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Monosomy 7 Predisposition Syndromes Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding germline pathogenic variants that predispose to the development of monosomy 7 and discuss medical management of monosomy 7 predisposition syndromes and risk assessment of at-risk asymptomatic relatives.

The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of monosomy 7 predisposition syndromes.

Goal 2

Review the genetic causes of monosomy 7 predisposition.

Goal 3

Provide an evaluation strategy to identify the genetic cause of monosomy 7 predisposition in a proband (when possible).

Goal 4

Review the differential diagnosis of monosomy 7 predisposition syndromes.

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Goal 5

Inform (when possible) medical management of monosomy 7 predisposition syndromes.

Goal 6

Provide a basic view of genetic risk assessment of at-risk asymptomatic relatives of a proband with a monosomy 7 predisposition syndrome to inform surveillance and to allow early diagnosis so that definitive therapy with bone marrow transplantation can be initiated prior to the emergence of a leukemic clone.

1. Clinical Characteristics of Monosomy 7 Predisposition Syndromes

Clinical Description

Monosomy 7 predisposition syndromes are typically characterized by childhood or young-adult onset of bone marrow insufficiency associated with an increased risk for severe cytopenias, variable adaptive immune deficiency, bone marrow aplasia, myelodysplastic syndrome (MDS), and/or acute myeloid leukemia (AML) [Babushok et al 2016]. Monosomy 7 is identified in peripheral blood and/or bone marrow cells and represents a clonal acquired cytogenetic alteration. To date, constitutional monosomy 7 has not been identified.

Systemic anomalies associated with monosomy 7 predisposition syndromes can include multiple organ system involvement and delays in growth and neurodevelopment (see Table 1).

Disorders that predispose to monosomy 7 were included in the 2016 revision of the World Health Organization (WHO) classification of myeloid neoplasms and AML, in a new category: "myeloid neoplasms with germline predisposition" [Arber et al 2016]; recognition of these disorders was also supported by the updated 2017 European LeukmiaNET (ELN) recommendations, with a new category of the same name [Döhner et al 2017].

Childhood to young adult onset. In large multicenter cohorts of children and young adults, monosomy 7 is found in approximately 20% of individuals with MDS and 5% of individuals with AML [Wlodarski et al 2018]. Notably, however, the frequency of monosomy 7 has been reported as high as 41% of single center cohorts of children with primary MDS [Schwartz et al 2017a]. A germline genetic predisposition to monosomy 7 can be identified in the majority of these individuals. Older adults with MDS and/or AML are less likely to have monosomy 7 and older individuals with monosomy 7 are less likely to have an identifiable genetic predisposition associated with the development of monosomy 7 [Schratz & DeZern 2020].

Bone marrow insufficiency. Most affected individuals present with clinical evidence of bone marrow insufficiency such as petechiae, easy bruising, fatigue, pallor, or opportunistic infections. Children presenting with refractory cytopenias often demonstrate thrombocytopenia and neutropenia, as opposed to the common presentation of isolated refractory anemia observed in adults [Kardos et al 2003]. Additional laboratory features include red cell macrocytosis and increased hemoglobin F concentration. Some individuals may have single-lineage isolated cytopenias, whereas others meet blood count criteria for severe aplastic anemia (granulocyte count <500/µL, platelet count <20,000/µL, absolute reticulocyte count <60,000/µL). In most individuals, bone marrow examination reveals hypocellularity, aplasia, or morphologic features consistent with refractory cytopenia of childhood (RCC) [Niemeyer & Baumann 2011]. RCC remains a provisional entity in the 2016 revision of the WHO classification grouping pediatric MDS without excess blasts into one category regardless of the degree of dysplasia or cellularity. In some individuals, however, the marrow will have normal or increased cellularity and evidence of excess blasts.

Note: Individuals meet WHO 2016 criteria for MDS [Arber et al 2016] if they have cytopenias, evidence of single or multilineage dysplasia, and up to 19% peripheral or bone marrow blasts. Individuals meet WHO 2016 criteria

for AML with MDS-related changes if they have bone marrow dysplasia and 20% or greater blood or bone marrow blasts.

G-banded cytogenetic analysis or deletion/duplication analysis (e.g., microarray, FISH, quantitative PCR) of peripheral blood or bone marrow cells demonstrates a 45,XX,-7 karyotype in females and 45,XY,-7 karyotype in males, typically mosaic with normal cells (i.e., 46,XX in females and 46,XY in males). While complete loss of chromosome 7 is most common, partial deletion of 7q (del7q), the unbalanced der(1;7)(q10;p10) translocation, and additional unbalanced translocations that also result in monosomy 7q are considered within the spectrum of monosomy 7 disorders [Inaba et al 2018]. Testing should be performed on unstimulated samples if possible (i.e., without PHA or other mitogens) because stimulation can mask 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 monosomy 7 predisposition syndromes may initially have a normal karyotype in peripheral blood and/or bone marrow and over time transition to develop clonal 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 preferred when performing longitudinal assessment of clonal percentage.

Family history. Monosomy 7 predisposition syndromes may occur *de novo* in the proband or be inherited. Affected family members can be asymptomatic and have normal laboratory evaluation; laboratory findings in affected family members may also be subtle and include macrocytic red blood cells (MCV >94 fL), increased hemoglobin F concentration, and mild cytopenias.

