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Microcephaly-Capillary Malformation Syndrome

Synonym: MIC-CAP Syndrome

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Summary

Clinical characteristics

The defining clinical characteristics of the microcephaly-capillary malformation (MIC-CAP) syndrome are typically present at birth: microcephaly and generalized cutaneous capillary malformations (a few to hundreds of oval/circular macules or patches varying in size from 1-2 mm to several cm), hypoplastic distal phalanges of the hands and/or feet, early-onset intractable epilepsy, and profound developmental delay. Seizures, which can be focal, tonic, and complex partial and can include infantile spasms, appear to stabilize after age two years. Myoclonus of the limbs and eyelids is common; other abnormal movements (dyskinetic, choreiform) may be seen. To date, the diagnosis has been confirmed in 18 individuals from 15 families.

Diagnosis/testing

The diagnosis of MIC-CAP syndrome is established in a proband with suggestive findings and biallelic pathogenic variants in *STAMBP* identified by molecular genetic testing.

Management

Treatment of manifestations: Supportive care by multidisciplinary specialists including a medical geneticist, neurologist, developmental pediatrician, and feeding specialist is recommended. Central hypotonia and peripheral hypertonia require attention to proper seating and bracing to maintain posture and prevent contractures. Seizures require management by an experienced pediatric neurology team, as multiple anticonvulsant medications are frequently required for adequate seizure control. A feeding tube is essential to optimize nutrition and weight gain while reducing the risk of aspiration.

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Surveillance: Regular follow up with a child neurologist for seizure management and a complex care / palliative care team or experienced pediatrician to monitor for complications associated with severe neurologic impairment.

Agents/circumstances to avoid: Valproic acid may or may not be associated with adverse effects.

Genetic counseling

MIC-CAP syndrome is an autosomal recessive disorder caused by biallelic *STAMBP* pathogenic variants. Typically, one pathogenic variant is inherited from each parent; however, in some instances both pathogenic variants are inherited from one parent (uniparental isodisomy).

- If both parents are known to be heterozygous for a *STAMBP* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- If the proband has MIC-CAP syndrome as the result of uniparental isodisomy, only one parent is heterozygous for a *STAMBP* pathogenic variant, and if neither parent has a chromosome rearrangement, each sib of an affected individual has at conception a 50% chance of being an asymptomatic carrier and an approximately 50% chance of being unaffected and not a carrier. The risk to sibs of a proband of being affected is unknown but is presumed to be less than 1%.

Once the *STAMBP* pathogenic variants have been identified in an affected family member (or – if the proband has MIC-CAP as the result of uniparental isodisomy – identification of the one familial *STAMBP* pathogenic variant), carrier testing for at-risk family members, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for microcephaly-capillary malformation (MIC-CAP) syndrome have been published.

Suggestive Findings

MIC-CAP syndrome **should be suspected** in individuals with the following clinical and neuroimaging findings and family history.

Clinical findings

- **Congenital microcephaly.** Occipitofrontal head circumference at birth is more than two standard deviations (SD) below the mean for sex, gestational age, and ethnicity, and may be as small as −8 SD.
- **Multiple generalized cutaneous capillary malformations** (pink or red, blanchable, roughly oval or circular macules or patches) present at birth and distributed over the scalp, torso, buttocks, limbs, and genitalia. The number ranges from a few to hundreds; size ranges from one to two millimeters to several centimeters [McDonell et al 2013] (full text; see Figure 1).
- **Neonatal-onset intractable epilepsy**
- **Hypoplastic distal phalanges and nails** of the hands and/or feet. Fingers (particularly 2, 3, and 4) may be tapered with hypoplastic nails. Toes (especially 3 and 4) may be hypoplastic with unusual implantation. Dorsa of the hands and feet may have non-pitting edema. Hands may have single or unusual palmar creases and fifth finger clinodactyly. Other findings can include cutaneous syndactyly, sandal gap, and deep-set and/or small, narrow nails [McDonell et al 2013] (full text; see Figure 1).
- **Facial dysmorphism** includes sloping forehead, low anterior hairline, round face, hypertelorism, epicanthus, long palpebral fissures, ptosis, short nose with upturned tip, low-set and posteriorly rotated

ears with fleshy lobules, high, arched palate, downturned corners of mouth, and micrognathia [McDonell et al 2013].
- Some may have an abnormal hair pattern in a "Mohawk" distribution (sparse laterally and longer along sagittal suture) and/or abnormal or multiple hair whorls.

