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BRIEF COMMUNICATION

Familial total anomalous pulmonary venous return with 15q11.2 (BP1-BP2) microdeletion

Yukiko Kuroda[1] · Ikuko Ohashi[1] · Takuya Naruto[1] · Kazumi Ida[1] · Yumi Enomoto[1] · Toshiyuki Saito[2] · Jun-ichi Nagai[2] · Sadamitsu Yanagi[3] · Hideaki Ueda[3] · Kenji Kurosawa[1]

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Abstract

A 15q11.2 microdeletion (BP1-BP2) is associated with congenital heart diseases (CHDs), developmental delay, and epilepsy. This deletion co-occurs with CHD in 20–30% patients, but a familial case of CHD and a 15q11.2 deletion has not been identified. Here we report the first familial (three siblings) case of total anomalous pulmonary venous return associated with 15q11.2 deletion. Array comparative genomic hybridization identified a ~395 kb deletion at 15q11.2 in patient 1. This deletion was confirmed by fluorescence in situ hybridization in patients 1 and 3 and their asymptomatic father. No deleterious mutation was identified by proband-only exome sequencing of patient 1. One healthy sibling and their mother did not carry the deletion. This deletion is often inherited from asymptomatic parents with an estimated low penetrance of 10.4%. Conversely, we observed high penetrance of this deletion, but secondary copy-number variants or pathogenic variants were not detected in this family.

Introduction

Total anomalous pulmonary venous return (TAPVR) is a rare, congenital heart malformation characterized by abnormal drainage of the pulmonary veins. Various genetic mutations have been associated with TAPVR, including low penetrant, autosomal dominant variations in *PDGFRA, SEMA3D*, and *ANKRD1* [1–3]. Several other TAPVR susceptibility genes have also been identified, including *SGCD* and *ACVRL1*, and genes comprising the retinoic acid signaling pathway, such as *RBP5, RDH10*, and *NODAL* [4, 5]. TAPVR accounts for ~1.5% cases of congenital heart disease (CHD) and although typically occurs without a family history, there is ~3–5% risk of recurrence in a sibling [6]. Despite more than 42 reported sibling cases of TAPVR [7], the genetic basis of the disease remains unclear for most patients.

Microdeletions at 15q11.2 between breakpoint 1 (BP1) and BP2 are typically ~500 kb in length and have been associated with CHDs, developmental delay, and epilepsy [8]. This region encompasses four characterized genes, *TUBGCP5*, *CYFIP1*, *NIPA2*, and *NIPA1*. Thus far, two patients with TAPVR have been reported to carry this 15q11.2 microdeletion [9, 10]. Here, we report the first familial case of a 15q11.2 deletion and TAPVR.

Clinical reports

Patient 1

Patient 1 was a 10 year-old male and the first child of nonconsanguineous and healthy 30-year-old parents (Fig. 1). He was delivered at a gestational age 37 weeks and 3 days after an uneventful pregnancy, with a birth weight of 2486 g (0.9 SD). An echocardiogram identified type 1a TAPVR and surgical repair was performed the following day (age 1 day). In terms of gross motor skills, the patient showed a normal pattern of controlled head movements at 4 months,

✉ Yukiko Kuroda
ykodama-hok@umin.ac.jp

✉ Kenji Kurosawa
kkurosawa@kcmc.jp

[1] Division of Medical Genetics, Kanagawa Children's Medical Center, Yokohama, Japan

[2] Department of Clinical Laboratory, Kanagawa Children's Medical Center, Yokohama, Japan

[3] Department of Cardiology, Kanagawa Children's Medical Center, Yokohama, Japan

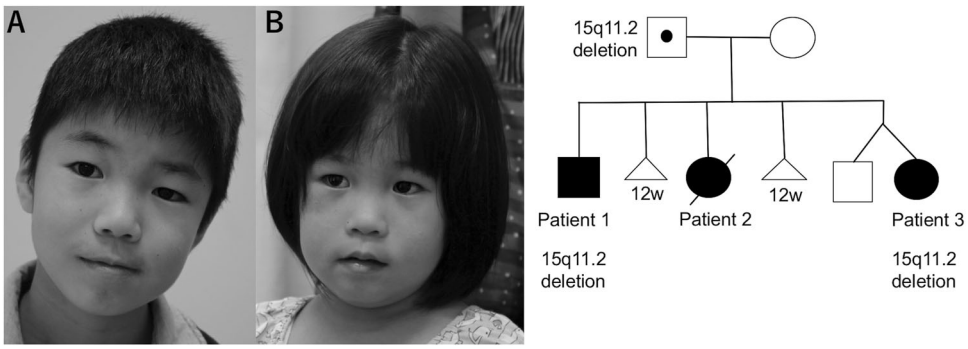

Fig. 1 Photographic images of patient 1 (**a**) and patient 3 (**b**) (left). No dysmorphic features were noted in either patient. Family pedigree (right)