Rapid progression is common once monosomy 7 has developed. Many individuals progress to advanced MDS or AML within months of monosomy 7 detection, though instances of more indolent progression have been reported [Rentas et al 2020]. Monosomy 7 may directly contribute to leukemogenesis due to the resultant haploinsufficiency of *EZH2* which encodes a histone methyltransferase that constitutes the catalytic component of PRC2. PRC2 functions as a tumor suppressor in myeloid progenitor cells. Deficient PRC2 activity primes the hematopoietic landscape for leukemic transformation and confers a poor prognosis despite treatment intensification in pediatric AML [Bond et al 2018]. EZH2 deficiency specifically confers treatment resistance [Göllner et al 2017]. At least one preclinical model has questioned the specificity of EZH2 deficiency leading to myeloid versus lymphoid leukemias [Simon et al 2012] and thus these pathways continue to require further explanation [Inaba et al 2018].

In individuals with monosomy 7 and progressive features of MDS or AML, prognosis is poor without aggressive chemotherapy and hematopoietic stem cell transplantation [Locatelli & Strahm 2018]. Even with treatment, nearly half of individuals die of MDS/AML or treatment complications if monosomy 7 is the main cytogenetic abnormality [Hasle and Niemeyer 2011]. Mortality is even higher for those with monosomy 7 as part of a complex karyotype [Göhring et al 2010].

Some individuals diagnosed in early childhood with a monosomy 7 predisposition syndrome in the absence of advanced MDS or AML may exhibit regression and resolution of the monosomy 7 clone(s) [Parker et al 2008, Csillag et al 2019]. At least eight individuals, ranging in age at diagnosis from eight months to three years, have been reported with transient monosomy 7 that regressed with age. Germline pathogenic variants in *SAMD9L* and *SAMD9* have been identified in individuals with transient monosomy 7 [Pastor et al 2018]. In these

individuals, the monosomy 7 clones either resolved with no other clonal hematopoiesis detected or were replaced by clones with uniparental disomy of 7q, resulting in a diploid copy of the normal *SAMD9* or *SAMD9L* allele located on 7q [Schwartz et al 2017b, Wong et al 2018, Csillag et al 2019]. To date, development of transient monosomy 7 and subsequent resolution has not been described in other monosomy predisposition syndromes.

2. Causes of Monosomy 7 Predisposition Syndromes

Table 1. Monosomy 7 Predisposition Syndromes: Genes and Clinical Features

Gene(s) [1]	Disorder (See footnotes for monosomy 7 predisposition references.)	MOI	% of All Monosomy 7 Predisposition	Typical Onset of Monosomy 7	Distinguishing Clinical Features
BLM (*RECQL3*)	Bloom syndrome [2]	AR	1%-5%	Childhood	Severe pre- & postnatal growth deficiency, immune abnormalities, sensitivity to sunlight, insulin resistance, high risk for early-onset cancers
BRCA2 *BRIP1* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* (>20 genes) [3]	Fanconi anemia [4]	AR XL [3]	5%-15%	Childhood to adult	Congenital anomalies, bone marrow failure, ↑ risk for malignancy
NF1	Neurofibromatosis 1 [5]	AD	5%-10%	Early childhood	Café au lait macules, axillary & inguinal freckling, cutaneous neurofibromas, Lisch nodules
CBL *KRAS* *NRAS* *PTPN11*	Rasopathies (See Noonan Syndrome.) [5, 6]	AD		Early childhood	Characteristic facial features, short stature, congenital heart disease, variable DD
CEBPA	*CEBPA*-assoc familial AML [7]	AD	1%-5%	Childhood to adult	No addl features aside from highly penetrant AML
DDX41	*DDX41*-assoc familial myelodysplastic syndrome & acute myeloid leukemia [8]	AD	1%-5%	Adult	No addl features aside from MDS/AML
DNAJC21 *ELF1* *SBDS* *SRP54*	Shwachman-Diamond syndrome [9]	AD AR	1%-5%	Childhood to adult	Exocrine pancreatic dysfunction w/malabsorption, malnutrition, & growth failure; hematologic abnormalities w/ single- or multilineage cytopenias & susceptibility to MDS & AML; bone abnormalities incl metaphyseal dysplasia

Table 1. continued from previous page.

