Updated November 2019

KIT Mutation

The *KIT* gene is associated with autosomal dominant piebaldism, gastrointestinal stromal tumors (GISTs), and familial mastocytosis.[1-3] The type of mutation identified in the *KIT* gene determines the symptoms/cancer risks that the individual may have. Pathogenic loss-of-function (LOF) mutations in the *KIT* gene are generally only associated with Piebaldism. However, pathogenic gain of function mutations in the *KIT* gene are associated with systemic mastocytosis and gastrointestinal stromal tumors.[4,5]

- **Piebaldism:** This is a rare condition characterized by the patchy absence of melanocytes in certain areas of the skin and hair. Melanocytes produce the pigment melanin, which contributes to hair, eye, and skin color. The absence of melanocytes leads to patches of skin and hair that are lighter than normal. These unpigmented areas are typically present at birth and do not increase in size or number.[6-8]

- **Gastrointestinal stromal tumors (GIST):** GISTs are tumors that occur in the gastrointestinal tract, most commonly in the stomach or small intestine. Small tumors may cause no signs or symptoms. However, some people with GISTs may experience pain or swelling in the abdomen, nausea, vomiting, loss of appetite, or weight loss. These tumors can be cancerous (malignant) or noncancerous (benign).

- **Mastocytosis:** This is a blood disorder that occurs when white blood cells called mast cells accumulate in one or more tissues (most commonly in the bone marrow). Mast cells normally trigger inflammation during an allergic reaction. When an environmental trigger activates mast cells, they release proteins that signal an immune response. In systemic mastocytosis, excess mast cells mean more proteins are being released in the tissues where the cells accumulate, leading to an increased immune response.

Data are limited regarding the lifetime risks to develop piebaldism, GISTs, or mastocytosis in individuals with germline *KIT* mutations. A meta-analysis published in October 2016 shows that only 37 reports have described 21 well-sequenced germline mutations in *KIT*.[9]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *KIT* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Gastrointestinal stroma tumor (Concept Id: C0238198) - MedGen - NCBI. (n.d.). Retrieved October 31, 2019, from https://www.ncbi.nlm.nih.gov/medgen/116049.
2. Mastocytosis (Concept Id: C0024899) - MedGen - NCBI. (n.d.). Retrieved October 31, 2019, from https://www.ncbi.nlm.nih.gov/medgen/9902.
3. Beghini, A. et al. (2001). Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. *Cancer*, *92*(3), 657–662. doi: 10.1002/1097-0142(20010801)92:3<657::aid-cncr1367>3.0.co;2-d.

4. Campos, P. D. M. et al. (2014). Familial systemic mastocytosis with germline KIT K509I mutation is sensitive to treatment with imatinib, dasatinib and PKC412. *Leukemia Research*, *38*(10), 1245–1251. doi: 10.1016/j.leukres.2014.07.010.
5. Dessinioti, C. et al. (2009). A review of genetic disorders of hypopigmentation: lessons learned from the biology of melanocytes. *Experimental Dermatology*, *18*(9), 741–749. doi: 10.1111/j.1600-0625.2009.00896.x.
6. Spritz, R. A. et al. (1993). Novel Mutations of the KIT (Mast/Stem Cell Growth Factor Receptor) Proto-Oncogene in Human Piebaldism. *Journal of Investigative Dermatology*, *101*(1), 22–25. doi: 10.1111/1523-1747.ep12358440.
7. Spritz, R. A. (1994). Molecular Basis of Human Piebaldism. *Journal of Investigative Dermatology*, *103*(5). doi: 10.1038/jid.1994.25.
8. Ke, H. et al. (2016). Germline mutations of KIT in gastrointestinal stromal tumor (GIST) and mastocytosis. *Cell & Bioscience, 6*(55). doi: 10.1186/s13578-016-0120-8.