could roll over at 5 months, sit at 7 months, and walk at 17 months. Furthermore, he spoke his first word at 12 months, and started to form two-word sentences at 3 years of the age. The patient later exhibited learning defects and subsequently required supported learning. At 9 years, his height was 141 cm (1.6 SD), and his body weight was 26.6 kg (−0.5 SD). A cranial MRI revealed a slight enlargement of the fourth ventricle.

Patient 2

Patient 2 was an 8 month-old female and the second child of the parents of patient 1 (Fig. 1). She was delivered at gestational age 38 weeks, with a birth weight of 3066 g (0 SD), birth length of 49.7 cm (0.3 SD), and occipital frontal circumference (OFC) of 34.5 cm (0.9 SD). Type 3 TAPVR with pulmonary venous obstruction (PVO) was diagnosed at 34 weeks gestation by fetal echocardiography. Consequently, surgical repair was performed immediately after birth. The patient died of renal failure due to chylothorax at age 8 months.

Patient 3

Patient 3 was a 5 year-old female, the fourth child, and younger sister of a dizygotic twin pair born to the parents of patient 1. She was delivered by emergency cesarean section at gestational age 36 weeks and 3 days because of a risk of premature delivery. She had a birth weight of 2823 g (0.4 SD), a birth height of 48.1 cm (0.4 SD), and an OFC of 34.5 cm (1.3 SD). Type 3 TAPVR with PVO was confirmed at gestational age 31 weeks and surgical repair was performed immediately after birth. By age 4.5 years, she exhibited a speech delay and normal growth (with a height of 106.2 cm (0.9 SD) and a weight of 19.05 kg (1.3 SD)).

Results

Karyotyping revealed a normal karyotype for patients 1 and 3. Deleterious mutations in disease-related genes were not identified by proband-only exome sequencing of patient 1, and no rare variations (minor allele frequency < 0.01) were found in the previously reported TAPVR candidate genes, *PDGFRA*, *ANKRD1/CARP*, *RBP5, RDH10*, *NODAL, SGCD*, and *ACVRL1*. DNA libraries were enriched for sequences using SureSelect Human All Exon V4 (Agilent Technologies Inc., Santa Clara, CA). The data were analyzed using BWA (version 6) and the GATK pipeline (Broad Institute) as described previously [11]. The mean sequencing depth was 91.77 per base, and the proportion of bases covered by at least ten reads was 85.2%.

Array CGH (Agilent SurePrint G3 Human CGH Microarray Kit 8 × 60 K) in patient 1 revealed a microdeletion at 15q11.2 of ~395 kb, spanning from position 22,784,523 to 23,179,948 bp (GRCh37/hg19) (Fig. 2). This microdeletion was also detected in patient 3. FISH confirmed this microdeletion in patients 1 and 3, as well as their asymptomatic father. The healthy sibling (the third child) and their mother did not carry this microdeletion.

Discussion

Here we report a case of familial TAPVR, in which two affected siblings and their asymptomatic father carry a microdeletion at 15q11.2 (BP1-BP2). CHD is relatively common in patients carrying a 15q11.2 (BP1-BP2) deletion, affecting 20–30% patients [10, 12]. The various congenital heart anomalies described include atrial septal defects, ventricular septal defects, coarctation of the aorta, teratology of Fallot, complex left sided, and TAPVR [9]. Although >27 patients with CHD and a 15q11.2 deletion have been identified [8, 10, 12, 13], ours is the first report of a familial case of TAPVR and 15q11.2 deletion.

