Received: 14 November 2018 | Revised: 22 January 2019 | Accepted: 4 February 2019

DOI: 10.1002/ajmg.a.61106

WILEY AMERICAN JOURNAL OF medical genetics PART A

CASE REPORTS IN DIVERSE POPULATIONS

Female-restricted syndromic intellectual disability in a patient from Thailand

Thivaratana Sinthuwiwat[1,2,3,4] | Chupong Ittiwut[2,3] | Thantrira Porntaveetus[5] | Vorasuk Shotelersuk[2,3]

[1]Interdisciplinary Program of Biomedical Sciences, Graduate School, Chulalongkorn University, Bangkok, Thailand

[2]Center of Excellence for Medical Genomics, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[3]Excellence Center for Medical Genetics, King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand

[4]Cytogenetics Unit, Research and International Relations Division, HRH Princess Chulabhorn College of Medical Science, Bangkok, Thailand

[5]Genomics and Precision Dentistry Research Unit, Department of Physiology, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand

Correspondence
Thantrira Porntaveetus, Genomics and Precision Dentistry Research Unit, Department of Physiology, Faculty of Dentistry, Chulalongkorn University, Bangkok 10330, Thailand.
Email: thantrira.p@chula.ac.th

Funding information
Chulalongkorn Academic Advancement into its 2nd Century Project; Faculty Research Grant, Faculty of Dentistry, Chulalongkorn University, Grant/Award Number: DRF62003; Thailand Research Fund, Grant/Award Number: RSA6280001, DPG6180001; The Newton Fund

Female-restricted syndromic intellectual disability (ID) is a neurodevelopmental disorder with developmental delay (DD)/ID, facial dysmorphism, and diverse congenital anomalies comprising heart defects, anal anomalies, choanal atresia, postaxial polydactyly, scoliosis, and brain abnormalities. Loss-of-function mutations in the *USP9X* gene inherited as X-linked dominance were identified as its etiology in females of different ethnic groups. Here, we report a 15-year-old Thai girl harboring a novel *de novo* heterozygous one-base pair deletion (c.3508delG, p.Val1170TrpfsX9) in exon 23 of *USP9X*. Her profound DD, dysmorphic face including attached earlobes, short stature, and congenital malformations including s-shaped thoracolumbar scoliosis, hip dislocation, and generalized brain atrophy shared common characteristics of X-linked syndromic ID. We have observed severely malformed oro-dental organs and a choledochal cyst, which have never been reported. Our study presents the first patient from Thailand expanding the phenotypic and mutational spectra of the syndrome.

KEYWORDS

female-restricted X-linked syndromic , intellectual disability, exome sequencing, intellectual disability, multiple anomalies, *USP9X*

1 | INTRODUCTION

Ubiquitin-specific protease 9 X-link (*USP9X*; OMIM 300072), encoding a conserved deubiquitinating enzyme, was first associated with intellectual disability (ID) in a single individual identified in a large-scale sequencing study of X-chromosome (Tarpey et al., 2009). Subsequently, a 4-year-old Chinese girl with ID, congenital anomalies, and autism spectrum disorder was found to harbor a truncating *USP9X* mutation (Brett et al., 2014). In 2016, Reijnders et al. defined an ID/developmental delay (DD) syndrome with distinct facial features, brain anomalies, and multiple congenital malformations based on 17 unrelated females having *de novo* loss-of-function mutations in *USPX9* (Reijnders et al., 2016). Common facial characteristics included prominent forehead, prominent nose with flared alae nasi, thin upper lip, long philtrum, and dysplastic ears. Congenital malformations comprised choanal atresia, cleft palate, asymmetric hypomastia, heart anomalies, progressive scoliosis, postaxial polydactyly, and anal defects. In 2017, one Canadian female and one Australian female with ID and *USP9X* mutations were reported, one with typical syndromic features having a frameshift mutation and the other with mild congenital anomalies having deletion in the 5′UTR of the *USP9X* gene

