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MPPH syndrome with aortic coarctation and macrosomia due to CCND2 mutations

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1 [Clinical Notes] MPPH syndrome with aortic coarctation and macrosomia due to CCND2 2mutations 3 4 Running title: MPPH syndrome with aortic coarctation 5 6 Tomohiro Sameshima, M.D.^{1,2}, Naoya Morisada M.D., Ph.D.^{3,4}, 7 Tsuyoshi Egawa M.D., Ph.D.², Masaaki Kugo, M.D., Ph.D.², 8 Kazumoto Iijima, M.D., Ph.D.⁴ 9 10 11 ¹Department of Pediatrics, Hyogo Prefectural Awaji Medical Center, 1-137, 1-chome, Shioya, Sumoto, 656-0021, Hyogo, Japan 12 ²Department of Pediatrics, Himeji Red Cross Hospital, 1-12-1, Shimoteno, Himeji, 670-13 8540, Hyogo, Japan 14

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15 Key words

14

aortic coarctation, CCND2, hydrocephalus, MPPH syndrome, postaxial polydactyly

- 1 Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome is a
- 2 rare autosomal dominant disorder, characterized by progressive megalencephaly,
- 3 polymicrogyria, and postaxial polydactyly. Patients with this syndrome have a high risk
- 4 of developing hydrocephalus, mild to severe intellectual disabilities, and epilepsy. The
- 5 clinical symptoms of megalencephaly-capillary malformation (MCAP) syndrome
- 6 overlap with those of MPPH syndrome.² Genetic mutations in phosphatidylinositol 3-
- 7 kinase (PI3K)-protein kinase B (AKT) pathway components cause both MPPH and
- 8 MCAP syndromes; AKT3, PIK3R2, and CCND2 are associated with MPPH syndrome, 1
- 9 whereas *PIK3CA* somatic mosaicism mutations are associated with MCAP syndrome.
- 10 The primary difference between these two syndromes is the presence of
- 11 hemihypertrophy and somatic vascular malformations in MCAP syndrome.
- A Japanese boy who presented with ventricular enlargement at 28-weeks
- gestational age was born at gestational age 38 weeks and 2 days. His birth weight was
- 4,102 g (+3.79 SD), height was 52.2 cm (+2.16 SD), and head circumference was 38.8
- cm (+4.44 SD). His Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. He also
- presented with forehead protrusion, sacral cusp depression, low auricle, depressed nasal
- bridge and postaxial polydactyly, but no somatic asymmetry. Echocardiography
- revealed a ortic coarctation (Fig. 1a), and no other cardiac malformations were observed.

- 1 The head magnetic resonance imaging performed at the age of 4 days confirmed
- 2 ventricular enlargement and polymicrogyria (Fig. 1b). At the age of 6 months, the
- patient had a height of 74.4 cm (+2.8 SD), a weight of 11.3 kg (+3.7 SD), and a head
- 4 circumference of 49.5 cm (+5.6 SD). He was diagnosed with epilepsy at the age of 1
- 5 year, 3 months and started valproate and clobazam. At the age of 1 year, 9 months, he
- 6 remained unable to hold up his neck but could roll over his trunk. At the age of 2 years,
- 7 his weight was 11.7 kg (+0.16 SD), his height was 88.0 cm (+0.85 SD) and head
- 8 circumference of 54.8 cm (+4.1 SD). His karyotype was 46,XY.
- 9 We clinically diagnosed him as MPPH syndrome or MCAP syndrome. To
- confirm the molecular diagnosis, we performed a genetic analysis of the patient at the
- age of 1 month, after obtaining written informed consent from his parents. All
- procedures were reviewed and approved by the Institutional Review Board of Kobe
- 13 University School of Medicine. DNA was extracted from peripheral blood mononuclear
- cells. We first performed next-generation sequencing, using the TruSight One
- 15 Sequencing (TS1) Panel (Illumina, San Diego, CA, USA), which can analyze 4,813
- genes, including AKT3, PIK3R2, and PIK3CA. However, we were unable to identify his
- causative gene using TS1. Next, we analyzed *CCND2*, at the age of 2 months, using
- 18 Sanger sequencing, and found a heterozygous missense variant in CCND2,