Imaging findings

- Simplified gyral pattern (reduced number of gyri and shallow sulci) with increased extra-axial space and progressive cerebral atrophy is seen on brain imaging.
- Cortical myelination may be reduced or abnormal.
- Other common neuroimaging findings include hippocampal hypoplasia, thinning of the corpus callosum, hypoplasia of the optic nerves and/or optic chiasm and other malformations of cortical development.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of MIC-CAP syndrome **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *STAMBP* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *STAMBP* variants of uncertain significance (or identification of one known *STAMBP* pathogenic variant and one *STAMBP* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with microcephaly and/or seizures may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and imaging findings suggest the diagnosis of MIC-CAP syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *STAMBP* is performed first to detect small intragenic deletions/insertions as well as missense, nonsense, and splice site variants. Pathogenic deep intronic variants are reported, and these can be investigated if strong clinical suspicion of MIC-CAP exists [McDonell et al 2013].

  Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Uniparental isodisomy testing can be considered in probands who appear to be homozygous for a pathogenic variant that is heterozygous in one parent and not present in the other [McDonell et al 2013].

- **Multigene panels** for brain malformations, neurodevelopmental disorders, microcephaly, limb anomalies, and vascular malformations that include *STAMBP* and other genes of interest (see Differential Diagnosis) are most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by microcephaly and/or seizures, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) can be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Microcephaly-Capillary Malformation Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
STAMBP	Sequence analysis [3]	15/15 families [4]
	Uniparental isodisomy [5]	1/15 families [4]
	Deletion/duplication analysis [6]	None reported to date

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Mirzaa et al [2011], McDonell et al [2013], Faqeih et al [2015], Naseer et al [2016], Demikova et al [2018], Hori et al [2018], Wu et al [2019]
5. Various methods (e.g., SNP analysis, quantitative PCR, MLPA, massively parallel sequencing) can detect uniparental isodisomy. Testing may require parental blood specimens.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The defining clinical characteristics of the microcephaly-capillary malformation (MIC-CAP) syndrome are typically present at birth: microcephaly and generalized cutaneous capillary malformations, early-onset intractable epilepsy, and profound developmental delay [Carter et al 2011, Isidor et al 2011, Mirzaa et al 2011, McDonell et al 2013]. Given the small number of affected individuals reported to date (18 individuals from 15 families), the natural history is not yet completely understood.

Microcephaly is present at birth in most cases, with occipitofrontal head circumference ranging from 0 to 8 SD below the mean. Head growth generally decelerates during the first several months of life.

Generalized cutaneous capillary malformations. Growth of capillary malformations (which are present at birth) is commensurate with growth of the rest of the body. They may fade somewhat with age.

Histologic examination shows dilated small-caliber vessels in the papillary dermis consistent with capillary malformations [Carter et al 2011, Mirzaa et al 2012].

Seizures. Onset may be in utero or appear within the first days to months after birth. Seizures are most often observed on the first day of life. Seizures are frequent (dozens to hundreds per day) in the first two years of life and have occurred in all reported individuals.

Multiple seizure types described include focal, tonic, and complex partial, as well as infantile spasms. Electroencephalogram shows diffuse epileptiform activity with frequent multifocal spikes, abnormally slow background activity, and/or burst suppression pattern.

In most individuals, seizures are refractory to anticonvulsant therapy and ketogenic diet. After age two years, the seizures may stabilize to some degree and fewer medications may be required to keep seizures under reasonable control.

Profound neurologic impairment. Developmental progress is minimal. Most individuals do not attain head control or independent sitting due to spastic quadriparesis with severe central hypotonia. Cognitive development is poor, likely because of the underlying brain abnormality and intractable epilepsy.