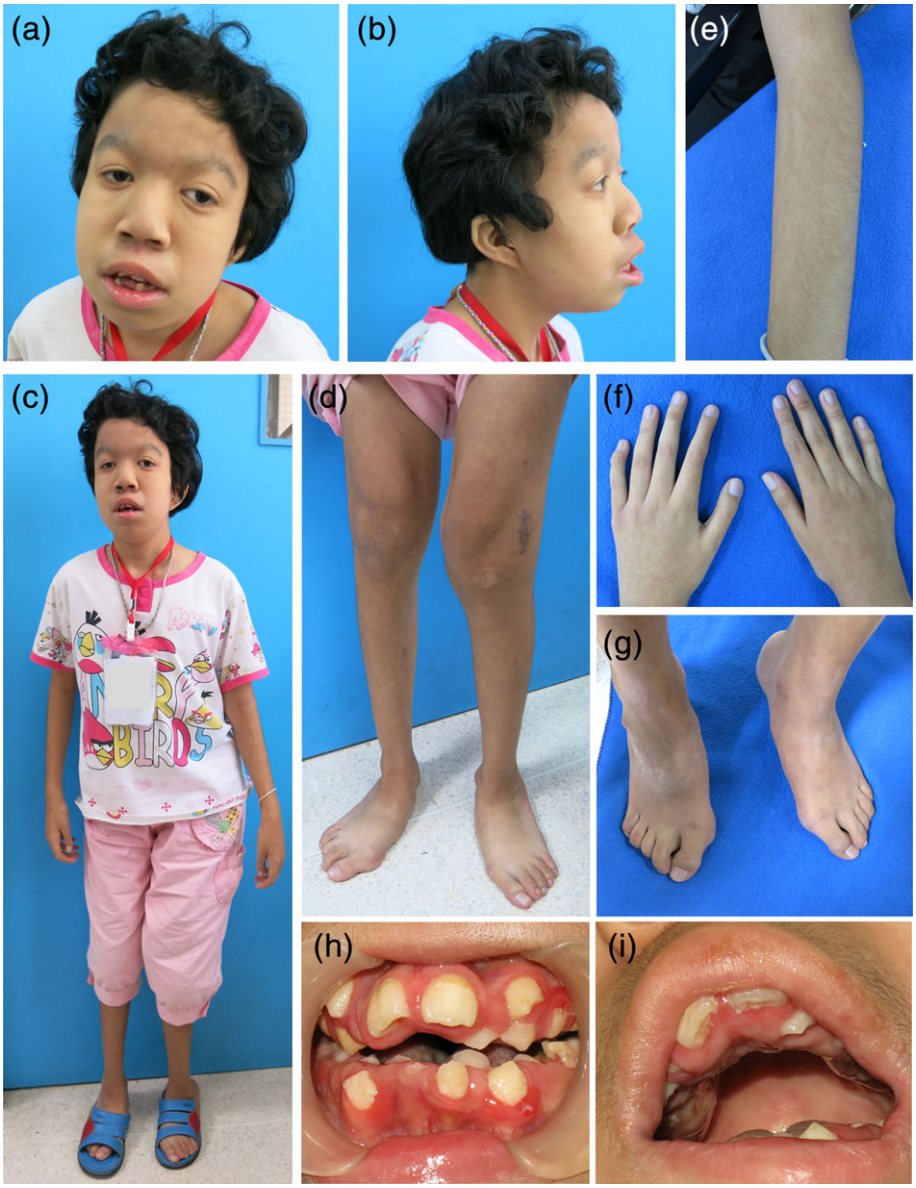

FIGURE 1 Clinical features of the proband (a–c). Dysmorphic facial characteristics at an age of 13 years showed curly hair, prominent nose with wide nasal base and flared alae nasi, telecanthus, full lips, long philtrum, hanging full cheeks, low-set ears, and attached earlobes. (d–g) Physical features included limb-length discrepancy, flat feet, double jointed thumbs, tapered fingers, halluces valgus, overlapping toes, and hypertrichosis. (h,i) Oral findings comprised severe malocclusion, irregular dental arches, gingival inflammation, and high-arched palate. a–i, age of 13 years; e, age of 14 years [Color figure can be viewed at wileyonlinelibrary.com]

(Au et al., 2017). In males, several missense mutations and a frameshift mutation in the last exon of *USP9X* were found to cause a nonsyndromic ID (Homan et al., 2014).

