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Familial Monosomy 7 Syndrome — RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Familial monosomy 7 is characterized by early-childhood onset of bone marrow insufficiency/failure associated with increased risk for myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). In all reported individuals, the monosomy 7 is believed to be an acquired cytogenetic abnormality within hematopoietic cells due to as-yet poorly defined inherited genetic predisposition. Identification of peripheral blood leukocytes with monosomy 7 usually precedes bone marrow failure/MDS/AML by a few months to years. Nearly all individuals reported with familial monosomy 7 have died of their disease.

Note: Only a minority of individuals with bone marrow failure/MDS/AML with monosomy 7 have familial monosomy 7.

Diagnosis/testing

Detection of cells with monosomy 7 during evaluation of a hematologic abnormality or malignancy or in the context of chromosomal studies in the diagnosis of unrelated conditions needs to be confirmed with bone marrow cytogenetic and interphase FISH studies. A bone marrow karyotype of 45,XX,-7 in females or 45,XY,-7 in males, often mosaic with normal cells (i.e., 46,XX in females and 46,XY in males), confirms the presence of monosomy 7. Of note, individuals with a family history of monosomy 7 (e.g., an affected sib) may initially have a normal karyotype in peripheral blood and/or bone marrow and later transition to mosaic monosomy 7 in peripheral blood and/or bone marrow.

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Management

Treatment of manifestations: Urgent referral to an oncologist should be considered for individuals with monosomy 7 (mosaic or non-mosaic). Definitive therapy is bone marrow transplantation (BMT) prior to the emergence of a leukemic clone. The suitability of sibs who are potential bone marrow donors may be evaluated with appropriate hematologic and cytogenetic studies to rule out bone marrow disease associated with familial monosomy 7. However, given that the underlying germline pathogenic variant may not be known, a matched sib donor may not be an ideal candidate (unless much older than the affected individual and with no evidence of hematologic disorders). An unrelated donor may be more suitable.

Prevention of secondary complications: It is unknown if the standard protocols for ablative therapy prior to BMT should be modified.

Surveillance: Annual monitoring of peripheral blood karyotype, hematologic status, and hemoglobin F levels helps identify emerging bone marrow abnormalities (cytopenias and bone marrow dysplasia) prior to the development of overt AML or MDS.

Evaluation of relatives at risk: In both children and adults with a family history of monosomy 7, otherwise unexplained signs and symptoms should be evaluated by a physician as possible early indications of the disorder.

Genetic counseling

The mode of inheritance of familial monosomy 7 is unknown.

Diagnosis

Suggestive Findings

Familial monosomy 7 **should be suspected** in an individual who has: (1) a relative who has been diagnosed with a hematologic disorder with monosomy 7; and (2) evidence of bone marrow dysfunction characterized by any of the following:

- Values consistent with laboratory age-related standards for:
  - Red cell macrocytosis
  - Increased hemoglobin F concentration
- Evidence of bone marrow insufficiency manifesting as any combination of:
  - Thrombocytopenia
  - Neutropenia
  - Anemia
  - Bone marrow aplasia
    Note: Severe aplastic anemia has been defined as follows:
    - Granulocyte count <500/mL
    - Platelet count <20,000/mL
    - Reticulocyte count <1% after correction for hematocrit
    - Bone marrow biopsy with <25% of the normal cellularity for age
- Myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML)
- Monosomy 7 in peripheral blood and/or bone marrow cells

Establishing the Diagnosis

The diagnosis of familial monosomy 7 **is established** in a proband with all of the following features:

- Monosomy 7 cells identified on peripheral blood examination or any of the following: bone marrow insufficiency, MDS, AML
- Monosomy 7 cell line identified on bone marrow examination
- Family member with characteristic hematologic findings and demonstration of monosomy 7
- Exclusion of other hematologic disorders with known clonal acquisition of monosomy 7 (e.g., normal chromosome breakage studies and telomere length assay; see Differential Diagnosis)

Note: Because monosomy 7 is typically sporadic, the proband is usually considered to be a simplex case (i.e., a single occurrence in a family) until an additional family member is found to have characteristic findings. Typically these asymptomatic family members have an unremarkable prior medical history; laboratory findings in these individuals are likely to include macrocytic red blood cells (MCV >94 fL), increased concentrations of hemoglobin F, and low normal platelet counts.

Cytogenetic and molecular testing approaches can include **G-banded cytogenetic analysis** and **deletion/duplication analysis**.