Individuals are often not visually responsive; those tested have cortical visual impairment and/or optic atrophy.

Most have normal hearing by brain stem auditory evoked potential testing and respond to voice and music.

The majority require gastrostomy tube feeding because of poor swallowing mechanism, poor control of oral secretions, and/or aspiration with recurrent pneumonia. A few (3/18) have required tracheostomy for recurrent apnea and/or to manage secretions.

One individual with molecularly proven MIC-CAP syndrome has only moderate developmental delays (see Genotype-Phenotype Correlations).

Abnormal movements

- Myoclonus of limbs and eyelids is common (8/18 reported individuals) and tends to persist with age.
- Dyskinetic and choreiform movements may also be seen in some individuals.

Vision impairment

- Optic atrophy (10/18 reported individuals)
- Cortical vision impairment, roving eye movements, and nystagmus (reported in a few individuals)

Other features

- Large anterior fontanelle at birth
- Small size for gestational age (birth weight and length 2-4 SD below mean)
- Postnatal growth deficiency and short stature
- Sensorineural hearing impairment (1 individual)
- Cerebellar angiomata (1 individual)
- Cleft palate (1 individual)
- Facial asymmetry due to bony deficiency of maxilla (1 individual)
- Adrenal insufficiency (1 individual)

- Hypoplastic scrotum and small testes (1 individual)
- Kidney malformations (duplicated collecting system in 1 individual; unilateral dysplastic kidney in 1 individual) and vesicoureteral reflux
- Structural cardiac defects such as ASD, VSD, PDA, PFO, and mild right ventricular hypertrophy (each reported in 1 individual)
- Umbilical or inguinal hernia (2 sibs)

Life span is unknown but shortened because of severe neurologic impairments. The oldest living individual known was 12 years old at last assessment. At least three children have died in infancy. The cause of death in one male age 12 months was thought to be septic shock following acute pancreatitis, possibly secondary to valproate therapy [Carter et al 2011]. The cause of death in others has not been reported.

Neuropathology. In one individual who died at age 12 months, brain autopsy showed a very small brain (weight approximately equivalent to a newborn brain) with disproportionately small cerebral hemispheres compared to the cerebellum, diffuse cortical atrophy, thin corpus callosum, and white matter loss in the centrum semiovale and hippocampi. The descending pathways were hypoplastic with small cerebral peduncles and pyramids. There was widespread gliosis of optic nerves and tracts, lateral geniculate nuclei, visual cortex, and subcortical white matter [Carter et al 2011].

Genotype-Phenotype Correlations

The effect of pathogenic variant(s) on the protein STAMBP likely influences the severity of the MIC-CAP syndrome phenotype, with complete absence of protein production leading to the most severe phenotypes.

One affected female had a milder phenotype with moderate developmental delay and a less severe form of epilepsy [Isidor et al 2011]. At birth her head circumference was within the normal range (−1.8 SD); at her last evaluation at age five years, head circumference was −2.5 SD. She is able to walk independently and can speak in short phrases. She has approximately 30 capillary malformations of the skin and characteristic hypoplastic fingers and toes. She has a homozygous noncoding intronic pathogenic variant (c.1005+358A>G) that activated a cryptic splice site leading to leaky splicing of the full-length transcript. She had a threefold reduction in *STAMBP* transcript expression; STAMBP protein expression was markedly reduced but not absent [McDonell et al 2013].

Prevalence

Prevalence is unknown. To date 18 affected individuals (including 3 sets of sibs) from 15 families worldwide have molecularly confirmed MIC-CAP syndrome.

Most reported individuals are of European descent; individuals from other ethnic backgrounds (African, Arab, Asian, and Polynesian) have also been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *STAMBP*.

Differential Diagnosis

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome, an autosomal dominant disorder caused by a heterozygous pathogenic variant in *EPHB4* or *RASA1*, is characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly on the face and limbs. About 24% of affected individuals also have associated arteriovenous malformations and/or arteriovenous fistulas, fast-flow

vascular anomalies that typically arise in the skin, muscle, bone, spine, and brain. Life-threatening complications of these lesions can include bleeding, congestive heart failure, and/or neurologic consequences.