2 | CASE REPORT

Here, we report a 15-year-old Thai girl presenting with ID, dysmorphic facial features, and multiple congenital anomalies. The proband, the second child of healthy non-consanguineous Thai parents, was born at 38 weeks gestation via breech assisted delivery with birth weight of 2,650 g (10–50th centile) and APGAR score of 1 at 1 min and 5 at 5 min. She had congenital right hip dislocation and subluxation of both knees. Prolonged jaundice led to the discovery of a choledochal cyst. She subsequently underwent Roux-en-Y choledochojejunostomy and appendectomy at 1 month of age. Echocardiogram during neonatal period showed atrial septal defect secundum that closed spontaneously. Delayed development was noted. Her IQ at 8 years old was 39. She had several orthopedic treatments including K-wire fixation, epiphysiodesis, hip spica cast, and shoe lifts. The patient was referred to our institute at 12 years of age for evaluation of profound ID and dysmorphic features. She had difficulty walking, delayed speech and motor development, recurrent respiratory infections, and short stature with a height of 132.8 cm (<3rd centile), weight of 26.8 kg (<3rd centile), and head circumference of 50 cm (25–50th centile). Her facial dysmorphisms consisted of prominent nose with wide nasal base and flared alae nasi, curly hair, telecanthus, low-set ears, attached earlobes, full lips, and long philtrum (Figure 1a–g). Her oral cavity exhibited

