Ravix, C., Cacciagli, P., El-Waly, B., Moncla, A., Milh, M., Girard, N., Chabrol, B., Philip, N., Villard, L., 2009. Deletion of YWHAE in a patient with periventricular heterotopias and marked corpus callosum hypoplasia. J. Med. Genet. 47, 132–136.

Mutchinick, O.M., Shaffer, L.G., Kashork, C.D., Cervantes, E.I., 1999. Miller-Dieker syndrome and trisomy 5p in a child carrying a derivative chromosome with a microdeletion in 17p13.3 telomeric to the LIS1 and the D17S379 loci. Am. J. Med. Genet. 85, 99–104.

Reiner, O., Carrozzo, R., Shen, Y., Wehnert, M., Faustinella, F., Dobyns, W.B., Caskey, C.T., Ledbetter, D.H., 1993. Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. Nature 364, 717–721.

Roos, L., Jonch, A.E., Kjaergaard, S., Taudorf, K., Simonsen, H., Hamborg-Petersen, B., Brondum-Nielsen, K., Kirchhoff, M., 2009. A new microduplication syndrome encompassing the region of the Miller-Dieker (17p13 deletion) syndrome. J. Med. Genet. 46, 703–710.

Shaffer, L.G., Theisen, A., Bejjani, B.A., Ballif, B.C., Aylsworth, A.S., Lim, C., McDonald, M., Ellison, J.W., Kostiner, D., Saitta, S., Shaikh, T., 2007. The discovery of microdeletion syndromes in the post-genomic era: review of the methodology and characterization of a new 1q41q42 microdeletion syndrome. Genet. Med. 9, 607–616.

Shimojima, K., Tanaka, K., Yamamoto, T., 2009. A de novo intrachromosomal tandem duplication at 22q13.1q13.31 including the Rubinstein-Taybi region but with no bipolar disorder. Am. J. Med. Genet. A 149A, 1359–1363.

Sreenath Nagamani, S.C., Zhang, F., Shchelochkov, O.A., Bi, W., Ou, Z., Scaglia, F., Probst, F.J., Shinawi, M., Eng, C., Hunter, J.V., Sparagana, S., Lagoe, E., Fong, C.T., Pearson, M., Doco-Fenzy, M., Landais, E., Mozelle, M., Chinault, A.C., Patel, A., Bacino, C.A., Sahoo, T., Kang, S.H., Cheung, S.W., Lupski, J.R., Stankiewicz, P., 2009. Microdeletions including YWHAE in the Miller-Dieker syndrome region on chromosome 17p13.3 result in facial dysmorphisms, growth restriction, and cognitive impairment. J. Med. Genet. 46, 825–833.