Unlike individuals with MIC-CAP syndrome, individuals with CM-AVM syndrome are not microcephalic and do not have intractable epilepsy or neurologic impairment.

Primary autosomal recessive microcephaly is characterized by congenital microcephaly with simplified gyral pattern but without other major brain or somatic malformations. The classic form is characterized by occipitofrontal head circumference more than 2 SD below the mean for sex, age, and ethnicity at birth and at least −3 SD after age six months; mild-to-severe cognitive impairment without major motor delay; absence of neurologic signs except mild seizures or hyperkinesia; normal facies except for a narrow, sloping forehead that often accompanies reduced cranial size; absence of malformations in other organ systems; and normal growth except for mildly short stature (up to −3 SD).

ASPM-related primary microcephaly is the most common form of primary microcephaly. To date, biallelic *ASPM* pathogenic variants explain 30%-50% of primary microcephaly depending on the geographic origin of the individual and the rate of consanguinity in the population.

MIC-CAP syndrome is distinguished from primary autosomal recessive microcephaly by the presence of capillary malformations, intractable epilepsy, severe neurologic impairment, and distal limb anomalies.

Management

No clinical practice guidelines for microcephaly-capillary malformation (MIC-CAP) syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with microcephaly-capillary malformation (MIC-CAP) syndrome, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with Microcephaly-Capillary Malformation Syndrome

System/Concern	Evaluation	Comment
Constitutional		
Neurologic	Neurologic eval	• To incl brain MRI • EEG if seizures are a concern
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Speech/Language		To assess need for alternative means of communication
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	To assess functional vision & for strabismus, refractive errors, & optic atrophy

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
Hearing	Audiologic eval	• To establish a baseline • To assess for hearing loss
Kidneys	Abdominal ultrasound exam	Assess for duplicated collecting system, unilateral dysplastic kidney, & vesicoureteral reflux.
Cardiovascular	Echocardiogram	Assess for structural defects.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MIC-CAP to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral; • Pediatric palliative care consultation.

ADL = activities of daily living; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Supportive care provided by multidisciplinary specialists including a medical geneticist, neurologist, feeding team, and developmental pediatrician is recommended.

Table 3. Treatment of Manifestations in Individuals with Microcephaly-Capillary Malformation Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Poor weight gain / Failure to thrive	• Feeding therapy to optimize nutrition & weight gain • Gastrostomy tube placement may be required for persistent feeding issues &/or ↑ risk of aspiration.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia &/or ↑ risk of aspiration
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Central visual impairment	No specific treatment; early intervention to stimulate visual development	
Hearing	Hearing aids may be helpful; per treating audiologist/ otolaryngologist.	Community hearing services through early intervention or school district
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

AED = antiepileptic drug; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 4. Recommended Surveillance for Individuals with Microcephaly-Capillary Malformation Syndrome

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	
Development	Monitor developmental progress & educational needs.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Valproic acid. One individual with MIC-CAP syndrome died from complications of pancreatitis after starting valproic acid for seizures [Carter et al 2011]. However, several other individuals with MIC-CAP syndrome have been treated with valproic acid without adverse effects. Therefore, it is unclear whether or not an association exists between MIC-CAP syndrome and adverse outcomes with valproic acid therapy. The benefits of use of valproic acid for seizure management in some patients may outweigh the potential risk for serious complications.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Microcephaly-capillary malformation (MIC-CAP) syndrome is an autosomal recessive disorder caused by biallelic *STAMBP* pathogenic variants. Typically, the proband has inherited one *STAMBP* pathogenic variant from each parent. Alternatively, the proband has MIC-CAP syndrome as the result of uniparental isodisomy for chromosome 2 (i.e., 2 copies of chromosome 2, with the *STAMBP* pathogenic variant inherited from 1 parent and no copy of chromosome 2 inherited from the other parent).