Gene(s) [1]	Disorder (See footnotes for monosomy 7 predisposition references.)	MOI	% of All Monosomy 7 Predisposition	Typical Onset of Monosomy 7	Distinguishing Clinical Features
ELANE *G6PC3* *GFI1* *HAX1* *JAGN* *TCRG1* *VPS45A*	Severe congenital neutropenia [10] (See *ELANE*-Related Neutropenia.)	AD AR	1%-5%	Childhood to adult	Severe neutropenia, recurrent infections
ERCC6L2	Bone marrow failure syndrome 2 (OMIM 615715) [11]	AR	1%-5%	Adult	Microcephaly, learning difficulties, DD
GATA1 [12]	*GATA1*-related Diamond-Blackfan anemia [13]	XL	<1%	Unknown [14]	Pure red cell aplasia
GATA2	*GATA2* deficiency [15] (OMIM 137295)	AD	35%-40%	Childhood to adult	MonoMAC syndrome (monocytopenia, nontuberculous mycobacterial infections), Emberger syndrome (lymphedema & monosomy 7), cutaneous warts, congenital deafness, neutropenia, alveolar proteinosis, DCML
LIG4	Ligase 4 syndrome [16] (OMIM 606593)	AR	<1%	Unknown [14]	Microcephaly, growth failure, DD, skeletal malformations, bone marrow failure, immunodeficiency, lymphoma
MLH1 *MSH2* *MSH6* *PMS2*	Constitutional mismatch repair deficiency [17] (See Lynch Syndrome.)	AR	<1%	Childhood	High risk for many cancers
RUNX1	*RUNX1* familial platelet disorder w/assoc myeloid malignancies [18]	AD	<1%	Adult	Thrombocytopenia, bleeding tendency
SAMD9	MIRAGE syndrome [19]	AD	10%-20%	Childhood	Recurrent infections, restricted growth, adrenal hyperplasia, genital abnormalities, enteropathy, renal abnormalities
SAMD9L	*SAMD9L* ataxia-pancytopenia syndrome [19]	AD		Childhood	Ataxia, pancytopenia, neutrophilic dermatosis
TP53	Li-Fraumeni syndrome [20]	AD	2%-5%	Childhood to adult	High risk for many cancers & therapy-related AML
WRN	Werner syndrome [21]	AR	<1%	Unknown [14]	Accelerated aging, cataracts, diabetes mellitus, osteoporosis

Table 1. continued from previous page.

Gene(s) [1]	Disorder (See footnotes for monosomy 7 predisposition references.)	MOI	% of All Monosomy 7 Predisposition	Typical Onset of Monosomy 7	Distinguishing Clinical Features
XPC	Xeroderma pigmentosum group C [22]	AR	<1%	Adult	Sensitivity to UV radiation, ↑ risk of skin cancer

AD = autosomal dominant; AML = acute myeloid leukemia; AR = autosomal recessive; DCML = dendritic cell, monocyte, and B and natural killer cell lymphoid deficiency; DD = developmental delay; MDS = myelodysplastic syndrome; MOI = mode of inheritance; XL = X-linked

1. Genes are listed alphabetically

2. Aktas et al [2000]

3. Listed genes represent the most common genetic causes of Fanconi anemia (FA). For other genes associated with this phenotype (>20 genes have been identified), see Fanconi Anemia. FA can be inherited in an autosomal recessive manner, an autosomal dominant manner (*RAD51*-related FA), or an X-linked manner (*FANCB*-related FA).

4. Rochowski et al [2012]

5. Niemeyer & Flotho [2019]

6. Although additional genes have been associated with Noonan syndrome, only those listed here have been definitively linked to monosomy 7.

7. Pabst et al [2008]

8. Sébert et al [2019]

9. Myers et al [2020]

10. Skokowa et al [2017]

11. Bluteau et al [2018]

12. Although 20 genes in addition to *GATA1* have been associated with Diamond-Blackfan anemia, only *GATA1*-related Diamond-Blackfan anemia has been definitively linked to monosomy 7.

13. Parrella et al [2014]

14. Too few cases described to determine age of onset

15. Wlodarski et al [2016]

16. Staines Boone et al [2019]

17. Wimmer & Etzler [2008]

18. Minelli et al [2004]

19. Narumi et al [2016]; Chen et al [2016]

20. Swaminathan et al [2019]

21. Seiter et al [2005]

22. Sarasin et al [2019]

3. Evaluation Strategies to Identify the Genetic Cause of Monosomy 7 Predisposition in a Proband

Establishing a specific genetic cause for predisposition to monosomy 7:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history. A detailed medical history is critical to distinguish disorders that predispose to monosomy 7 (Table 1) and to assess for comorbid medical conditions:

- **Hematologic.** Results from CBC and bone marrow examinations including cytopenias, marrow cellularity, and red cell macrocytosis; symptoms of cytopenias including easy bruising, prolonged bleeding, fatigue, pallor, and frequent bacterial infections
- **Immune/infection.** Prior immunologic testing, autoimmune/rheumatologic symptoms, lymphedema, atypical infections (e.g., viral, mycobacterial, fungal)

- **Birth history / congenital anomalies.** Intrauterine growth restriction, low birth weight, prematurity; congenital heart, genitourinary, renal, vertebral, radioulnar, and digit anomalies; tracheoesophageal fistula
- **Dermatologic conditions.** History of birthmarks, rashes, or skin lesions requiring prior dermatologic care/removal
- **Malignancies.** Location, pathologic/molecular classification, and therapies received
- **Other.** Endocrine disorders (adrenal insufficiency, short stature); gastrointestinal abnormalities (steatorrhea, other symptoms of pancreatic insufficiency); failure to thrive; symptoms of hepatic dysfunction; chronic pulmonary disease; neurologic/developmental abnormalities
- **Environmental exposures.** Personal/family occupation history; travel history; medication, supplement, and recreational drug use

Physical examination. Findings on physical examination may suggest a specific monosomy 7 predisposition disorder:

