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Tuberous sclerosis (T.S.) and gene linkage

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Over 1300 names representing a patient or family with TS have been identified. Questionnaires resulted in data from over 450 TS patients. Partial tabulations of data revealed that ages of TS patients varied from one day to 80 years. Problem(s) which first aroused parental suspicion: Developmental delay, 8.5% (38/448) seizures, 82.3% (372/452), skin lesions, 5.9% (26/436) and a variety of renal, cardiac, eye, bone or pulmonary lesions in 4.5%. Currently 78.7% are delayed/retarded, 94% have or have had seizures; all have skin lesions; approximately 40% report hamartomatous lesions involving the eye, kidney, bone, heart and lung; 27 of the families reported multiple cases involving one generation in 3 families; 2 generations in 15 families; 3 generations in 7 families and 4 generations in 2. The mother was a

carrier in 25 families resulting in 20 affected males and 28 affected females. The father was the carrier in 12, resulting in 16 affected males and 14 affected females. Mental retardation was less common in the familial than in the sporadic cases but males in both groups tended to be more severely retarded than females. Eight families have been entered into a gene linkage study. All affected and non-affected are examined including head CT scan and renal ultrasound. Blood has been obtained for protein, red cell enzyme and DNA polymorphisms. This approach does hold promise for ultimately identifying the TS gene(s). It is postulated there is more than one gene for TS; perhaps one or more modifying genes which explain the inter- and intra-family variability in expression.

Estimation of the genetic risk of radiation and chemical mutagens

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There are two main approaches in making genetic risk estimates. One of these, termed the direct method, expresses risks in terms of expected frequencies of genetic changes induced per unit dose, the other, referred to as the doubling dose method or the indirect method, expresses risks in relation to the observed incidence of genetic disorders now present in man.

The indirect method used experimental data only for the determination of the doubling dose. The quality of the risk estimation depends on assumptions of the persistence of the induced mutations and the ability to determine the current incidence of the genetic diseases. The direct estimation is based on the induced frequency for dominant skeletal defects and dominant cataract mutations in mice.

For the verification of these quantifications one can use the data of Hiroshima and Nagasaki. According to the estimation with the direct method one would expect less than 1 radiation-induced dominant cataract in 19,000 children with one or both parents exposed. The expected overall frequency of dominant mutations in the first generation would be 20–25, based on radiation-induced dominant cataract mutations. If we use for the estimation the data on dominant mutations affecting the skeleton one would expect a maximum of 60 cases. The same approach can be used to determine the impact of chemical mutagens.