Prenatal diagnosis and long-term follow-up of a Chinese patient with mosaic variegated aneuploidy and its molecular analysis

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Abstract
Mosaic variegated aneuploidy (MVA) is a rare genetic disorder caused by mutations in BUB1B, CEP57, or TRIP13. We describe the prenatal diagnosis, molecular characterization, and clinical management of a long-lived patient with BUB1B-related MVA.

KEYWORDS
molecular diagnosis, mosaic variegated aneuploidy, prenatal diagnosis
Mosaic variegated aneuploidy (MVA, OMIM 257300) is a congenital autosomal recessive disorder characterized by mosaic aneuploidies, predominantly trisomies, and monosomies, involving multiple chromosomes and tissues. Mutations in \(BUB1B\), \(CEP57\), and \(TRIP13\) genes, which are involved in mitotic spindle and microtubule stabilization, are responsible for the molecular pathogenesis of MVA. The clinical features of MVA syndrome include severe pre/postnatal growth retardation, microcephaly, central nervous system anomalies, intellectual disability, minor congenital malformation, and predisposition to malignancy. There is some genotype-phenotype correlation (Table 1). Intellectual disability, microcephaly, brain malformations, epilepsy, and cancer predisposition are more common in \(BUB1B\) subtype. Rhizomelic shortening of the upper limbs, skull anomalies with conserved head circumference, and absence of malignancy are more common in \(CEP57\) subtype. In addition, \(TRIP13\) subtype has growth retardation with microcephaly and developmental delay, but there is no other structural abnormality and dysmorphic facial feature as in \(BUB1B\) subtype.

Several cases of MVA were diagnosed in prenatal period, followed by the termination of pregnancy. Here we reported a Chinese patient with the longest survival in literature, with cytogenetic and antenatal findings together with her long-term postnatal course and molecular finding.

3 | DISCUSSION

Premature chromatid separation (PCS) and asynchrony of mitotic stages is described to be the pathogenic mechanism for mosaic variegated aneuploidies (MVA). PCS/MVA manifests cytogenetically as a variety of mosaic aneuploidies, especially trisomies, double trisomies, and monosomies. The proportion of aneuploid cells varies but is usually >25% and is substantially greater than in normal individuals. Conventional cytogenetic analysis with at least two independent amniocyte cultures should always be performed to diagnose prenatal MVA. In our case, amniocyte, placenta, and cord blood lymphocytes culture demonstrated that the proportion of aneuploidy cells was more than 25%, which confirmed the prenatal diagnosis of MVA.

The phenotype is highly variable across individuals of MVA. Common abnormalities of MVA include intrauterine growth retardation, microcephaly, dysmorphic features, and mental retardation. There is also a high risk of early-onset childhood cancer like Wilms tumor, rhabdomyosarcoma, or leukemia. Facial dysmorphic features in MVA syndrome include micrognathia, frontal bossing, triangular face, epicanthic folds, hypertelorism, low-set ears, and broad nasal bridge. Cardiovascular, neurological, skeletal anomalies like rhizomelic shortening of the upper limbs, gastrointestinal, and dermatological anomalies, immunodeficiency, and endocrine problem like hypothyroidism have also been described.

Microcephaly was most commonly observed in MVA cases, described in general 90% patients. Prenatal ultrasound findings in association with MVA included intrauterine growth restriction, microcephaly, Dandy-Walker malformation, cerebral ventricular dilatation, fetal ascites, oligohydramnios, and
**TABLE 1** Subtype of Mosaic Variegated Aneuploidy syndrome and genotype-phenotype correlation