- Short stature is seen in many conditions including Shwachman-Diamond syndrome, Fanconi anemia, and MIRAGE syndrome
- Microcephaly is seen in Fanconi anemia, ligase 4 syndrome, and *ERCC6L2*-related bone marrow failure syndrome
- Café au lait macules may be seen in Fanconi anemia and neurofibromatosis I. Axillary freckling and cutaneous neurofibromas are specific to neurofibromatosis 1.
- Cardiac murmurs may be identified in Fanconi anemia and rasopathies due to underlying congenital heart disease.
- Lymphedema and pulmonary auscultation abnormalities may be features of *GATA2* deficiency.
- Cerebellar ataxia is seen in *SAMD9L* ataxia-pancytopenia syndrome.
- Bruising and petechiae may be associated with any monosomy 7 predisposition syndrome after onset of severe cytopenias; however prolonged bleeding in the absence of severe thrombocytopenia or advanced MDS or AML may be suggestive of *RUNX1* familial platelet disorder with associated myeloid malignancies.
- Hepatosplenomegaly is infrequently present in early-stage MDS, but is associated with advanced myeloid malignancy; however, rasopathies associated with monosomy 7 and myeloproliferative diseases are most commonly associated with hepatosplenomegaly.
- Skeletal dysplasia may be a feature of Shwachman-Diamond syndrome.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of monosomy 7 predisposition syndromes and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing. Specific family history features of monosomy 7 predisposition syndromes include the following:

- Early-childhood deaths and/or maternal history of miscarriages
- Early-onset or atypical cancer diagnoses. Excessive toxicity associated with cancer treatment
- Syndromic features/congenital anomalies
- Consanguinity
- Neonatal transient cytopenias
- Bone marrow failure or immune deficiencies
- Lymphedema
- History of atypical and/or prolonged bleeding
- Severe developmental delay and other neurologic abnormalities

Laboratory testing

- Fanconi anemia chromosome breakage studies (mitomycin C / diepoxybutane)

- Telomere length analysis

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel or serial single-gene testing) and comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

Note: Skin (considered gold standard) or buccal fibroblasts are the preferred tissue type for germline molecular testing for individuals suspected to have a monosomy 7 predisposition syndrome due to somatic revertant mutation or functional deletion of germline pathogenic variants through chromosome loss or loss of heterozygosity that can occur in bone marrow and blood cells from individuals with monosomy 7. In situations where rapid therapy decision making is required, molecular genetic testing may be initially performed on blood or bone marrow samples, and subsequently performed on cultured skin fibroblasts which may take longer to obtain results.

- **Serial single-gene testing** can be considered if clinical findings and/or family history indicate that pathogenic variants in a particular gene are most likely (see Table 1).
- **A multigene panel** that includes some or all of the genes listed in Table 1 is 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.

  Note: Identification of a variant(s) of uncertain significance in one of the genes listed in Table 1 does not establish or rule out the diagnosis.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may 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.

4. Differential Diagnosis of Monosomy 7 Predisposition Syndromes

The differential diagnosis of monosomy 7 predisposition syndromes includes:

- Sporadic monosomy 7 MDS/AML;
- Secondary monosomy 7 arising from acquired bone marrow failure disorders;
- Secondary monosomy 7 MDS/AML arising due to prior cancer treatment;
- MDS/AML predisposition syndrome associated with acquisition of pathogenic variants or cytogenetic abnormalities other than monosomy 7.

Sporadic Monosomy 7 MDS/AML

Sporadic monosomy 7 MDS/AML refers to monosomy 7 MDS/AML that arises without evidence of germline genetic predisposition and in the absence of other predisposing medical conditions or treatments. Monosomy 7 MDS/AML that occurs in older adults is typically considered to be sporadic (i.e., the result of a chance occurrence of a disorder or abnormality that is not expected to recur in a family) and is associated with clonal hematopoiesis of indeterminate potential, a common age-related phenomenon [Babushok et al 2016]. In childhood- or young adult-onset monosomy 7, while most individuals are found to have either a known monosomy 7 predisposition syndrome preceding bone marrow failure, or prior cancer therapy, there are many individuals in whom a predisposing condition cannot be identified. It is currently unknown if some individuals with childhood or young-adult onset represent sporadic acquisition of monosomy 7 or if monosomy 7 has arisen as the result of an unidentified germline molecular cause. Individuals with no prior personal or family history of malignancies, bone marrow failure, or immune deficiency are more likely to have sporadic monosomy 7, whereas those with a family history of monosomy 7 (i.e., multiple affected family members) should be suspected of having a monosomy 7 predisposition syndrome even in the absence of an identified pathogenic variant in a known predisposition gene.

Secondary Monosomy 7 Arising from Acquired Bone Marrow Failure

Monosomy 7 is the most common somatic cytogenetic abnormality identified in persons with secondary MDS/AML who were previously diagnosed with an acquired bone marrow failure disorder (e.g., acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria) [Dumitriu et al 2015]. In a large North American series of individuals with pediatric aplastic anemia treated with immune suppression therapy, monosomy 7 occurred in 3.5% of individuals [Rogers et al 2019]. In adult-onset acquired aplastic anemia, the percentage of individuals that develop monosomy 7 may be as high as 5%-10% [Stanley et al 2017]. Monosomy 7 also occurs frequently in individuals who initially develop clonal paroxysmal nocturnal hemoglobinuria (PNH) as the predominant acquired bone marrow failure manifestation but later transition to MDS/AML [Araten et al 2001, Sun & Babushok 2020]. Notably in these individuals, the clone with monosomy 7 is thought to replace the PNH clone rather than occur as an additional hit within the PNH clone itself.