G-banded cytogenetic analysis demonstrates a 45,XX,-7 karyotype in females and 45,XY,-7 karyotype in males, often mosaic with normal cells (i.e., 46,XX in females and 46,XY in males). This testing should be performed on unstimulated samples (i.e., without PHA or other mitogens), because stimulation can mask the cells with monosomy 7. A minimum of three in 20 cells lacking a chromosome 7 confirms the diagnosis of monosomy 7. Additionally, a high percentage of monosomy 7 marrow cells by G-banded cytogenetic analysis of unstimulated cells can be attributable to either replacement of normal bone marrow cells by abnormal cells or high endogenous mitotic activity of the abnormal cells. A minimum of 20 unstimulated metaphase cells should be analyzed for a complete cytogenetic analysis.

Note: (1) Individuals with familial monosomy 7 may initially have a normal karyotype in peripheral blood and/or bone marrow and over time transition to mosaic monosomy 7 in peripheral blood and/or bone marrow. Thus, normal cytogenetic studies in either peripheral blood or bone marrow at the onset of hematologic disease do not eliminate the possibility of subsequent loss of a chromosome 7 associated with bone marrow failure, MDS, and/or AML. (2) In some individuals, treatment with steroids, which inhibit the growth of cells in culture, can mask the cytogenetic identification of monosomy 7. However, monosomy 7 would be identifiable by fluorescence in situ hybridization (FISH) or microarray analysis; therefore, FISH or microarray is favored when performing longitudinal assessment of clonal percentage.

Deletion/duplication analysis. Monosomy 7 can be detected by multiple molecular methods that determine copy number. Genome sequencing or chromosome-targeted approaches can be applied.

- **Genomic microarray technologies.** Chromosome microarray analysis (CMA) using oligonucleotide arrays or SNP genotyping arrays can detect mosaic monosomy 7.
- **Chromosome-targeted deletion analysis.** Chromosome-targeted methods include fluorescence in situ hybridization (FISH) and quantitative PCR.

Note: A pre-onset monosomy is not detectable with the presently available deletion/duplication methodology. Thus, a sib of a person with known monosomy 7 should be under continuous surveillance for emergence of hematologic anomalies.

Table 1. Molecular Genetic Testing Used in Familial Monosomy 7 Syndrome

Method		Pathogenic Variants Detected [1]	Proportion of Probands w/a Pathogenic Variant Detectable by Method
G-banded karyotype		Monosomy 7 / deletion 7q	100%
Deletion/ duplication analysis [2]	Chromosomal microarray (CMA) [3]	Deletion / monosomy mosaicism	100% [4]
	FISH	Deletion / monosomy mosaicism	100% [5]
	Quantitative PCR [6]	Deletion / monosomy	100% w/a sensitivity of ~1:100,000

1. See Molecular Genetics for details.
2. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
3. Additional acquired cytogenetic abnormalities have been seen. Occasionally, rearrangement of chromosome 7 material results in retention of the short arm (7p) and loss of the long arm (7q) resulting in monosomy of 7q (sometimes called "partial monosomy 7").
4. Minimal detection for mosaicism depends on laboratory cut-off values; typical range: 20%-30%.
5. Minimal detection for mosaicism depends on laboratory cut-off values; typical range: 10%-20%.
6. Porta et al [2007]

Clinical Characteristics

Clinical Description

Familial monosomy 7 is typically characterized by early-childhood onset of evidence of bone marrow insufficiency/failure associated with increased risk for myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (reviewed in Hess [2001], Gaitonde et al [2010], Liew & Owen [2011]). MDS or AML associated with either complete or partial monosomy 7 has been reported in at least 14 pedigrees. For further detailed clinical information regarding affected individuals in some of these pedigrees, click here.

Early-childhood onset. The majority of persons described are children. Abnormal hematologic findings have been seen in children as young as age nine months and mosaic monosomy 7 in children as young as age five years. Some individuals have been diagnosed as teenagers. In some individuals a neurologic disorder (cerebellar ataxia or atrophy) is recognized prior to the onset of hematologic anomalies and somatic monosomy 7.

Bone marrow insufficiency. Most affected individuals present with evidence of bone marrow insufficiency such as petechiae, easy bruising, and/or anemia.