- 1 NM_001759.3:c.842C>G, p.Pro281Arg (Fig. 1c), which is a known disease-causing
- 2 mutation (HGMD CM144536, ClinVar RCV000133499.3). The in-silico analyses also
- 3 indicated the mutation to be pathogenic (CADD score; 30, SIFT; deleterious,
- 4 PolyPhen2; probably damaging, Mutation Taster; disease causing and PROVEAN;
- 5 deleterious), as evaluated by wANNOVAR.³ We did not perform a segregation analysis
- 6 on his parents.
- 7 The PI3K-AKT pathway is one of the most important intracellular signaling
- 8 pathways, associated with cellular proliferation and cancer formation. Germline or
- 9 somatic mutations in genes associated with this pathway have been reported to cause
- several overgrowth syndromes, including Proteus syndrome (AKT1), Cowden
- syndrome, and CLOVES syndrome (*PIK3CA*). Our patient had megalencephaly, which
- can indicate either MPPH or MCAP syndrome, and these syndromes have some
- overlapping phenotypes (Supplemental Table 1). We were unable to identify any
- pathogenic variants in the TS1 panel, which includes AKT3, PI3R2, and PIK3CA, but
- were able to identify the responsible mutation in *CCND2* by additional Sanger
- sequencing.
- 17 Clinical phenotypical differences in MPPH syndrome among three gene
- mutations have been reported. MPPH syndrome associated with an AKT3 mutation may

- show connective tissue laxity and cutaneous capillary malformations. Hypoglycemia
- 2 was reported in patients with overgrowth syndromes, especially those with PIK3CA or
- 3 *CCND2* mutations. ⁴ However, our patient showed no glucose abnormalities. Patients
- 4 with MPPH syndrome caused by CCND2 mutation tend to present more severe clinical
- 5 manifestations, including intellectual disabilities and polymicrogyria. Congenital
- 6 cardiovascular defects, such as ventricular or atrial septal defects, have been observed in
- 7 some patients with MPPH syndrome, 1 but no reports regarding patients with MPPH
- 8 syndrome caused by CCND2 mutations who present with aortic coarctation exist.
- 9 MPPH syndrome caused by CCND2 mutations is extremely rare; therefore, further
- investigation and the identification of more patients is necessary to better understand
- 11 MPPH syndrome.
- In conclusion, we were able to successfully and rapidly diagnose MPPH
- 13 syndrome using a comprehensive genetic analysis and clinical diagnosis. Aortic
- coarctation can be viewed as a new phenotype for MPPH syndrome.

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Disclosures

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6 Author contributions

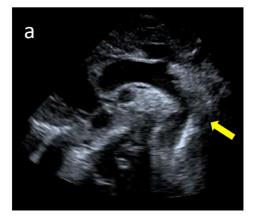
- 7 T.S. designed the study and wrote the manuscript. T.E. and M.K. evaluated the patient
- 8 and collected and interpreted the data. N.M. performed the genetic analysis and genetic
- 9 counselling for the family. K.I. evaluated the patient, discussed the results, and gave
- final approval. All authors read and approved the final manuscript.

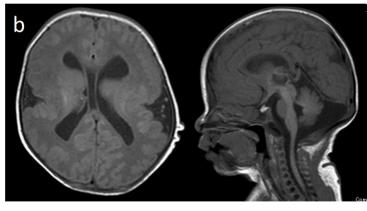
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- significant manifestation of PIK3CA- and CCND2-associated segmental
- overgrowth. Clin Genet. 2018; 93: 687-92.

1 Figure Legend

- 2 Fig. 1 Echocardiogram at the age of 2 days. The coarctation is indicated by a yellow
- 3 arrow (30 mm) (a). Brain magnetic resonance imaging of the patient at the age of 4 days
- 4 (b). Bilateral enlargement of the ventricle and polymicrogyria can be observed. Sanger
- 5 sequencing of CCND2 for the patient (c).





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