Monosomy 7 Secondary to Prior Cancer Therapy

Monosomy 7 occurs in 27%-32% of therapy-related myeloid neoplasms [Kuzmanovic et al 2020, Schwartz et al 2021] and has long been associated with exposure to alkylating chemotherapy, including cyclophosphamide [Higgins & Shah 2020]. Recent evidence, however, suggests that as many as 20% of these myeloid neoplasms presumed to be therapy-related may actually be driven by germline monosomy 7 predisposition disorders that increased the risk for both the primary tumor and MDS [Takahashi 2019]. Therefore, persons with (presumed) therapy-related myeloid neoplasms associated with monosomy 7 should be investigated for monosomy 7 predisposition disorders.

Additionally, germline variants in genes encoding proteins involved in the glutathione S-transferase pathway and other drug metabolism pathways have been identified to alter susceptibility to therapy-related monosomy 7 [Churpek & Larson 2013], suggesting that the spectrum of germline predisposition to therapy-related myeloid diseases may be distinct from the spectrum of disorders associated with predisposition to monosomy 7 (as listed in Table 1).

Germline Genetic Disorders Associated with Myeloid Neoplasms Not Specifically Associated with Monosomy 7

Other germline predisposition disorders in which MDS and leukemia have been reported without a specific association with monosomy 7 are summarized in Table 2.

Table 2. Disorders that Predispose to Myeloid Neoplasms without Monosomy 7

Gene(s)	Disorder	MOI	Nonhematologic Findings	Hematologic Findings
ACD *CTC1* *DKC1* *NHP2* *NOP10* *PARN* *RTEL1* *TERC* *TERT* *TINF2* *WRAP53*	Telomere biology disorders incl dyskeratosis congenita	AR AD XL	Immune deficiency, pulmonary fibrosis, hepatopulmonary syndrome, cancer predisposition incl leukoplakia, nail dystrophy, reticular rash, early graying	Bone marrow failure; 30% develop MDS/AML; rarely, other types of lymphoma/leukemia
ANKRD26	*ANKRD26*-related thrombocytopenia	AD	None	Mild-to-moderate thrombocytopenia w/ normal platelet size; erythrocytosis; ~10% develop MDS/AML.
ATM	Ataxia-telangiectasia	AR	Progressive cerebellar ataxia, telangiectasias, immune deficiency, infections, high risk for solid tumors	Lymphoma, T-cell leukemia; AML less common but occurs w/complex karyotype
ETV6	*ETV6* thrombocytopenia & predisposition to leukemia	AD	Predisposition to solid tumors incl colorectal cancer	Thrombocytopenia, acute lymphoblastic leukemia (most common hematologic malignancy), MDS, AML, mixed-phenotype acute leukemia, lymphoma
MPL	Congenital amegakaryocytic thrombocytopenia (OMIM 604498)	AR	Organ dysfunction due to hemorrhagic events	Transfusion-dependent thrombocytopenia, progression to aplastic bone marrow failure; rarely, myeloid neoplasms
NBN	Nijmegen breakage syndrome	AR	Microcephaly, craniofacial features, growth deficiency, recurrent infections due to immune deficiency; DD, solid tumors	Lymphoma, neutropenia; rarely, myeloid leukemia w/complex karyotypes
RPL5 *RPL11* *RPL35a* *RPS10* *RPS17* *RPS19* *RPS24* *RPS26* [1]	Diamond-Blackfan anemia	AD	Craniofacial, upper limb, heart, & genitourinary malformations; poor growth; DD	Pure red cell aplasia, aplastic anemia, up to 20% develop MDS/AML.
SRP72	Bone marrow failure syndrome 1 (OMIM 614675)	AD	Congenital deafness	Pancytopenia, myelodysplasia

AD = autosomal dominant; AML = acute myeloid leukemia; AR = autosomal recessive; DD = developmental delay; MDS = myelodysplastic syndrome; MOI = mode of inheritance; XL = X-linked

1. Eleven additional ribosomal proteins have been associated with autosomal dominant Diamond-Blackfan anemia, though each at lower frequencies than the genes included in Table 2.

5. Management: To Inform (When Possible) Medical Management of Monosomy 7 Based on Genetic Cause

Evaluations Following Initial Diagnosis

Measures include urgent referral to a hematologist for evaluation of cytopenias and bone marrow abnormalities that appear prior to the development of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and urgent referral to a hematopoietic stem cell transplantation (HSCT) specialist to identify potential donors and determine a transplant strategy. Consultation with a clinical geneticist and/or genetic counselor is recommended.

Laboratory studies for hematologic status should include the following.

Peripheral blood studies

- CBC, differential, reticulocyte count, and peripheral blood smear review monitored weekly to monthly based on stability
- Serum lactate dehydrogenase, uric acid, BUN, and creatinine
- Liver function studies including transaminases, alkaline phosphatase, total and conjugated bilirubin, total protein, albumin, and liver-dependent clotting factors
- Immunologic evaluation including quantitative immunoglobulins and quantitative lymphocyte subsets
- HLA typing of the affected individual, full sibs, and biological parents to identify suitable donors for HSCT (See Treatment of Manifestations for further evaluation of potential related donors.)

