Constitutional Mismatch Repair Deficiency (CMMRD)

What You Should Know About CMMRD

Constitutional Mismatch Repair Deficiency, or CMMRD, is a rare condition that is caused by inheriting two mutations, one from each parent, in any of the following genes: *MLH1, MSH2, MSH6, PMS2, EPCAM*. CMMRD causes risks for colon cancer, small bowel cancer, hematologic (blood) cancers, brain cancers, colon polyps, and dark marks on the skin (called Café Au Lait macules). These cancers often occur in childhood or adolescence in individuals with CMMRD.

The genes that cause CMMRD also cause a condition called Lynch syndrome (or hereditary non-polyposis colorectal cancer, HNPCC) in individuals who only inherit one mutation. Lynch syndrome increases the risk for adult-onset cancers, particularly colorectal and uterine cancers.

Risks for Cancer in Individuals with CMMRD

There is limited data on the risks for cancer in individuals with CMMRD. The information below comes from one study of 23 children with CMMRD from 2014:

Brain cancer: This is believed to be the most common type of cancer in children with CMMRD, seen in 48% of cases.

Gastrointestinal cancers: This includes cancers of the colon and small bowel. These cancers were seen in 32% of cases.

Hematologic cancers: This includes blood cancers such as leukemia. These cancers were seen in 15% of cases.

Café Au Lait macules: These are flat, pigmented birthmarks. The name café au lait is French for "coffee with milk" and refers to their light-brown color. These are seen in nearly 100% of children with CMMRD and may commonly be found on the arms, legs, or abdomen.

Managing the Risk for Cancer

The following surveillance guidelines were developed by the International Consortium of Childhood CMMRD:

Colon Cancer

- Colonoscopy every year starting at age 3 is recommended. This should be continued into adulthood.

Upper GI/Small Bowel

- Esophagogastroduodenoscopy (EGD) every year starting at age 3 and continued into adulthood.
- Video capsule endoscopy every year starting at age 3 and continued into adulthood.

Brain

- Ultrasound of the brain at birth and follow-up brain MRI every 6 months. This should be continued into adulthood.

Leukemia/Lymphoma

- Complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase done every 4 months beginning at birth or as soon as condition is diagnosed

Uterus

- Ultrasound of the uterus every year beginning in adulthood (although the exact age is not specified)

Upper Urinary Tract

- Ultrasound and urine cytology test every year beginning in adulthood (although the exact age is not specified)

Risks to Family Members

CMMRD is inherited in an autosomal recessive fashion. This means that a child must inherit two copies of a mutation, one from each parent, in order to be affected. Having just one copy of a mutation in one of the genes that causes CMMRD will also cause a higher risk for cancer, however individuals with a single mutation do not have CMMRD. Individuals with a single mutation have a condition called Lynch syndrome. Lynch syndrome also causes cancer risks, but these cancers tend to occur in adulthood, not childhood.

Since a child with CMMRD has two mutations, one from each parent, this means that, in most cases, both parents have Lynch syndrome. This also means that brothers and sisters of a child with CMMRD have a risk to have either CMMRD, if they inherit a mutation from both parents (there is a 25% risk of this), or Lynch syndrome, if they only inherit one mutation (there is a 50% risk for this). Brothers and sisters also have a 25% chance to have no mutation at all.

Children with CMMRD often have a family history of cancer, since their parents and family members may have Lynch syndrome. However, some children have been found to have CMMRD without a strong family history of cancer.

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