TAPVR was evident in two siblings of this family harboring the CNV (copy number variation), thus indicating its high penetrance, which was previously estimated as 10.4% [14]. We did not detect any secondary CNVs or pathogenic variants to explain this high level of penetrance; however, regardless of secondary CNV status, there is no difference in CHD prevalence in those carrying a 15q11.2 deletion

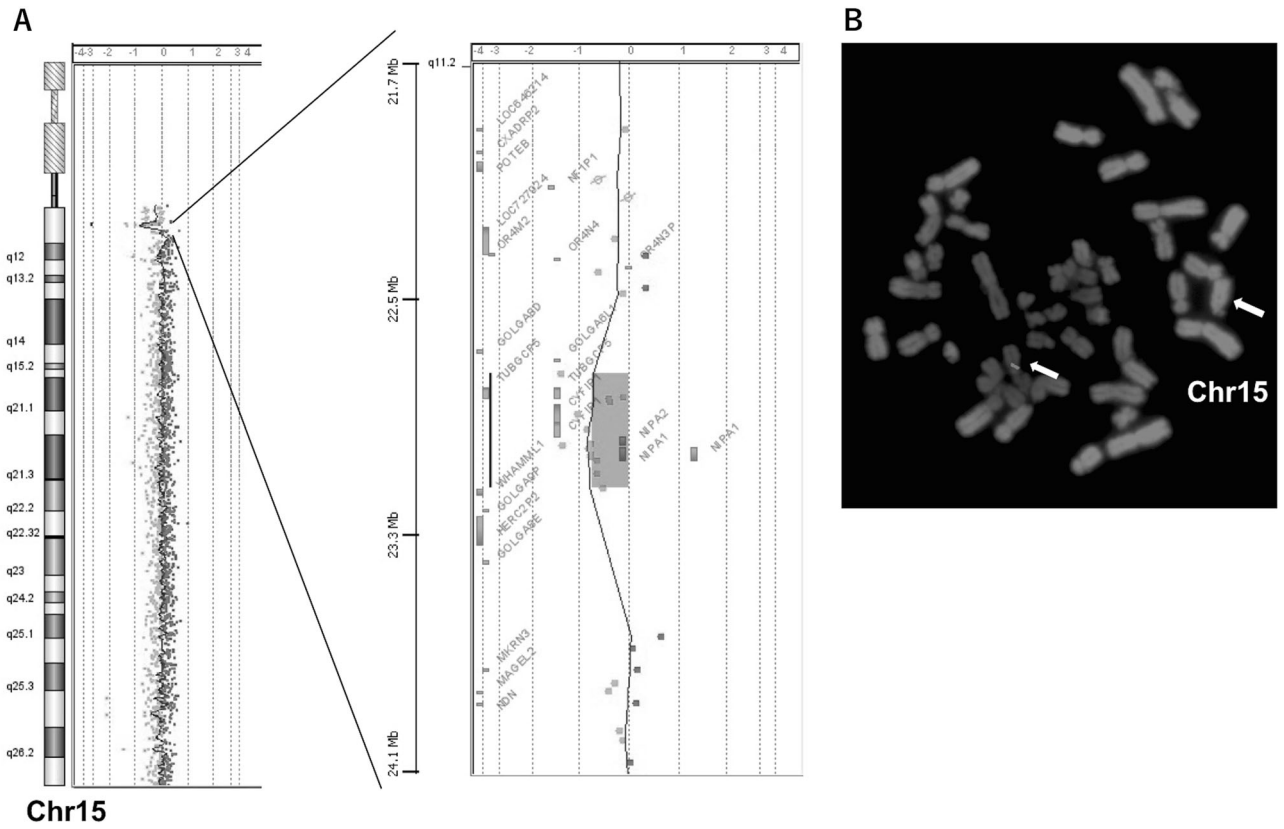

Fig. 2 Analysis of deletion of 15q11.2 in patient 1. **a** Array comparative genomic hybridization showing the 395 kb deleted region at 15q11.2. **b** Metaphase fluorescence in situ hybridizaton on lymphocytes using the RP11-289D12 (chr15: 22.7-23.1 Mb) clone as a probe specific for 15q11.2 (red). The patient lymphocytes generated one signal consistent with a deletion at 15q11.2 (white arrows)

[12]. Previous reports suggest that this CNV is often inherited from asymptomatic parents (52.9%) with no parent sex bias [10]. However, parental study of ten patients with CHD showed that seven patients inherited the condition from the paternal line, only one patient inherited the condition from the maternal line, and two patients had de novo CNVs [8, 10, 13]. A "parent-of-origin" effect may thus contribute to the occurrence of CHD. In Prader–Willi syndrome (PWS) resulting from the paternal BP1 (or BP2) –BP3 deletion or maternal uniparental disomy, CHDs were also frequent (in 4.4% of the patients) [15]. Although four RefSeq genes located in the BP1-BP2 were not imprinted [16], it is possible that the loss of function of genes located in the BP1-BP2 may affect the expression of paternally expressed genes located in PWS responsible region.