Rapid progression is common in familial cases. Most reports indicate that once cells with monosomy 7 are identified in peripheral blood, an individual progresses to bone marrow failure/MDS/AML within months to three years. As with sporadic AML/MDS with monosomy 7, the prognosis is poor, particularly in individuals with a high percentage of monosomy 7 cells in the bone marrow. Nearly all individuals reported with familial monosomy 7 have died of their disease.

Penetrance

Penetrance for familial monosomy 7 is unknown.

Nomenclature

Before the advent of chromosome banding, chromosomes were grouped by size and morphology (location of the centromere) because it was not possible to distinguish individual chromosomes. Using this system, chromosome 7 is categorized as a "C-group" chromosome (C-group chromosomes: 6-12 and X); thus, familial "C-group monosomy" reported prior to 1972 is presumed to be familial monosomy 7.

Prevalence

Familial monosomy 7 is rare; 14 kindreds have been reported in the literature.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with familial monosomy 7; however, monosomy 7 is seen as a secondary finding in a number of monogenic disorders (see Differential Diagnosis).

Differential Diagnosis

Although rare, sporadic myelodysplastic syndrome (MDS) has been described in children; monosomy 7 is seen in 25%-30% of such cases. Although most MDS associated with monosomy 7 is not familial, these individuals also had a poor response to therapy and were candidates for bone marrow transplantation.

Monosomy 7 can also be seen in sporadic acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms. Although the discovery of monosomy 7 in these individuals portends a poor outcome, the majority are not associated with the familial entity.

Monosomy 7 has been reported in multiple family members with the following disorders:

- Cerebellar ataxia/atrophy-pancytopenia syndrome (OMIM 159550). In five sibs in one family, cerebellar ataxia segregated with either hypoplastic anemia or acute myelogenous leukemia (AML) with monosomy 7 (C-group monosomy) [Li et al 1978, Li et al 1981]. Four of the five sibs died from bone marrow failure or AML. It is unclear whether this is part of the diagnostic spectrum of familial monosomy 7 or a distinct entity.
- Familial platelet disorder with propensity to AML (FPD/AML) (OMIM 601399) [Minelli et al 2001, Minelli et al 2004, Jongmans et al 2010], associated with pathogenic variants in *RUNX1*

Monosomy 7 has been reported in individuals with the following disorders:

- Aplastic anemia (OMIM 609135)
- Juvenile myelomonocytic leukemia (JMML) (OMIM 607785)
- Neurofibromatosis type 1 (NF1) [Kelleher & Carbone 1991, Maris et al 1997]. JMML with monosomy 7 occurs in individuals with NF1 at an average age of two years (95% of individuals are diagnosed before age 4 years).
- Noonan syndrome [Choong et al 1999, Kratz et al 2005]. Additionally, individuals with Noonan syndrome are at an increased risk for JMML or a JMML-like disease in infancy [Choong et al 1999, Kratz et al 2005].
- Bloom syndrome [Aktas et al 2000]
- Paroxysmal nocturnal hemoglobinuria (PNH) (OMIM 300818)
- Dyskeratosis congenita
- Fanconi anemia
- Shwachman-Diamond syndrome

Management

Evaluations Following Initial Diagnosis

Urgent referral to an oncologist for evaluation of cytopenias and bone marrow abnormalities that appear prior to the development of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) is indicated. Laboratory studies for hematologic status and hemoglobin F levels, as well as cytogenetic studies in unstimulated peripheral blood are recommended.

Consultation with a clinical geneticist and/or genetic counselor is recommended.

Treatment of Manifestations

The goal of management in familial monosomy 7 is early diagnosis so that definitive therapy with bone marrow transplantation (BMT) can be initiated prior to the emergence of a leukemic clone. Once transformation into AML occurs, the probability that BMT will fail to cure the disease increases significantly.

Any child or young adult with detectable monosomy 7 in combination with cytopenias and marrow dysplasia should, therefore, proceed to BMT as soon as possible, unless rising blast count warrants cytoreductive chemotherapy prior to transplant. Since BMT is the only effective treatment for the management of hematologic disease and the familial status of the disorder may not be known, rigorous evaluation of related donors is strongly suggested.

The suitability of sibs who are potential bone marrow donors may be evaluated with appropriate hematologic and cytogenetic studies to rule out bone marrow disease associated with familial monosomy 7. However, given that the underlying germline pathogenic variant may not be known, a matched sib donor may not be an ideal candidate (unless much older than the affected individual and with no evidence of hematologic disorders) and an unrelated donor may be more suitable.

