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Association studies

© SPMM Course the disease this will be detectable as increased allele sharing at the marker. This approach has been successful in identifying susceptibility loci for disorders such as type 1 diabetes. The main drawback is that susceptibility loci of very small effect (such as conferring a relative risk of less than 2) may require large numbers of sib pairs in the region of 600 to 800 to be detected. In a disorder such as schizophrenia the relative risk in a sibling of an affected individual is about 10; thus, if several additive genes are involved, none may individually have a relative risk of more than 2’. (Excerpts from McGuffin & Martin, BMJ. 1999 Jul 3; 319(7201): 37–40) Whole genome scan It is a type of linkage analysis in which markers placed at regular intervals covering the whole genome are typed. It is tedious but often the first approach when no genetic information is available about a particular phenotype. A good example is that of neuregulin. Stefansson et al. typed 950 microsatellite markers covering the whole genome in 110 Icelandic patients with reconstructed genealogical relationships, and found that neuregulin-1 is a candidate gene for schizophrenia (Malats & Calafell, 2003). Association studies Association studies are more straightforward to carry out than linkage studies. Here a case control design is often adapted, and a sample of cases affected by a disorder is compared with controls. The frequency of alleles at the marker locus is then compared in the two groups. This method, though increasingly used, cannot make strong causal inferences. The locus chosen for study must predispose to illness. Thus, loci chosen for association studies are often known as candidate genes. If the locus does not predispose to illness, then the results of an association study should be negative. However, false positive results can occur if the two populations are not carefully matched for ethnic background. One alternative control group is the parents or relatives of affected individuals (the alleles not transmitted to the affected child compose the "control group"—this is known as the Transmission Disequilibrium Test or TDT). In Genome Wide Association Studies (GWAS), ‘candidate gene’ approach is not used. Instead, several thousands of single nucleotide polymorphisms are assayed in thousands of individuals. This is the new ‘hot’ study technique in psychiatric genetics. Questions Most appropriate method Is the phenotype familial? Family study What is the relative contribution of genetic and environmental factors? (Heritability) Twin studies, adoption studies What is the mode of transmission? Segregation analysis Where might be the ‘culprit’ genes? Linkage analysis (known ancestries) What are the actual genes responsible? Association analysis (population level)

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