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Cancer Prone Disease Section

Mini Review

Piebaldism

Lidia Larizza, Alessandro Beghini

Department of Biology and Genetics for Medical Sciences, Medical Faculty, University of Milan, Via Viotti 3/5, 20133 Milan, Italy (LL, AB)

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Identity

Note
Defect in melanocyte development; one of the first genetic disorders for which a pedigree was presented in 1786.

Inheritance
Autosomal dominant; frequency is about $2.5/10^5$ newborns.

Clinics

Phenotype and clinics

Congenital patches of white skin and white hair, principally located on the scalp, forehead, chest and abdomen and on the limbs; several patients report lifelong severe constipation; a hierarchical correlation has been elaborated between severe or mild phenotypic traits and the associated KIT mutations; in a few patients with interstitial deletions, mental retardation and congenital anomalies have been also described.
Etiology: defective melanoblasts proliferation, survival and migration from the neural crest during development and defective migration of enteric-plexus ganglion cells from the neural crest to the gut.
Pathology: white spotting in human piebaldism results from the absence of melanocytes from the nonpigmented patches of skin and from hairbulbs in the white patches of hair; occasionally, individuals lack ganglion cells of the intestinal enteric neural plexus, which, like melanoblasts, are derived from the neural crest.

Neoplastic risk

An increased risk of epithelioma has been reported.

Prognosis

In contrast to vitiligo, piebaldism is both congenital and non-progressive.

Cytogenetics

Inborn conditions

A few patients with interstitial deletions of chromosome 4q12-q21.1 have been identified; they are charaterized by multiple congenital anomalies, short stature and mental retardation.

Genes involved and proteins

KIT

Location
4q12

DNA/RNA
Description: 21 exons

Protein
Description: Transmembrane SCF/MGF receptor with tyrosine kinase activity; binding of ligand (SCF) induces receptor dimerization, autophosphorylation and signal transduction via molecules containing SH2- domains.

Mutations
Germinal: Loss of function mutations resulting in haploinsufficiency of the receptor; different kinds of point mutations have been identified (diagram).

- Missense substitutions (Glu583Lys; Phe584Leu; Ala621Thr; His650Pro; Gly664Arg; Gly791Arg; Val812Gly; Glu861Ala) and small deletions (641del2; 892del12) in the intracellular tyrosine kinase domain; correlate with severe piebald

phenotypes, because of dominant-negative inhibition of the KIT receptor via formation of impaired receptor heterodimers between a normal and a mutant KIT monomer, and a 75% decrease of KIT- dependent signal transduction.

- Proximal frameshifts (84del1; 249del4); Trp557Term; and missense mutations (Cys136Arg; Ala178Thr; Met318Gly) associated with a mild piebald phenotype, the result of pure haploinsufficiency due to a 50% decrease of KIT-dependent signal transduction.

- Distal frameshifts: 630insA; and splice junction mutations (IVS1+4G-A; IVS12+1G-A), located near the intracellular TK domain associated with variable phenotypes, as the truncated polypeptides via incorporation into nonfunctional receptor heterodimers would decrease KIT-dependent signal transduction by 50-75%, depending on their stability.

- Complete deletions of the entire KIT gene (null mutations) result in a mild-intermediate phenotype.

PDGFRA

Location
4q12

Note
PDGFRA is also deleted in patients with interstitial cytogenetic deletions (contiguous gene syndrome).

SCF/MGF

Location
12q22

Note
No alteration of this gene has been so far identified in typical patients; at difference with the mouse system, where steel mice bearing SCF mutations show the white spotting phenotype likewise W mice bearing kit mutations; however, as mutations of KIT could not be detected in a consistent fraction of these patients, involvement of SCF is still an open question.

References

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