In conclusion, we have identified a 15q11.2 deletion in two of three siblings with TAPVR and speech or learning disorder. The secondary contributing factors predisposing to TAPVR and thus leading to the high penetrance observed in this family remain unclear.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bleyl S, Nelson L, Odelberg SJ, Ruttenberg HD, Otterud B, Leppert M, et al. A gene for familial total anomalous pulmonary venous return maps to chromosome 4p13-q12. Am J Hum Genet. 1995;56:408–15.
2. Cinquetti R, Badi I, Campione M, Bortoletto E, Chiesa G, Parolini C, et al. Transcriptional deregulation and a missense mutation define ANKRD1 as a candidate gene for total anomalous pulmonary venous return. Hum Mutat. 2008;29:468–74.
3. Degenhardt K, Singh MK, Aghajanian H, Massera D, Wang Q, Li J, et al. Semaphorin 3d signaling defects are associated with anomalous pulmonary venous connections. Nat Med. 2013;19:760–5.
4. Nash D, Arrington CB, Kennedy BJ, Yandell M, Wu W, Zhang W, et al. Shared segment analysis and next-generation sequencing implicates the retinoic acid signaling pathway in total anomalous pulmonary venous return (TAPVR). PLoS ONE. 2015;10:e0131514.

5. Li J, Yang S, Pu Z, Dai J, Jiang T, Du F, et al. Whole-exome sequencing identifies SGCD and ACVRL1 mutations associated with total anomalous pulmonary venous return (TAPVR) in Chinese population. Oncotarget. 2017;8:27812–9.
6. Hoffman JI. Congenital heart disease: incidence and inheritance. Pediatr Clin North Am. 1990;37:25–43.
7. Kim HS, Jeong K, Cho HJ, Choi WY, Choi YE, Ma JS, et al. Total anomalous pulmonary venous return in siblings. J Cardiovasc Ultrasound. 2014;22:213–9.
8. Doornbos M, Sikkema-Raddatz B, Ruijvenkamp CA, Dijkhuizen T, Bijlsma EK, Gijsbers AC, et al. Nine patients with a microdeletion 15q11.2 between breakpoints 1 and 2 of the Prader-Willi critical region, possibly associated with behavioural disturbances. Eur J Med Genet. 2009;52:108–15.
9. Soemedi R, Wilson IJ, Bentham J, Darlay R, Töpf A, Zelenika D, et al. Contribution of global rare copy-number variants to the risk of sporadic congenital heart disease. Am J Hum Genet. 2012;91:489–501.
10. Vanlerberghe C, Petit F, Malan V, Vincent-Delorme C, Bouquillon S, Boute O, et al. 15q11.2 microdeletion (BP1-BP2) and developmental delay, behaviour issues, epilepsy and congenital heart disease: a series of 52 patients. Eur J Med Genet. 2015;58:140–7.
11. Tsurusaki Y, Ohashi I, Enomoto Y, Naruto T, Mitsui J, Aida N, et al. A novel UBE2A mutation causes X-linked intellectual disability type Nascimento. Hum Genome Var. 2017;4:17019.
12. Hashemi B, Bassett A, Chitayat D, Chong K, Feldman M, Flanagan J, et al. Deletion of 15q11.2(BP1-BP2) region: further evidence for lack of phenotypic specificity in a pediatric population. Am J Med Genet A. 2015;167A:2098–102.
13. Barone C, Novelli A, Bianca I, Cataliotti Del Grano A, Campisi M, Ettore C, et al. 15q11.2 microdeletion and hypoplastic left heart syndrome. Eur J Med Genet. 2015;58:608–10.
14. Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013;15:478–81.
15. Torrado M, Foncuberta ME, Perez MF, Gravina LP, Araoz HV, Baialardo E, et al. Change in prevalence of congenital defects in children with Prader-Willi syndrome. Pediatrics. 2013;131:e544–9.
16. Chai JH, Locke DP, Greally JM, Knoll JH, Ohta T, Dunai J, et al. Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet. 2003;73:898–925.