Monosomy 7 in children with *de novo* AML (i.e., with no clinical history of MDS, myeloproliferative disorder, or exposure to potentially leukemogenic therapies or agents) has an adverse prognosis, and thus children with monosomy 7 AML are treated on high-risk AML protocols and offered bone marrow transplantation in first remission [Hasle et al 2007].

Prevention of Secondary Complications

Individuals with monosomy 7 and certain underlying bone marrow failure syndromes including Fanconi anemia, dyskeratosis congenita, and Shwachman-Diamond syndrome have increased sensitivity to chemotherapy and radiation doses used in conventional ablative BMT approaches, and therefore require reduction in conditioning intensity. For individuals with monosomy 7 but without these above conditions, data remain too limited to determine whether standard protocols for ablative therapy prior to BMT should be modified.

Surveillance

If transplant therapy is not pursued due to lack of donor availability or family preference, annual monitoring of bone marrow karyotype and FISH for chromosome 7, hematologic status, and hemoglobin F levels should be coordinated by specialists in oncology and bone marrow transplantation. The goal is to identify bone marrow abnormalities (cytopenias and bone marrow dysplasia) prior to the development of AML or MDS by annual monitoring of cytogenetic studies in unstimulated peripheral blood, hematologic status, and hemoglobin F levels.

Evaluation of Relatives at Risk

Because the goal of management in familial monosomy 7 is early diagnosis for initiation of BMT prior to the emergence of a leukemic clone, it is appropriate to evaluate relatives at risk including sibs and potentially maternal first cousins, based on kindreds described in Mode of Inheritance.

In sibs and cousins of individuals with a history of familial monosomy 7, signs and symptoms that cannot be accounted for otherwise should be evaluated by their physicians as potential early indications of the cytopenias and bone marrow dysplasia which appear prior to the development of AML or MDS.

To evaluate sibs at risk, perform cytogenetic studies/chromosomal microarray (CMA) on bone marrow or unstimulated peripheral blood (FISH and/or conventional cytogenetics), hematologic studies, and hemoglobin F assessment. If these are normal, repeat of hematologic studies on a yearly basis is reasonable, followed by chromosomal studies if abnormalities are detected.

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

The mode of inheritance of familial monosomy 7 is unclear. Autosomal dominant disease with reduced penetrance or an imprinting disorder have been suggested.

In one kindred, eight of 14 first cousins (the offspring of 3 sisters) developed aplastic anemia or acute myeloid leukemia (AML); in those with cytogenetic studies, the karyotype evolved to monosomy 7 (or group C monosomy) [Chitambar et al 1983]. Thus, in this family approximately 50% of maternal first cousins inherited a trait that resulted in aplastic anemia or AML with frequent loss of chromosome 7. Another kindred with five maternally related first cousins from two sibships shows a similar pattern of inheritance. In both of these kindreds, male and female cousins were affected, suggesting that this is not an X-linked trait. This pattern of inheritance would be consistent with an autosomal dominant disorder with incomplete penetrance [Bödör et al 2012], a maternally inherited (mitochondrial) disorder, or a paternally imprinted gene with lack of maternal expression leading to disease. Because parents of these probands do not appear to be affected, autosomal recessive inheritance has been suggested (OMIM 252270); however, there is no report of relationships between the fathers of these kindreds, making autosomal recessive inheritance less likely. Although regions of chromosome 7 are imprinted, evidence suggests that the predisposing locus is not present on chromosome 7, and either maternal or paternal chromosome 7 may be lost (see Molecular Pathogenesis). Loss of function of a maternally expressed gene or genes on chromosomes other than 7 may predispose individuals to chromosome 7 loss, and could account for the reported pedigrees. This hypothesis would explain why individuals with familial

monosomy 7 inherit the predisposition exclusively from their mothers, but the maternally inherited chromosome 7 is not exclusively lost.

Risk to Family Members

Parents of a proband. Monosomy 7 has not been reported in the peripheral blood or bone marrow of the parents of an individual with familial monosomy 7. There is one report in which a mother-daughter pair presented with AML and an inversion of 3q21q26 and monosomy 7 [Lawrie et al 2012]. This likely reflects a separate entity as monosomy 7 is the most common secondary abnormality in AML with inversion 3q. This lack of documentation does not rule out risk to the parents of a proband; however, to date no increased risk has been documented.

