Propionic acidemia (PA) is an autosomal recessive metabolic disorder caused by defects in the propionyl-CoA carboxylase (PCC) enzyme. PCC is involved in catabolism of branched-chain amino acids, odd chain fatty acids and cholesterol. Disrupted function of PCC leads to mitochondrial accumulation of propionyl-CoA and its by-products. A characteristic urine organic acid profile shows 3-hydroxypropionate, methylcitrate, tiglyglycine and propionylglycine. The clinical signs and symptoms include acute deterioration, hypotonia, metabolic acidosis, ketonuria, hypoglycemia and hyperammonemia, which usually present during infancy and early childhood. Without treatment, these can progress to coma and death. Patients who survive the neonatal period mostly have episodes of metabolic acidosis and hyperammonemia. It has been shown that mutations in either the PCCA (chromosome 3q21-q22) genes encoding alpha or beta subunits of the PCC enzyme, respectively, can cause propionic acidemia. Mutations in PCCA are heterogeneous without a predominant mutation in the population studied, whereas PCCB has a limited number of mutations in various ethnic groups. Missense mutations are the most common defects identified in the PCCB gene. The incidence of PA ranges from 1:50,000 to 1:150,000. A high frequency of PA has been reported in some populations, for example, 1 in 1,000 among the Greenlandic Inuit population due to a founder effect and 1 in 1,000 among the Thai patients whereas PCCA mutations have never been reported in Thai. Here we describe a 6-year-old Thai boy with PA who was born to consanguineous parents. Exome sequencing identified a novel homozygous frameshift insertion (c.379_380insA; p.T127NfsX160) in the PCCB gene, expanding its mutational spectrum.
DNA into millions of short fragments and is followed by massively parallel sequencing of all exons in all genes, giving an output of >10 GB in one run. It is suitable for detection of single-nucleotide substitutions, insertions or deletions smaller than 8–10 nucleotides.\textsuperscript{16} Compared with a conventional mutation detection technique involving PCR–Sanger sequencing, WES is both less time consuming and less expensive to identify mutations in these two genes causing PA. Moreover, it provides an opportunity to find new causative genes and actionable pathogenic variants.\textsuperscript{17}

PCCA has 24 coding exons ranging from 37 to 335 bp in length, whereas PCCB have 15 exons of 57–183 bp.\textsuperscript{18} The approximate cost of PCR–Sanger sequencing is USD 45 for one exon. Setting up a molecular diagnostic test for PA using conventional sequencing of all these 39 exons would cost almost USD 2,000 in Thailand. The time consuming and less expensive to identify mutations in these two genes causing PA. Moreover, it provides an opportunity to find new causative genes and actionable pathogenic variants.\textsuperscript{17}

WES reveals a homozygous frameshift mutation in PCCB expected to result in unstable mRNA, which might be degraded by nonsense-mediated mRNA decay. It has never been previously described. His parents were heterozygous for the mutation. It is expected to result in unstable mRNA, which might be degraded by nonsense-mediated mRNA decay. It has never been previously described. His parents were heterozygous for the mutation. It is absent in 100 exome Thai controls.

In conclusion, we identified a novel homozygous frameshift insertion, c.379_380insA; p.T127NfsX160 in the PCCB gene associated with PA in a Thai family.

\textbf{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.ﬁ

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\textbf{COMPETING INTERESTS}

The authors declare no conflict of interest.

\textbf{REFERENCES}

1 Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Scriver CR, Beaudet AR, Sly W, Valle D (eds). The Metabolic and Molecular Basis of Inherited Disease. 8th edn McGraw-Hill: New York, USA, 2001; 2165–2193.
2 Pena L, Franks J, Chapman KA, Gropman A, Ah Mew N, Chakrapani A et al. Natural history of propionic acidemia. Mol Genet Metab 2012; 105: 5–9.
3 Dionisi-Vici C, Deodato F, Röschinger W, Pérez-Bernabeu C, Richard E et al. Overview of mutations in the PCCA and PCCB genes causing propionic acidemia. Hum Mut 1999; 14: 275–282.
4 Lamhomwah AM, Barankiewicz TJ, Willard HF, Maharaj DJ, Quan F, Gravel RA. Isolation of cDNA clones coding for the alpha and beta chains of human propionyl-CoA carboxylase: chromosomal assignments and DNA polymorphisms associated with PCCA and PCCB genes. Proc Natl Acad Sci USA 1986; 83: 4864–4868.
5 Rodríguez-Pombo P, Hoenicka J, Muro S, Pérez B, Pérez-Cerdá C, Richard E et al. Human propionyl-coa carboxylase β subunit gene: exon-intron definition and mutation spectrum in Spanish and Latin American propionic acidemia patients. Am J Hum Genet 1998; 63: 360–369.
6 Desviat LR, Pérez B, Pérez-Cerdá C, Rodríguez-Pombo P, Clavero S, Ugarte M. Propionic acidemia: mutation update and functional and structural effects of the variant alleles. Mol Genet Metab 2004; 83: 28–37.
7 Chace DH, DiPerna JC, Kalas TA, Johnson RW, Naylor EW. Rapid Diagnosis of Methylmalonic and Propionic Acidemias: Quantitative Tandem Mass
Spectrometric Analysis of Propionylcarnitine in Filter-Paper Blood Specimens Obtained from Newborns. Clin Chem 2001; 47: 2040–2044.

10 Yorifuji T, Kawai M, Muroi J, Mamada M, Kurokawa K, Shigematsu Y et al. Unexpectedly high prevalence of the mild form of propionic acidemia in Japan: presence of a common mutation and possible clinical implications. Hum Genet 2002; 111: 161–165.

11 Niu D-M, Chien Y-H, Chiang C-C, Ho H-C, Hwu W-L, Kao S-M et al. Nationwide survey of extended newborn screening by tandem mass spectrometry in Taiwan. J Inherit Metab Dis 2010; 33: 295–305.

12 Ravn K, Chloupkova M, Christensen E, Brandt NJ, Simonsen H, Kraus JP et al. High incidence of propionic acidemia in Greenland is due to a prevalent mutation, 1540insCCC, in the gene for the β-subunit of propionyl CoA carboxylase. Am J Hum Genet 2000; 67: 203–206.

13 Rashed M, Ozand Pt Fau—al Aqeel A, al Aqeel A Fau—Gascon GG, Gascon GG. Experience of King Faisal Specialist Hospital and Research Center with Saudi organic acid disorders. Brain Dev 1994; 16: Suppl: 1–6.

14 Vatanavicharn N, Lammongkolkul S, Sakamoto O, Kamolsilp M, Sathienkijkanchai A, Wasant P. Clinical characteristics and mutation analysis of propionic acidemia in Thailand. World J Pediatr 2014; 10: 64–68.

15 Shotelersuk V, Srivuthana S, Wacharasindhu S, Dhamcharee V, Jaruratanasirikul S, Pangkanon S et al. Establishing gas chromatography-mass spectrometry to diagnose organic acidemias in Thailand. Southeast Asian J Trop Med Public Health 2014; 35: 64–68.

16 Biesecker LG, Biesecker BB. An approach to pediatric exome and genome sequencing. Curr Curr Opin Pediatr 2014; 26: 639–645.

17 Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med 2013; 15: 565–574.

18 Campeau E, Desviat LR, Leclerc D, Wu X, Pérez B, Ugarte M et al. Structure of the PCCA gene and distribution of mutations causing propionic acidemia. Mol Genet Metab 2001; 74: 238–247.

19 Collins FS, Hamburg MA. First FDA authorization for next-generation sequencer. N Engl J Med 2013; 369: 2369–2371.