Risk to Family Members

Parents of a proband

- In most families, both parents of an affected child are carriers (i.e., heterozygotes) for a *STAMBP* pathogenic variant.
- Less commonly, only one parent is heterozygous for a *STAMBP* pathogenic variant and the child has MIC-CAP syndrome as the result of uniparental isodisomy and consequent homozygosity for the *STAMBP* pathogenic variant from the carrier parent [McDonell et al 2013].
- Accurate recurrence risk counseling relies on carrier testing of both parents to determine if both are heterozygous for a *STAMBP* pathogenic variant. If carrier testing detects the pathogenic variant in only one parent:
  - And the child appears to have homozygous *STAMBP* pathogenic variants, possible explanations include a large deletion on one allele (if not previously tested for) and uniparental isodisomy for chromosome 2 [McDonell et al 2013];
  - And the child has compound heterozygous *STAMBP* pathogenic variants, the child may theoretically have one inherited pathogenic variant and one *de novo* pathogenic variant (*de novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017]).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *STAMBP* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- If the proband has MIC-CAP syndrome as the result of uniparental isodisomy, only one parent is heterozygous for a *STAMBP* pathogenic variant, and neither parent has a chromosome rearrangement, each sib of an affected individual has at conception a 50% chance of being an asymptomatic carrier and an approximately 50% chance of being unaffected and not a carrier; the risk to sibs of a proband of being affected is unknown but is presumed to be less than 1%.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with MIC-CAP syndrome are not known to reproduce.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is heterozygous for a *STAMBP* pathogenic variant, the parent's family members are at risk of being carriers.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *STAMBP* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *STAMBP* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for MIC-CAP are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedLine Plus**
  Microcephaly-capillary malformation syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Microcephaly-Capillary Malformation Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
STAMBP	2p13.1	STAM-binding protein	STAMBP	STAMBP

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Microcephaly-Capillary Malformation Syndrome (View All in OMIM)

606247	STAM-BINDING PROTEIN; STAMBP
614261	MICROCEPHALY-CAPILLARY MALFORMATION SYNDROME; MICCAP

Molecular Pathogenesis

STAMBP encodes the deubiquitinating isopeptidase STAM-binding protein (STAMBP). It belongs to the JAMM (JAB1/MPN/MOV34) family of deubiquitinating enzymes that regulate ubiquitin signaling through polymeric ubiquitin chain disassembly and through target-protein ubiquitin removal. STAMBP also interacts with GRB2, a component of the interconnected RAS-MAPK and PI3K-AKT-mTOR transduction pathways [Tanaka et al 1999, McCullough et al 2006, Tsang et al 2006, Sierra et al 2010, Davies et al 2011].

Observations of patient-derived cell lines suggest that ubiquitin-conjugated protein aggregation and ensuing progressive apoptosis as a potential mechanism for microcephaly. In addition, interrogation of several endpoints in the RAS-MAPK and PI3K-AKT-mTOR pathways has shown elevated and insensitive signal transduction in patient-derived cell lines. The constitutive activation of these two interconnected pathways as a result of

impaired STAMBP function is believed to play a role in the vascular malformations and developmental characteristics typical of MIC-CAP syndrome [McDonell et al 2013].

Mechanism of disease causation. To the authors' knowledge, all patient-derived cell lines with *STAMBP* pathogenic variants have demonstrated either reduced or absent STAMBP expression compared to wild type controls [McDonell et al 2013].

Chapter Notes

Author Notes

Dr Melissa Carter continues to collect clinical information about MIC-CAP syndrome. Through Dr Carter, families affected by MIC-CAP syndrome may connect with some of the families who made this research possible. Email: mcarter@cheo.on.ca.

Dr Ghayda Mirzaa studies the developmental basis of developmental brain disorders with a particular focus on disorders of abnormal brain size at Seattle Children's Research Institute.

Dr Kym Boycott's research is focused on elucidating the molecular pathogenesis of rare inherited diseases using next-generation sequencing approaches. She leads two nationwide collaborative Canadian initiatives studying more than 1,000 rare disorders. For further information please visit www.care4rare.ca.

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- 18 March 2021 (bp) Comprehensive update posted live
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- 17 July 2013 (mtc) Original submission

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