

The McCune-Albright Syndrome: A Lethal Gene Surviving by Mosaicism

The etiology of this disease is unknown. There is no evidence of a hereditary basis, since there is no convincing report of a family incidence except one report involving monozygotic twins. Dr. R. Happle of Germany theorizes that the syndrome is caused by a gene that is dominant and lethal, unless the effect is diluted through mosaicism. He postulates that patients with this syndrome are mosaics for the gene.

Happle states that pigmented lesions often show a unilateral arrangement, strictly respecting the ventral midline. He also states that one important fact has been overlooked previously: Based on his observation of a patient, plus a review of the literature, pigmentation in this syndrome follows the lines of Blaschko. As a general rule, nevroid skin lesions following the lines of Blaschko result from the dorso-ventral outgrowth of two different populations of cells during early embryogenesis, thus reflecting mosaicism. Since patients suffering from the McCune-Albright syndrome have this cutaneous pattern for their pigmentation,

Happle believes it is likely that these patients have two different clones of cells.

Happle postulates that if the gene for McCune-Albright syndrome were merely functional, one would expect that the syndrome would be inherited. However, all cases are sporadic. This can best be explained by the presence and action of a "dominant" lethal gene that kills the embryo during its development. Patients with this gene could survive only if they were mosaics. If this thesis is correct, the mosaic state could be produced either by a gametic half chromatid mutation or by an early somatic mutation. Unilateral or even more circumscribed involvement would result from a mutation occurring at a later time in embryogenesis.

This theory could explain the scattered and asymmetric distribution of bone lesions. It could explain the protean variability of endocrine disturbances. It could also explain the occurrence of incomplete forms of the syndrome, which would be attributed to a minor proportion of mutant cells within the total cell population. The mosaicism resulting from a gametic half chromatid mutation could also explain the simultaneous occurrence observed in a set of monozygotic twins.

continued on page 10

McCune-Albright Syndrome

continued from page 9

Happle concluded that both males and females with the McCune-Albright syndrome are able to produce offspring. For the practical purpose of genetic counseling, the action of a lethal gene would explain why the risk of recurrence is not increased for the patient's siblings and children. The concept would imply that affected women should have an increased rate of spontaneous abortions. The loss of the zygote,

however, might occur at the time of implantation and thus remain unnoticed. Special attention will be given to this question in further clinical studies.

Happle R. *Clinical Genetics* 1986; 29:321-324.

Editor's comment—*This is a fascinating postulate. Happle has previously written about mosaicism and the occurrence of certain dermatological lesions that follow the lines of Blaschko. In an article in Human Genetics (1985; 70:200-206) which is entitled "Lyonization and the lines of Blaschko," Happle writes that the lines of*

Blaschko represent a nonrandom developmental pattern of the skin fundamentally differing from the system of dermatomes. He found a causal relationship between lyonization and the lines of Blaschko to be quite obvious. Apparently, in women affected with X-linked skin disorders, the lines of Blaschko visualize the clonal proliferation of two functionally different populations of cells during embryogenesis. The lesions arise probably from cells in which the X chromosome that bears the mutation is the active one, whereas the normal skin develops from cells in which the normal cell is active.