

Contiguous Gene Syndromes: A Component of Recognizable Syndromes

There are now seven disorders in humans in which some patients with the disorder have visible chromosomal abnormalities and others do not. The conditions in which visible chromosomal deletions are sometimes seen include Prader-Willi syndrome, in which approximately half of the patients have deletions at 15q11; DiGeorge's syndrome, in which about 5% of patients have deletions at 22q11; Langer-Giedion syndrome (trichorhino-phalangeal syndrome type II), in which 80% of the patients have deletion at 8q24; Miller-Dieker syndrome, in which approximately 90% of patients have deletion at 17p13; retinoblastoma, in which 5% of patients have deletion at 13q14; the triad of Wilms' tumor, aniridia, and genitourinary tract malformation, in which about 95% of patients have deletion at 11p13; and the Beckwith-Wiedemann syndrome, in which 5% of patients have duplication of distal 11p. Patients with any of these conditions should have chromosome studies done to establish whether or not the cytogenetic abnormality is present. Frequently, both blood lymphocytes and fibroblasts need to be studied.

These syndromes are particularly interesting, since it is not at all clear whether a specific gene has been deleted or duplicated by the chromosomal abnormalities associated with the syndrome or whether the syndrome is produced by abnormalities in and interactions between a set of genes. The sizes of chromosomal abnormalities are quite variable among patients who are clinically very similar. These seven conditions represent a new category of disorders in which visible chromosomal changes may be seen.

Schmickel RD. *J Pediatr* 1986;109:231-241.

Editor's comment—As we learn more about molecular genetics and single gene mutations, we realize that many mutations are actually deletions of genes or parts of genes. Thus, it is not surprising that the larger the deletion, the more likely that more than one gene is involved in the deletion. However, we are only beginning to realize that specific syndromes may actually be the products of multiple gene deletions. The interesting point among the cases reported so far is that in no condition is there uniformity as to the absence of visible chromosome material in all cases of the condition.

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, nevoid 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,

Thus, we cannot equate the syndrome per se to chromosome deletion. It is not at all clear at this time what the relationship of the deletion is to the production of the abnormality. Also interesting is that two of the conditions, the Beckwith-Wiedemann and Prader-Willi syndromes, have overgrowth, while three of the conditions have cancerous overgrowth. Thus, the gene(s) involved is (are) altered in such a way as to upset normal growth mechanisms. This certainly is an interesting group of diseases, and the etiologies will become clearer as progress is made in molecular genetics.

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.

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