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Panel Discussion II: Linkage Studies in Tuberous Sclerosis

Current Status and Future Prospects

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Beginning in 1987 with the report of linkage of tuberous sclerosis (TSC) to the ABO blood group locus on chromosome 9, several research groups attempted to define a precise location for one or more TSC genes. At this conference, further studies on genetic linkage in TSC were reported.

The panel discussion, which also included comments from the audience, focused on several issues: the current status of TSC linkage research, banking of cell lines and tissues, clinical and cytogenetic investigations of TSC families and individuals, and possible pathogenetic mechanisms in TSC.

CURRENT STATUS

Thus far, research in TSC demonstrates at least two genetic phenotypes, one of which is linked to chromosome 9q34 and a second that is probably linked to markers on chromosome 11q. Research also suggests a third phenotype, possibly on chromosome 14. Prior to this meeting, various investigators collaborated in building a TSC linkage dataset. Analyses of the pooled TSC linkage data by different investigators consistently demonstrate genetic heterogeneity in TSC.

CELL AND TISSUE BANKING

To facilitate localization of the causative TSC genes, cell banking can be used. Already, cells from several TSC families are stored in the NIH Human Genetic Mutant Cell Repository in Camden, New Jersey. It was noted that the Camden Repository is not accepting further TSC cell lines. In some cases, the costs of retrieving the cell lines from the Repository may hinder their use. Although banking by individual investigators is also expensive, potential mixups in cell lines can be avoided by using DNA fingerprinting to identify the cell lines. A similar discussion was held concerning a TSC tissue bank. Researchers may find it useful to have frozen samples from biopsied lesions or cell lines derived from tissues; however, it was not resolved where and how such tissues would be obtained and stored, or how access to the tissues would occur. Despite concerns about storage,

it was clear that investigators will continue to search for large families in which multiple generations are affected by TSC. Although more genetic markers on the chromosomes of interest will be useful, the identification of further large, multigenerational TSC families will remain a high priority.

CLINICAL EVALUATIONS

It was suggested that issues of genetic heterogeneity may be more readily clarified if detailed clinical characteristics of pertinent TSC families were available. Among the families that have cell lines banked in Camden, the chromosome 9-linked family submitted by Dr. M. Smith (referred to as TS-1; Camden Repository pedigree number GM 1036) had a thorough clinical evaluation by Dr. M. Gomez. The chromosome 11-linked family, "the Stanford family" (referred to as TS-16; Camden Repository pedigree number GM 2150), has also been thoroughly evaluated. Because there is no clinical impression at this time of distinct TSC clinical phenotypes, it was questioned whether extensive clinical evaluations would be of benefit. This lack of distinct phenotypes is in contrast to the situation with neurofibromatosis (NF) in which clinicians had suspected the existence of more than one clinical phenotype, as subsequently confirmed by localization of NF1 (peripheral NF) to chromosome 17 and NF2 (central or acoustic NF) to chromosome 22. Furthermore, TSC family individuals who are asymptomatic or mildly affected may not be interested in neuroimaging or other evaluations, even if funds are available to pay for these tests.

Which evaluations are needed and how many organ systems must be evaluated? Although neuroimaging (CT and MRI) and renal imaging (ultrasound, CT and MRI) are accepted investigations to help determine affected status, the use of echocardiograms for this purpose seems to be highest in younger persons. However, even with all available clinical evaluations, the inability to unequivocally distinguish between an unaffected member of a TSC family and an asymptomatic gene carrier still remains.

KARYOTYPE INVESTIGATIONS

The question was raised as to whether cytogenetic analysis is clinically indicated in patients with TSC or at least one proband of a TSC family. Chromosomal translocations that occur in a person with TSC can help to pinpoint the location of the responsible gene, as occurred with the patient who had chromosome 11 translocation, discussed earlier in the meeting. A survey of the audience was taken to determine a rough proportion of chromosomal abnormalities in tested individuals with TSC. Among more than 170 individuals with TSC, peripheral blood karyotypes were all normal. Cytogenetic investigation was abnormal in 1 of 12 tumors.

PATHOGENESIS

The pathogenesis of the variable manifestations of TSC remains uncertain, but an analogy was made to the second-hit hypothesis of retinoblastoma. In this situation, a recessive tumor suppressor gene has an initial abnormality in one allele of the gene followed by a mutation of the other allele—the second hit—

resulting in the development of retinoblastoma. As support for this concept in TSC, the photograph of a patient with TSC shown by Dr. Connor was mentioned. On the leg of this patient was a hypopigmented stripe conforming to the lines of Blaschko which are thought to represent the embryonic routes of migration of neural crest-derived pigment cells. In this case, a "second" mutation in a precursor cell of a patient who had inherited the genetic lesion of TSC may predispose to the formation of a hypopigmented streak. Similar "second" mutations in various cells conceivably could relate to altered neuronal migration and differentiation as well as development of hamartomas. Furthermore, in contrast to retinoblastoma in which only retinal cells are vulnerable, multiple cell types may be vulnerable in TSC if a "second" mutation occurs in a cell type that is the precursor to multiple cell types. It was felt that the different manifestations of TSC in monozygotic twins, such as epilepsy in one but not the other, might also provide support for the second-hit hypothesis.

Given the clonal origin of cells in the central nervous system, and if the second-hit hypothesis is reasonable, one would expect cases of unilateral TSC. Even if such cases occur, however, they may be underestimated because they do not fulfill current criteria for the diagnosis of TSC. For example, how does one account for unilateral cases of angiomyolipoma of the kidney, isolated hypopigmented macules, one retinal hamartoma, and other single lesions? In some instances, such individuals have children with TSC. Specifically cited was a woman who had a single angiomyolipoma and who had a child with TSC. Alternatively and analogous to segmental neurofibromatosis, mutations of a TSC gene in somatic clonal cells, in the absence of germ cell mutations, may produce lesions typical of TSC, but separate from the inherited form of TSC.

A possible way to account for the differing recurrence estimates in TSC may relate to gonosomal mosaicism in which mosaicism occurs in both the germ cells and other somatic cells. For example, a parent with minimal or no manifestations of TSC, who is a gonosomal mosaic, might then have a child with TSC. An example of gonadal mosaicism in an autosomal dominant disorder was cited in which two children who had osteogenesis imperfecta had different mothers but the same father. The concept was criticized as not readily testable in TSC. However, as a precedent for the relatively common occurrence of gonadal mosaicism, it was mentioned that the Rett syndrome data has been used to estimate the frequency of gonadal mosaicism as 1 in 75.