Sibs of a proband. Sibs of a proband with familial monosomy 7 may have as much as a 50% chance of developing a related disorder, though given the known familial variability and likely genetic heterogeneity of these disorders, the exact risk within an individual family is not known. However, given the high frequency of sporadic cases of monosomy 7 in hematologic malignancies [Hasle & Olsen 1997], the overall risk for the sib of a single individual in the family affected by monosomy 7 is much lower. Thus, two sibs may acquire a myeloid neoplasm with monosomy 7 by random chance given the high rate of chromosome 7 loss in AML and myelodysplastic syndrome (MDS). However, given the possibility of familial monosomy 7, hematologic and cytogenetic analysis should be considered for the donor if a matched-related allogeneic transplant is a therapeutic option.

Offspring of a proband. As only two individuals with familial monosomy 7 are known to have reproduced and no data are available on their offspring, assertions regarding risk to offspring are theoretic and have yet to be proven empirically. If familial monosomy 7 is inherited in an autosomal dominant manner with reduced penetrance, risk to offspring of a proband is as high as 50%. If familial monosomy 7 is inherited as an imprinted locus, risk to offspring of a proband would differ depending on the sex of the transmitting parent.

Other family members. As it is suspected that a transmissible predisposing condition may be affecting other branches of the family, and as there is no way of establishing such predisposition presently, other members of the family are to be considered at increased risk. There is, however, no way of establishing the magnitude of the risk, though sibs and cousins who are maternally related are at greatest risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for estimating genetic risk 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 affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology (e.g., GWAS and genome sequencing) and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individual and their family members.

Prenatal Testing

At this time prenatal testing is not possible as mutation of a specific gene responsible for familial monosomy 7 is unknown. Monosomy 7 is not expected to be present in tissues sampled prenatally.

Preimplantation genetic testing is not currently possible, as there is no known gene or locus.

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.

No specific resources for Familial Monosomy 7 Syndrome have been identified by *GeneReviews* staff.

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 B. OMIM Entries for Familial Monosomy 7 Syndrome (View All in OMIM)

252270	MONOSOMY 7 OF BONE MARROW

Molecular Pathogenesis

In familial monosomy 7 affected individuals are predisposed to acquiring monosomy 7 or partial deletion of the long arm of chromosome 7 in hematopoietic cells. It is not known whether other tissues may also be affected.

Hematologic malignancies (e.g., MDS or AML) result from the loss of the minimal segment(s) on the long arm of chromosome 7, with most involving regions between 7q21.3 and 7q34 [Curtiss et al 2005, Cigognini et al 2007, Asou et al 2009]. The genetic etiology that underlies the disorder and leads to loss of chromosome 7 is unknown.

The loss of chromosome 7 or segmental loss of 7q is thought to delete a tumor suppressor locus [Curtiss et al 2005, Asou et al 2009]. Initially, the loss of one chromosome 7 was thought to result in a loss of heterozygosity (LOH), with a submicroscopic pathogenic variant in the retained allele on 7q. However, sibs who lose chromosome 7 do not invariably lose the chromosome inherited from the same parent, suggesting that the original hypothesis of LOH is incorrect. [Shannon et al 1989, Minelli et al 2001, Maserati et al 2004].

In a recently reported family, a germline pathogenic variant in *GATA2* (OMIM 137295), located on chromosome 3, segregated with acquired monosomy 7 [Bödör et al 2012]. In the family described, two cousins with the *GATA2* pathogenic variant acquired both a monosomy 7 clone and an *ASXL1* pathogenic variant. In this family, the parents of the affected individuals are brother and sister – in contrast to families previously described, in which the parents were always sisters.

Pathogenic variants in *CEBPA* (OMIM 116897), located on chromosome 19 and encoding CCAAT/enhancer binding protein-α, have been identified in individuals with familial AML [Pabst et al 2008]. In at least one of these families monosomy 7 was seen in multiple individuals at presentation.

Monosomy 7 represents a small proportion of chromosome aberrations found in AML, but is a common finding in therapy-related AML after alkylator chemotherapy.

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Chapter Notes

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Revision History

- 19 November 2020 (ma) Chapter retired: does not reflect current use of genetic testing
- 21 January 2016 (me) Comprehensive update posted live
- 7 February 2013 (me) Comprehensive update posted live
- 8 July 2010 (me) Review posted live
- 13 November 2009 (jm) Original submission

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