Bone marrow studies

- Unilateral or bilateral bone marrow aspirate and biopsy
- Morphologic assessments including bone marrow cellularity and assessment for dysplasia
- Assessment for bone marrow blasts by flow cytometry or immunostains
- Reticulin stain to assess for fibrosis
- Iron stain to assess for ringed sideroblasts
- Karyotype analysis on metaphase cells
- FISH to assess for copy number changes or translocations involving chromosome 7 and changes in other chromosomes including 1, 3, 5, 8, 17, and 20
- Molecular testing for somatic pathogenic variants in *SETBP1*, *ASXL1*, *RUNX1*, and RAS pathway genes associated with monosomy 7 (*CBL*, *KRAS*, *NRAS*, *PTPN11)*

Treatment of Manifestations

Individuals with a monosomy 7 predisposition syndrome who develop monosomy 7 clones require treatment by hematologists, oncologists, and HSCT specialists with expertise in the management of MDS and AML. In the majority of individuals with monosomy 7, the key to successful treatment is early diagnosis so that definitive therapy with HSCT can be initiated prior to the emergence of a leukemic clone. Once transformation into AML occurs, the probability that HSCT will fail to cure the disease increases significantly [Hasle & Niemeyer 2011].

Any child or young adult with monosomy 7 in combination with cytopenias and multilineage marrow dysplasia should, therefore, proceed to HSCT as soon as possible, unless rising blast count warrants cytoreductive chemotherapy prior to transplant. The optimal pre-transplant therapy for individuals with MDS and a monosomy 7 predisposition syndrome has yet to be defined [Nakano et al 2020]. Several monosomy 7 predisposition syndromes are associated with increased morbidity due to prolonged cytopenias following intensive chemotherapy prior to transplant, or due to preexisting immunodeficiency as seen in *GATA2*

haploinsufficiency. Thus for many syndromes, proceeding directly to HSCT without preceding cycles of cytoreductive chemotherapy is a standard approach [Peffault de Latour & Soulier 2016].

Since HSCT 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.

- In individuals with a known germline pathogenic variant associated with monosomy 7 predisposition, potential related donors should have site-specific testing for the known variant.
- In individuals without an identified germline pathogenic variant, the matched related donor should undergo CBC and consider bone marrow analysis for hematopoietic abnormalities. A matched related donor with a normal CBC and bone marrow analysis may not be an ideal candidate for individuals with monosomy 7 in whom a germline predisposition is unidentified; a fully matched unrelated donor may be more suitable.

AML. Prognosis is poor for those with AML and monosomy 7. Thus, children with monosomy 7 AML are often treated on high-risk AML protocols and offered HSCT with best available donor in first remission [Hasle et al 2007].

- In individuals with bone marrow failure syndromes (e.g., Fanconi anemia) and monosomy 7 associated AML, transplant conditioning may need to be started during the aplastic phase after a chemotherapy cycle is administered, as these individuals may not exhibit appropriate count recovery following an AML induction chemotherapy cycle [Peffault de Latour & Soulier 2016].
- Furthermore, individuals with monosomy 7 predisposition caused by Fanconi anemia and other inherited bone marrow failure syndromes (e.g., Shwachman-Diamond syndrome) may exhibit excess toxicity to conventional chemotherapy and radiation doses used in myeloablation, and therefore may require reduction in conditioning intensity.
- For individuals with other monosomy 7 predisposition syndromes, data remain too limited to determine whether standard protocols for myeloablation prior to HSCT should be modified.

Surveillance

In individuals with childhood-onset monosomy 7 detected in the absence of other clonal genetic abnormalities, multilineage dysplasia, or increased blasts in bone marrow or peripheral blood, close serial surveillance of bone marrow aspirates and biopsies that includes blast quantitation, karyotype, FISH, and molecular analysis for somatic pathogenic variants commonly acquired in MDS/AML may be considered as an alternative to HSCT. In some individuals, the monosomy 7 clone may show regression (e.g., *SAMD9*- and *SAMD9L*-related monosomy 7).

- Initially, bone marrow examination may need to be performed every one to two months to assess for chromosome abnormalities and/or acquisition of somatic pathogenic variants in MDS-related genes, until monosomy 7 clone size stability and absence of further clonal progression has been established.
- Thereafter, bone marrow examination may be decreased to twice yearly as long as the monosomy 7 clone persists. Worsening blood cytopenias, growth in monosomy 7 clone size, acquisition of additional chromosome abnormalities or somatic pathogenic variants in MDS-related genes, progression toward multilineage dysplasia, or excess blasts indicate need for curative HSCT.

If HSCT is not pursued due to the presence of severe medical comorbidities that would impair successful transplant outcome (e.g., severe pulmonary disease), annual bone marrow examination is recommended to provide prognostic information regarding anticipated timing of hematologic disease progression.

6. Risk Assessment and Surveillance of At-Risk Relatives for Early Detection and Treatment of Monosomy 7 Predisposition Syndromes

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.

Genetic Risk Assessment

Monosomy 7 predisposition syndromes can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner.