| Title | Mosaic variegated aneuploidy syndrome 3; MVA3 | Mosaic variegated aneuploidy syndrome 1; MVA1 | Mosaic variegated aneuploidy syndrome 2; MVA2 | Our case |
|-------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|----------|
| Inheritance | Autosomal recessive | Autosomal recessive | Autosomal recessive | Autosomal recessive |
| Molecular basis | Caused by mutation in the thyroid hormone receptor interactor 13 gene (TRIP13) | Caused by mutation in the budding uninhibited by benzimidazoles 1 beta gene (BUB1B) | Caused by mutation in the 57-kD centrosomal protein gene (CEP57) | Caused by mutation in the budding uninhibited by benzimidazoles 1 beta gene (BUB1B) |
| Laboratory abnormalities | Aneuploidy | Mitotic lymphocyte and fibroblast cultures show mosaic variegated aneuploidy | Mitotic lymphocyte and fibroblast cultures show mosaic variegated aneuploidy (50%) affecting all chromosomes | Mitotic lymphocyte and fibroblast cultures show mosaic variegated aneuploidy |
| | Premature chromatid separation | More than 50% of mitotic cells show premature chromatid separation (PCS) affecting all chromosomes | Chromosomal structural abnormalities | More than 50% of mitotic cells show premature chromatid separation (PCS) affecting all chromosomes |
| | Chromosome instability | Anaphase loss or nondisjunction with trisomies, tetrasomies, monosomies | Anaphase loss or nondisjunction with trisomies, tetrasomies, monosomies | Anaphase loss or nondisjunction with trisomies, tetrasomies, and monosomies |
| Growth | Height | Weight | Height | Weight |
| | Short stature | Low birthweight | Intrauterine growth retardation (IUGR) | Low birthweight |
| | Other | Low postnatal weight | Low postnatal weight | Other |
| | Growth retardation | Postnatal and prenatal | Growth retardation, prenatal and postnatal | Growth retardation, prenatal and postnatal |
| Head & neck | Head | Face | Ears | Eyes |
| | Microcephaly (in some patients) | Microcephaly, severe | High forehead | Hypertelorism |
| | | Brachycephaly | Midface hypoplasia | | |
| | | Mesomphalia | Micrognathia | | |
| | | Long philtrum | Long philtrum | | |
| | | Ears | Ears | | |
| | | Low-set ears | Low-set ears | | |
| | | Posteriorly rotated ears | Posteriorly rotated ears | | |
| | | Hypertelorism | Hypertelorism | | |
| | | Upsettal palpebral fissures | Deep-set eyes (1/4 patients) | | |
| | | Epicanthal folds | Short palpebral fissures (1/4 patients) | | |
| | | Cataracts | Downslanting palpebral fissures (in 2/4 patients) | | |
| | | Nystagmus | Epicanthal folds (3/4 patients) | | |
| | | Nose | Small nose (2/4 patients) | | |
| | | Short, wide nose | Flat nasal bridge (in 2/4 patients) | | |

(Continues)
## TABLE 1 (Continued)

| Title | Mosaic variegated aneuploidy syndrome 3; MVA3 | Mosaic variegated aneuploidy syndrome 1; MVA1 | Mosaic variegated aneuploidy syndrome 2; MVA2 | Our case |
|-------|---------------------------------|---------------------------------|---------------------------------|---------|
| Cardiovascular | Heart | Congenital heart defects (in 2/4 patients) | Atrial septal defect | Congenital heart defects |
| | | | Ventricular septal defect | Pericardial effusion |
| | | | Aortic valve regurgitation | |
| | | | Vascular | |
| | | | Aortic coarctation | |
| | | | Subaortic stenosis | |
| Respiratory | Heart | | | Pleural effusion, chylothorax |
| | Lung | | Abnormal lung lobation (in 1/4 patients) | |
| Chest | Ribs | Sternum Clavicles and Scapulae | Gastrointestinal | Gastrointestinal |
| | | Short sternum | | | pleural effusion, chylothorax |
| Abdomen | Gastrointestinal | | Gastrointestinal | Gastrointestinal |
| | | Feeding difficulties | | | ascites, duplication cyst of gut |
| Genitourinary | Ambiguous genitalia | External Genitalia (Male) | Kidneys | Wilms tumor |
| | | Micropenis | | | glomerulosclerosis |
| | | Hypospadias | | | |
| | | Bifid scrotum | | | |
| | Internal Genitalia (Male) | Cryptorchidism | | |
| | | Kidneys | | | |
| | | Renal cysts | | | |
| | | Wilms tumor | | | |
| Skeletal | Delayed bone age (in 1/4 patients) | Skull | | |
| | | Epidermoid cysts (in 1/4 patients) | Limbs | |
| | | Rhizomelic shortening of the upper limbs (in 2/4 patients) | Hands | |
| | | | Clinodactyly (in 2/4 patients) | |
| Skin, nails, & hair | Skin | Pigmentary abnormalities | Skin | Cafe-au-lait spot (in 1/4 patients) |
| | | | | Cafe-au-lait spot |
| Neurologic | Central Nervous System | Developmental delay, profound | Central Nervous System | Mild mental retardation (in 1/4 patients) |
| | | Mental retardation, profound | | Hypotonia (in 1/4 patients) |
| | | Hypotonia, generalized | | Sleep apnea (in 1/4 patients) |
| | | Seizures, generalized tonic-clonic | | |
| | | Seizures, myoclonic | | |
| | | Hypoplastic cerebrum | | |
| | | Pachy宏观经济ry | | |
| | | Cerebral oligogyria | | |
| | | Hypoplasia of the corpus callosum | | |
| | | Agenesis of the corpus callosum | | |
| | | Posterior fossa malformations | | |
| | | Dandy-Walker malformation | | |
| | | Enlarged ventricles | | |
| | | Hydrocephalus | | |
| | | Cerebellar hypoplasia | | |

