Mosaic variegated aneuploidy syndrome

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Identity

Other names
MVA

Inheritance
Autosomal recessive; rare with unknown incidence.

Clinics

Phenotype and clinics
A broad spectrum of clinical features has been observed in individuals with MVA syndrome. Microcephaly, pre- and/or postnatal growth retardation, variable developmental delay and dysmorphic facial features are frequently described. Seizures and other neurological abnormalities, eye anomalies including cataracts and strabismus, skeletal/hand and foot abnormalities including clinodactyly and dermatological anomalies such as café au lait patches and haemangioma have also been described. Less common abnormalities include gastrointestinal defects, renal anomalies and cardiac defects. The clinical spectrum ranges from a severe and even lethal course to a mild phenotype without microcephaly or mental retardation.

Neoplastic risk
The risk of malignancy in MVA is high with Wilms tumour, rhabdomyosarcoma, leukaemia and granulosa cell tumour of the ovary reported in several cases. Myelodysplastic syndrome has also been observed.

Treatment
Clinical management of patients with MVA syndrome is based upon the affected individual's specific needs and may include surgical treatments and intervention and/or special education if developmental delay is detected. Standard treatment for specific neurological, ophthalmological, cardiac or renal anomalies may also be indicated. Due to the increased cancer risk, cases with a diagnosis of MVA syndrome should be offered Wilms tumour surveillance. Current UK recommendations include renal ultrasonography every three to four months until five years. There is no particular screening that is helpful for the other tumours known to be associated with MVA syndrome, but any suspicious clinical symptoms should be investigated with minimal delay.

Prognosis
The prognosis for an individual with MVA syndrome is based on the malformations present in the individual. There is early mortality in a significant proportion of cases due to failure to thrive and/or complications of congenital abnormalities, epilepsy, infections or malignancy.

Cytogenetics

Inborn conditions
MVA is characterised by mosaic aneuploidies, predominantly trisomies and monosomies, involving multiple different chromosomes and tissues (examples are shown in figure 1). The proportion of aneuploid cells varies but is usually >10% and is substantially greater than in normal individuals. Some patients with MVA also demonstrate premature chromatid separation in colchicine-treated blood lymphocyte and fibroblast cultures.
Cytogenetics of cancer
Gain of chromosomes 8 and 13 and loss of chromosomes 9 and 14 have been observed in the embryonal rhabdomyosarcoma from an individual with MVA. Gain of chromosome 8 has also been identified in the embryonal rhabdomyosarcoma from a further patient with MVA syndrome.

Other findings
Cells from BUB1B mutation-positive cases demonstrate an abnormal response to nocodazole-induced mitotic checkpoint activation.

Genes involved and proteins

BUB1B
Location
15q15.1
DNA/RNA
Description
BUB1B spans 60 kb and is composed of 23 exons.

Protein
Note
Protein name: BUBR1
Description
1050 amino acids, 120 kDa.
Expression
Ubiquitously expressed. Preferentially expressed in tissues with a high mitotic index.
Localisation
Cytoplasmic in interphase cells. Bound to BUB3 or CENPE, it can be localised to nuclear kinetochores. BUBR1 also localises to centrosomes during interphase.
Function
A central component of the mitotic spindle checkpoint that directly inhibits the anaphase-promoting complex/cyclosome until sister chromatids are correctly attached to the spindle, thus ensuring proper chromosome segregation during cell division.

Figure 1. Examples of karyotypic abnormalities identified in individuals with MVA.

Figure 2. Schematic representation of BUB1B demonstrating the relative exon sizes.
Also binds the motor protein CENPE, an interaction required for regulation of kinetochore-microtubule interactions and checkpoint signalling.

**Homology**
BUBR1 is the mammalian homologue of yeast Mad3, a significant difference being that BUBR1 possesses a kinase domain which is absent in Mad3.

**Mutations**
**Germinal**
Biallelic germline mutations have been found in eight MVA pedigrees (figure 4).
Each family carries one missense mutation and one mutation that results in premature protein truncation or an absent transcript. Monoallelic truncating mutations have also been reported in several cases.

**CEP57**

**Location**
11q21

**DNA/RNA**

**Description**
CEP57 spans over 42 kb and is composed of 11 exons.

**Protein**

**Description**
500 amino acids, 57 kDa.

**Expression**
Ubiquitously expressed.

**Localisation**
Nucleus, cytoplasm, cytoskeleton, centrosome.

**Function**
Centrosomal protein required for microtubule attachment to centrosomes.
Also involved in intracellular bidirectional trafficking of factors such as FGF2 along microtubules.

**Homology**
The CEP57 gene is conserved in chimpanzee, dog, cow, mouse, rat, chicken, and zebrafish.

**Mutations**
**Germinal**
Biallelic, loss-of-function mutations have been found in three MVA pedigrees (figure 7).
Figure 5. Schematic representation of CEP57 demonstrating the relative exon sizes.

Figure 6. Schematic representation of CEP57 demonstrating significant functional or structural domains.

Figure 7. Schematic representation of CEP57 demonstrating the relative exon sizes and positions of known mutations. Biallelic mutations are represented by coloured lines, with mutations in the same individual in matching colours.

References


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