

Title: Familial Mosaic Monosomy 7 Syndrome *GeneReview* —Natural History: Supplementary Material

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Natural History: Supplementary Material

Carroll et al [1985] reported a family in which the proband had petechiae at age nine months with thrombocytopenia, anemia, and neutropenia. When evaluated at age 6½ years for easy bruising and epistaxis, she was found to have macrocytic red blood cells, 17% hemoglobin F, and monosomy 7 in 100% of bone marrow cells. Evaluation of her healthy asymptomatic five-year-old brother as a potential bone marrow donor revealed mild thrombocytopenia, macrocytic red blood cells (MCV 98 fl), 8% hemoglobin F, and monosomy 7 in 100% of bone marrow cells. The proband died of bone marrow failure eight weeks following the start of therapy. Over the next three years her sibling developed hepatosplenomegaly, circulating blasts, and monosomy 7; he died at age 8½ years from post-transplant infections following a bone marrow transplant from his mother.

A second family reported in Carroll et al [1985] had a similar history, in which a four-year-old boy presented with monosomy 7 and AML. During evaluation as a potential donor, his 2½ -year-old brother was found to have peripheral pancytopenia and bone marrow monosomy 7.

Monosomy 7 has been described in one family with late onset of familial AML [Kwong et al 2000]. All three sibs either presented with myeloid malignancies or rapidly progressed from refractory anemia (RA) with an excess of blasts (RAEB) into AML (in the case of the 18-year-old proband). Hematologic examination of these three sibs did not identify macrocytic red blood cells or persistence of hemoglobin F, which could be the manifestation of a different condition associated with monosomy 7 or another natural history of the disorder due to the difference of age of presentation.

In a large kindred described by Chitambar et al [1983] eight of 14 maternal first cousins developed either aplastic anemia or AML (with or without a preleukemic myelodysplastic phase). Those who were studied cytogenetically had either monosomy 7 or monosomy for a C-group chromosome. Hemoglobin F was not mentioned in the report. The fact that half sibs with the same mother developed and died from either aplastic anemia or AML suggests the possibility of a maternally inherited trait that predisposes to monosomy 7 and bone marrow failure.

In another kindred of interest, Larsen & Schimke [1976] reported five maternal first cousins (one sibship of three and one sibship of two) who died of AML with group C monosomy. The mode of inheritance of monosomy 7 was confounded by a history of paternally inherited Noonan syndrome in the sibship of three. The other sibship in the kindred did not have Noonan syndrome or a family history of Noonan syndrome.

However, individuals with Noonan syndrome are at an increased risk for juvenile myelomonocytic leukemia (JMML) or a JMML-like disease in infancy [Choong et al 1999, Kratz et al 2005]. The most common abnormality in JMML is monosomy 7.

Another recent report described a family with two sibs with monosomy 7 [Gaitonde et al 2010]. The proband was a 24-year-old woman with a seven year history of pancytopenia. When she presented for evaluation she was pregnant and transfusion dependent, at which time she was found to have a monosomy 7 clone. She was given the diagnosis of a hypocellular MDS. Her sister was an HLA identical match, but was found to be pancytopenic and upon further evaluation was also found to have monosomy 7 with hypoplastic MDS. The proband underwent a successful bone marrow transplant from an unrelated donor and had full engraftment. The sisters reported no known related family history.

Bödör et al [2012] published a family of two first cousins with germline *GATA2* (c.1061C>T) pathogenic variants. In addition to the germline pathogenic variants, the cousins had acquired monosomy 7 and identical acquired *ASXL1* pathogenic variants (c.1934dupG). The proband presented at the age of 23 with cytopenias and was given a diagnosis of refractory anemia with excess blasts-2 (RAEB2) and monosomy 7. This individual relapsed seven months later and was given an allogeneic bone marrow transplant, but succumbed to sepsis four months post transplant. His father was later shown to be a carrier for the *GATA2* pathogenic variant. The proband's cousin presented at the age of 18 years and was found to have RAEB1 and monosomy 7. He underwent an allogeneic transplant from a mismatched unrelated donor, but died two years later from relapsed disease. The mutation status of his mother was unavailable. Of interest, the grandmother reportedly died of AML and the maternal great uncle reportedly died from leukemia. Another first cousin was found to be a carrier of the *GATA2* pathogenic variant when she presented at the age of 31 with neutropenia and monocytopenia, but did not have monosomy 7, or any evidence of bone marrow failure. Her father was also a carrier of the *GATA2* pathogenic variant.

In this family [Bödör et al 2012] the pathogenic variant in *GATA2* was likely passed down from the grandmother to three of her children, none of whom had a history of bone marrow failure or monosomy 7. However, two of their children had monosomy 7 and died of relapsed myeloid disease. This pattern of inheritance may be indicative of an autosomal dominant condition with incomplete penetrance.

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