In individuals with a suspected monosomy 7 predisposition syndrome in whom no germline molecular diagnosis is found, the mode of inheritance that is most likely may be elucidated by taking a detailed, three-generation family history with attention to relatives with manifestations of monosomy 7 predisposition syndromes and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

The family history may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations), autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity), or X-linked inheritance (e.g., no male-to-male transmission) or the proband may appear to be the only affected family member (in which case he or she may have monosomy 7 predisposition syndrome as the result of a *de novo* pathogenic variant).

Note: If a proband has a specific syndrome associated with monosomy 7, counseling for that disorder is indicated (see Table 3).

Table 3. Modes of Inheritance of Hereditary Disorders Known to be Associated with Monosomy 7 Predisposition Syndrome

MOI	Disorder	Genes
AD	Neurofibromatosis 1	*NF1*
	Rasopathies (See Noonan Syndrome.)	*CBL*, *KRAS*, *NRAS*, *PTPN11*
	CEBPA-assoc familial AML	*CEBPA*
	DDX41-assoc familial myelodysplastic syndrome & acute myeloid leukemia	*DDX41*
	GATA2 deficiency [1]	*GATA2*
	RUNX1 familial platelet disorder w/assoc myeloid malignancies [2]	*RUNX1*
	MIRAGE syndrome	*SAMD9*
	SAMD9L ataxia-pancytopenia syndrome	*SAMD9L*
	Li-Fraumeni syndrome	*TP53*
AD or AR	Shwachman-Diamond syndrome	*DNAJC21*, *ELF1*, *SBDS*, *SRP54*
	Severe congenital neutropenia (See *ELANE*-Related Neutropenia.)	*ELANE*, *G6PC3*, *GFI1*, *HAX1*, *JAGN*, *TCRG1*, *VPS45A*

Table 3. continued from previous page.

MOI	Disorder	Genes
AR	Bloom syndrome	*BLM*
	Bone marrow failure syndrome 2 [3]	*ERCC6L2*
	Ligase 4 syndrome [4]	*LIG4*
	Constitutional mismatch repair deficiency (See Lynch Syndrome.)	*MLH1*, *MSH2*, *MSH6*, *PMS2*
	Werner syndrome	*WRN*
	Xeroderma pigmentosum group C	*XPC*
AR, AD, or XL	Fanconi anemia	*BRCA2*, *BRIP1*, *FANCA*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI* (>20 genes) [5]
XL	*GATA1*-related Diamond-Blackfan anemia	*GATA1*

AD = autosomal dominant; AML = acute myeloid leukemia; AR = autosomal recessive; DD = developmental delay; MDS = myelodysplastic syndrome; MOI = mode of inheritance; XL = X-linked

1. Wlodarski et al [2016]

2. Minelli et al [2004]

3. Bluteau et al [2018]

4. Staines Boone et al [2019]

5. Listed genes represent the most common genetic causes of Fanconi anemia (FA). For other genes associated with this phenotype (>20 genes have been identified), see Fanconi Anemia. FA can be inherited in an autosomal recessive manner, an autosomal dominant manner (*RAD51*-related FA), or an X-linked manner (*FANCB*-related FA).

Autosomal Dominant Inheritance – Risk to Family Members in Families with a Known Predisposing Germline Pathogenic Variant

Parents of a proband

- Some individuals with an autosomal dominant monosomy 7 predisposition syndrome may have inherited a predisposing germline pathogenic variant from a parent. A heterozygous parent may or may not have hematologic abnormalities and/or other related manifestations.
- Alternatively, an individual diagnosed with a monosomy 7 predisposition syndrome may have a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband (if feasible, use of DNA derived from nonhematopoietic tissue [e.g., skin fibroblasts, hair roots] may be considered, as germline pathogenic variants may not be detectable in leukocytes in some individuals). If the pathogenic variant found in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental leukocyte DNA; and (2) parental identity testing has confirmed biological maternity and paternity; if parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline mosaicism.
  - The proband inherited a pathogenic variant from a parent with somatically acquired loss of heterozygosity with preferential loss of the chromosome with the predisposing pathogenic variant. This somatic change (e.g., due to monosomy 7 or uniparental disomy 7) often occurs in hematopoietic tissue and results in a decreased fraction of cells with the variant, and may cause a false negative molecular result when testing leukocyte DNA.
- Although rarely reported, the clinical family history of some individuals diagnosed with monosomy 7 predisposition syndromes may appear to be negative because of failure to recognize the disorder in family

members, reduced penetrance, or phenotypic modification resulting from a natural protective second genetic event. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing (optimally using DNA derived from nonhematopoietic tissue) has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the predisposing pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. The likelihood that a sib who inherits a pathogenic variant will have abnormal hematologic findings and/or other related manifestations depends on penetrance of the familial disorder and the possibility of phenotypic modification.
- If the proband has a known predisposing pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism and the possibility of a false negative result in a parent due to preferential loss of the chromosome with the pathogenic variant.
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, sibs are still presumed to be at increased risk for the monosomy 7 predisposition syndrome because of the possibility that a parent either: (1) has germline mosaicism; or (2) is heterozygous but does not have apparent manifestations of the disorder because of reduced penetrance or phenotypic modification resulting from a natural protective second genetic event.
- The suitability of sibs who are potential bone marrow donors may be evaluated with molecular genetic testing (preferably using DNA from nonhematopoietic tissue) for the germline pathogenic variant identified in the proband (see Management, Treatment of Manifestations).