(Continues)
TABLE 1  (Continued)

| Title                  | Mosaic variegated aneuploidy syndrome 3; MVA3 | Mosaic variegated aneuploidy syndrome 1; MVA1 | Mosaic variegated aneuploidy syndrome 2; MVA2 | Our case                                      |
|------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|-----------------------------------------------|
| Endocrine features     |                                             |                                             |                                             | • Growth hormone deficiency (in 1/4 patients) |
|                        |                                             |                                             |                                             | • Hypothyroidism (in 2/4 patients)            |
| Immunology             | • Combined immunodeficiency (reported in 1 patient) |                                             |                                             |                                               |
| Neoplasia              | • Wilms tumor                               | • Propensity to tumor development           | • Propensity to tumor development           |                                               |
|                        | • Wilms tumor                               | • Wilms tumor                               | • Wilms tumor                               |                                               |
|                        | • Nephroblastoma                            | • Nephroblastoma                            | • Nephroblastoma                            |                                               |
|                        | • Rhabdomyosarcoma                          | • Rhabdomyosarcoma                          | • Sertoli-Leydig cell tumor                 |                                               |
|                        | • Leukemia                                  | • Leukemia                                  |                                             |                                               |
| Prenatal manifestations| Amniotic Fluid                              | • Oligohydramnios                           | Biochemical serum screening                 |                                               |
|                        | • Delivery                                  | • Premature labor                           | • raised maternal serum alpha fetoprotein   |                                               |
| Miscellaneous          | • Onset of Wilms tumor in early childhood    | • Variable phenotype                        | • Four patients have been reported (as of July 2011) |                                               |
|                        | • Highly variable phenotype other than Wilms tumor | • Heterozygous parents are phenotypically normal but their cells show premature chromatid separation trait (PCS, OMIM 176430) | • Highly variable phenotype                 |                                               |
|                        |                                             |                                             | • Facial dysmorphic features are mild       |                                               |

Note: Modified and updated from: https://omim.org/clinicalSynopsis/table?mimNumber=617598,614114,257300

FIGURE 1  Chromosome study and facial feature of the MVA patient. A, One representative cultured amniocyte metaphase image showing karyotype result of 48,XX,+8,+17. B, Subtle facial dysmorphism at 4, 8, and 22 years old: The patient has microcephaly, failure to thrive with all growth parameters less than 3rd percentile, and subtle dysmorphism (hypertelorism, high forehead, epicanthic fold, and midface hypoplasia). The hypertrichosis at 22 years old was due to side effect of cyclosporine A after renal transplantation.
increased nuchal translucency. According the literature on the prenatal cases of MVA, fetal growth restriction is the commonest feature. In this case, the main prenatal sonographic features include fetal growth restriction, microcephaly, pericardial effusion, ascites, and congenital heart disease. In the long-term follow-up of this patient, she manifested with failure to thrive, microcephaly, mild intellectual disability, and cancer predisposition. As the clinical phenotype is highly heterogeneous in MVA, especially in prenatal period, MVA syndrome is usually under-recognized and missed.

Genetic defect of chromosome segregation in cell mitosis might be associated with MVA, and mutations of BUB1B involved in the mitotic spindle checkpoint might underlie MVA. The compound heterozygous variants NM_001211.5(BUB1B):c.[1402-5A>G];[2387-11A>G] found in this patient are located at the RNA splicing acceptor site of exons 11 and 19 of BUB1B, and reported in the literature. Reduced BUB1B expression on the spindle checkpoint is dose-dependent. An analogous mutation (in mice) to the human MVA BUB1B (encodes protein BUBR1) has a reduced lifespan and develop several age-related phenotypes at an accelerated rate. Sustained high expression of BUBR1 preserves genomic integrity and reduces tumorigenesis by correcting mitotic checkpoint impairment and microtubule-kinetochore attachment defects.

Clinical management of patients with MVA syndrome includes symptomatic support and tumor surveillance, particularly for BUB1B subtype. Early molecular diagnosis might enable risk stratification for tumor surveillance. Common tumors reported in BUB1B-associated MVA syndrome are Wilms tumor, rhabdomyosarcoma, leukemia and granulosa cell tumor of the ovary. In this case, patient suffered from infantile neuroblastoma and Sertoli-Leydig cell tumor. It is recommended that patients with MVA syndrome have regular abdominal ultrasound surveillance, to particularly look for Wilms tumor. However, as the incidence rate of other rare tumor in MVA is unknown, there is still no evidence to indicate that routine screening is beneficial. But high index of suspicion is necessary. In case there are any clinical symptoms of malignancy, further investigation should be carried out.

We have reported the longest Chinese survivor of BUB1B-related MVA syndrome in the literature, its clinical course, and management.

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CONFLICT OF INTEREST
There is no any conflict of interest in relation to the work.

AUTHOR CONTRIBUTIONS
Sheng Mou Lin and Ho Ming Luk: involved in conceptualization, methodology, drafting, and writing manuscript. Ivan Fai Man Lo: involved in data collection and curation. Wai-Keung Tam and Kelvin Yuen Kwong Chan: carried out investigation. Hei-Yee Tse, Wing Cheong Leung, and Mary Hoi Yin Tang: involved in data curation and validation. Anita Sik Yau Kan: involved in conceptualization, reviewing, and editing.

INFORMED CONSENT
Written informed consent was obtained from the patient.

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