

Cancer Prone Disease Section

Mini Review

Piebaldism

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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 characterized by multiple congenital anomalies, short stature and mental retardation.

Genes involved and proteins

KIT

Location

In 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; Arg796Gly; Val812Gly; Glu861Ala) and small deletions (641del2; 892 del12) 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

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.

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