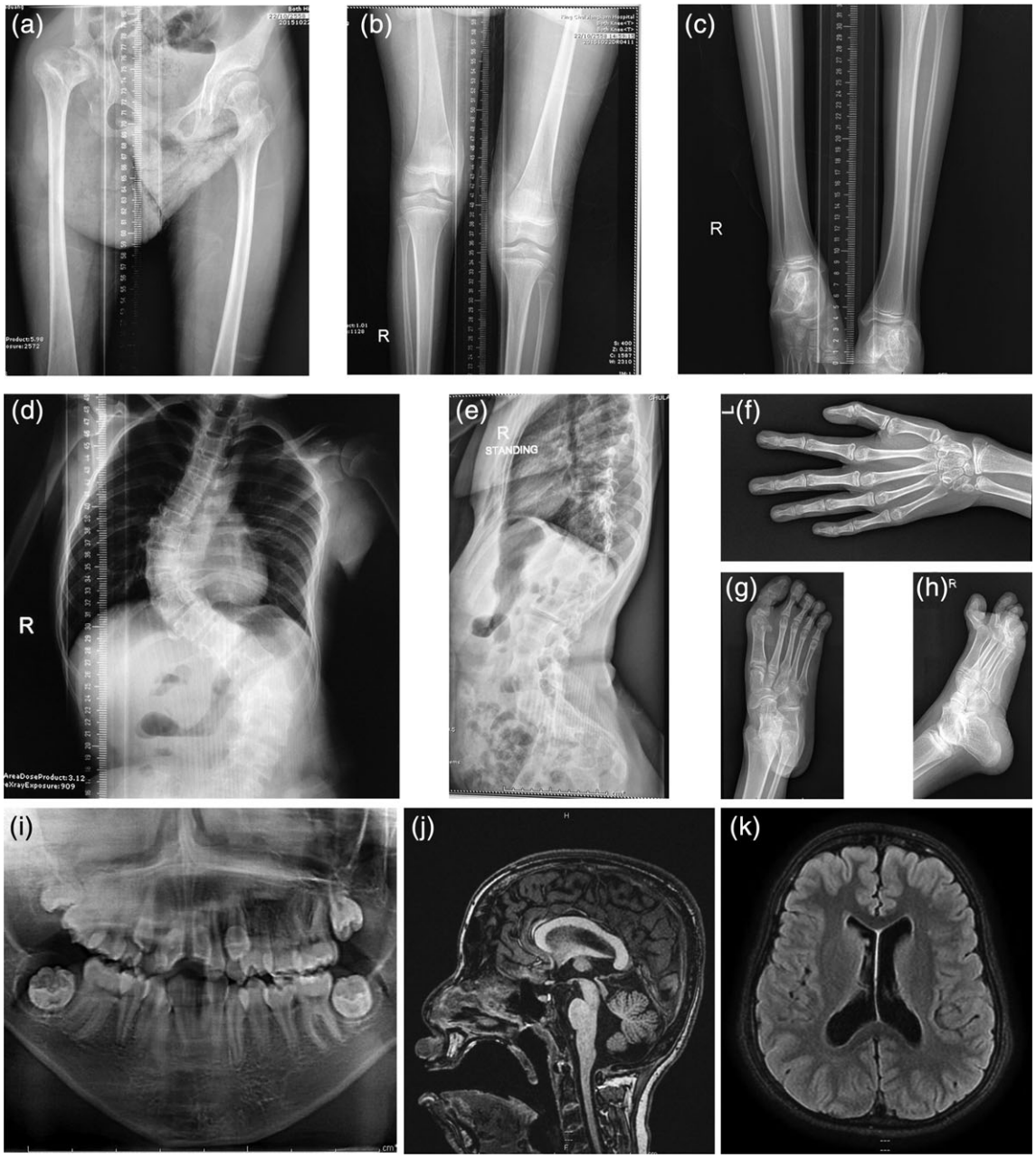

FIGURE 2 Radiographs of the proband (a–c) right hip dislocation and asymmetric length of legs were present at 12.5 years of age. (d, e) The spine radiographs showed severe s-shape thoracolumbar scoliosis. The apex of the spine positioned toward the right at T8/T9 level (cobb angle of about 62°) and toward the left at L1/2 level (cobb angle of about 56°). (f) Hand radiograph showed delayed bone age around 7 months. (g, h) flexion of the first interphalangeal joints of the feet and extra bone exostosis were present. (i) Disorganized dentition. (j, k) Magnetic resonance imaging of the brain showed generalized brain atrophy, thin brainstem, dilated fourth ventricle, hypoplasia of the cerebellar vermis, cerebellum, and corpus callosum, and no enlargement of the posterior fossa. J, axial T2 FLAIR FS; k, sagittal T1. a–c, age of 12.5 years; d–h and j, k, age of 15 years, i, age of 13 years

severely misaligned teeth, gingival hypertrophy, dysmorphic alveolar bone, and high-arched palate (Figure 1h,i). Limb-length discrepancy, flat feet, double jointed thumbs, slender fingers, halluces valgus, overlapping toes, mild hypotonia, and limited joint mobility were found. Hypertrichosis became evident at 14 years of age. The scoliosis and leg length discrepancy were progressed. Radiographic examinations revealed right hip dislocation, severe S-shaped thoracolumbar scoliosis, leg-length inequality, diffuse osteopenia, flexion of the first interphalangeal joint of the feet, and malocclusion (Figure 2a–i). Her bone age was 7 months delayed. Breast development was Tanner Stage 1 at 12 years and Stage 2 at 15 years of age, indicating delayed puberty. Heart sounds, hearing, vision screenings, blood chemistry, thyroid hormone levels, and ultrasonography of the kidneys and urinary bladder were normal. Magnetic resonance imaging of the brain showed generalized brain atrophy, thin brainstem, dilated fourth ventricle, hypoplasia of the cerebellar vermis, cerebellum, and corpus callosum, and no enlargement of the posterior fossa, suggesting Dandy-Walker variant (Figures 2j,k). Her karyotype was 46,XX. Exome and sanger sequencing of the proband identified a *de novo* heterozygous one-base pair deletion, c.3508delG, p.Val1170TrpfsX9, in exon 23 of the *USP9X* gene (NM_001039590.2) (Supporting Information Figure S1). This variant was not present in ExAC (http://exac.broadinstitute.org/),

dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/), and our in-house 1,600 Thai Exome databases.