Offspring of a proband. Each child of an individual with an autosomal dominant monosomy 7 predisposition syndrome has a 50% chance of inheriting the causative germline pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the causative germline pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members in Families with Known Predisposing Germline Pathogenic Variants

Parents of a proband

- The parents of a child with an autosomal recessive monosomy 7 predisposition syndrome are obligate heterozygotes (i.e., presumed to be carriers of one predisposing pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a predisposing pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygous for a pathogenic variant in a gene associated with autosomal recessive monosomy 7 predisposition have no known increased risk of developing monosomy 7-associated myeloid malignancies. However, individuals who are heterozygous for a pathogenic variant in a subset of these genes — including genes associated with Fanconi anemia and constitutional mismatch repair deficiency (see Lynch Syndrome) — are at increased risk for development of other forms of leukemia and nonhematologic cancer and require genetic counseling and routine screening for those conditions.

Sibs of a proband

- If both parents are known to be heterozygous for a predisposing pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting two causative pathogenic variants, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Individuals who are heterozygous for a pathogenic variant in a gene associated with autosomal recessive monosomy 7 predisposition have no known increased risk of developing monosomy 7-associated myeloid malignancies. However, individuals who are heterozygous for a pathogenic variant in a subset of these genes — including genes associated with Fanconi anemia and constitutional mismatch repair deficiency (see Lynch Syndrome) — are at increased risk for development of other forms of leukemia and nonhematologic cancer and require genetic counseling and routine screening for those conditions.
- The suitability of sibs who are potential bone marrow donors may be evaluated with molecular genetic testing for the germline pathogenic variants identified in the proband (see Management, Treatment of Manifestations).

Offspring of a proband. The offspring of an individual with an autosomal recessive monosomy 7 predisposition syndrome are obligate heterozygotes for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a pathogenic variant.

Heterozygote detection. Heterozygote testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

X-Linked Inheritance – Risk to Family Members in Families with a Known Predisposing Germline Pathogenic Variant

Parents of a male proband

- The father of a male with an X-linked monosomy 7 predisposition syndrome will not have the disorder nor will he be hemizygous for the pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the familial pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the variant will be heterozygotes and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

- The suitability of sibs who are potential bone marrow donors may be evaluated with molecular genetic testing for the germline pathogenic variant identified in the proband (see Management, Evaluations Following Initial Diagnosis and Treatment of Manifestations).

Offspring of a male proband. Affected males transmit the predisposing pathogenic variant to: all their daughters – who will be heterozygotes and will usually not be affected – and none of their sons.

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having a predisposing pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote detection. Identification of female heterozygotes requires prior identification of the predisposing pathogenic variant in the family.

Surveillance

It is appropriate to evaluate apparently asymptomatic at-risk relatives of individuals with a history of a monosomy 7 predisposition syndrome as early as possible in order to allow initiation of HSCT prior to the emergence of a leukemic clone.

Family members of a proband with a known germline pathogenic variant(s) predisposing to monosomy 7. If a definitive germline pathogenic variant is identified in an affected family member (or if both definitive germline pathogenic variants are identified in a proband with an autosomal recessive predisposing disorder), molecular genetic testing can be performed in at-risk relatives to clarify their genetic risk:

- In families with an autosomal dominant monosomy 7 predisposing syndrome, those identified as heterozygous for the pathogenic variant present in the affected family member and thus at high risk for developing myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) should seek consultation with a hematologist, oncologist, or HSCT specialist with expertise in monosomy 7 predisposition syndromes in order to develop an individualized treatment and surveillance plan.
- In families with an autosomal recessive predisposing syndrome, those identified as having biallelic predisposing pathogenic variants and thus being at high risk for developing MDS or AML should seek consultation with a hematologist, oncologist, or HSCT specialist as recommended above.
- In families with an X-linked monosomy 7 predisposing syndrome, males identified as hemizygous for the pathogenic variant present in the affected family member and thus at high risk for developing MDS or AML should seek consultation with a hematologist, oncologist, or HSCT specialist as recommended above.
- Provided that genetic testing was performed using a germline, nonhematologic DNA sample, those without the monosomy 7-related pathogenic variant(s) defined as causal in the proband are no longer considered to be at increased risk for MDS or AML and thus may be discharged from hematologic surveillance.

Family members of a proband in whom the specific genetic cause of monosomy 7 predisposition has not been identified. Complete blood counts should be performed in all asymptomatic first-degree relatives (adults and children) of an individual with monosomy 7 predisposition syndrome in whom a germline pathogenic variant(s) has not been identified. If blood counts are normal, repeat of hematologic studies on a yearly basis is reasonable. If blood counts show cytopenias or RBC macrocytosis, these first-degree relatives should undergo bone marrow aspirate/biopsy studies including cytogenetic studies such as FISH and/or conventional cytogenetics to assess for presence of monosomy 7.

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 affected, are carriers, or at risk of being affected or 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 germline pathogenic variant(s) known to be associated with a monosomy 7 predisposition syndrome have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Note: Monosomy 7 is not expected to be present in most fetal tissues sampled prenatally.

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.

Chapter Notes

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