3 | DISCUSSION

Except one patient with a deletion in the 5′UTR of *USP9X* expected to have residual functional gene product, all female patients with *USPX9* mutations reported by Reijnders et al., 2016 and Au et al., 2017 shared certain phenotypes including mild to moderate ID/DD, dysmorphic facial features, short stature, hearing loss, and congenital defects notably postaxial polydactyly, progressive scoliosis, asymmetric hypomastia, choanal atresia, cleft palate/bifid uvula, heart defects, and anal anomalies. These overlap with our patient's characteristics (Supporting Information Table 1). Interestingly, one reported patient by Reijnders et al., 2016 was the child of Swedish and Thai ancestry. Unlike our patient, she had hearing and visual impairment, respiratory insufficiency, and acute lymphoblastic leukemia.

In conclusion, we report the first Thai girl with female-restricted X-linked syndromic ID syndrome having severely malformed oro-dental organs and choledochal cyst associated with a novel one-base pair deletion in *USP9X*, expanding its phenotypic and mutational spectra.

ACKNOWLEDGMENTS

This study was supported by the Thailand Research Fund (TRF) (RSA6280001, DPG6180001), the Newton Fund, Faculty Research Grant (DRF62003), and Chulalongkorn Academic Advancement into its 2nd Century Project.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

TP, VS contributed to conception, data acquisition and analysis, drafting, and critical revision of the manuscript; TS, CI contributed to data analysis, and critical revision of the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

ORCID

Thantrira Porntaveetus https://orcid.org/0000-0003-0145-9801

REFERENCES

Au, P. Y. B., Huang, L., Broley, S., Gallagher, L., Creede, E., Lahey, D., … Dyment, D. A. (2017). Two females with mutations in USP9X highlight the variable expressivity of the intellectual disability syndrome. *European Journal of Medical Genetics*, *60*, 359–364. https://doi.org/10.1016/j.ejmg.2017.03.013

Brett, M., McPherson, J., Zang, Z. J., Lai, A., Tan, E. S., Ng, I., … Tan, E. C. (2014). Massively parallel sequencing of patients with intellectual disability, congenital anomalies and/or autism spectrum disorders with a targeted gene panel. *PLoS One*, *9*, e93409. https://doi.org/10.1371/journal.pone.0093409

Homan, C. C., Kumar, R., Nguyen, L. S., Haan, E., Raymond, F. L., Abidi, F., … Jolly, L. A. (2014). Mutations in USP9X are associated with X-linked intellectual disability and disrupt neuronal cell migration and growth. *American Journal of Human Genetics*, *94*, 470–478. https://doi.org/10.1016/j.ajhg.2014.02.004

Reijnders, M. R., Zachariadis, V., Latour, B., Jolly, L., Mancini, G. M., Pfundt, R., … Kleefstra, T. (2016). De novo loss-of-function mutations in USP9X cause a female-specific recognizable syndrome with developmental delay and congenital malformations. *American Journal of Human Genetics*, *98*, 373–381. https://doi.org/10.1016/j.ajhg.2015.12.015

Tarpey, P. S., Smith, R., Pleasance, E., Whibley, A., Edkins, S., Hardy, C., … Stratton, M. R. (2009). A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation. *Nature Genetics*, *41*, 535. https://doi.org/10.1038/ng.367

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Sinthuwiwat T, Ittiwut C, Porntaveetus T, Shotelersuk V. Female-restricted syndromic intellectual disability in a patient from Thailand. *Am J Med Genet Part A*. 2019;1–4. https://doi.org/10.1002/ajmg.a.61106