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Linkage Exclusion Mapping: Rare Diseases Get SAMPLE'd

Homozygosity mapping has been the favored method for linkage mapping in recessive diseases since the landmark paper by Lander and Botstein (*Science 236:1567–1570, 1987*). This method relies mainly on genotyping entire pedigrees and scanning for regions of identity by descent. These data are often examined from the opposite perspective, looking for allele sharing in consanguineous parents, and excluding all other regions (linkage exclusion mapping). However, manual exclusion mapping with microsatellite data is tedious, sparsely distributed (by today's standards), and subject to errors of false heterozygosity in polyallelic microsatellite data which could mask regions of identity, thus excluding the actual disease locus.

With dense SNP genotyping, homozygosity mapping can link to smaller candidate regions. But with severe early onset diseases it is difficult to obtain enough DNA from affected individuals for genome-wide genotyping, especially from fixed tissue. Carr et al. (*Hum Mutat 30:1642–1649, 2009*) demonstrate a novel software application that circumvents this difficulty. Their software tool, SAMPLE (Shadow Autozygosity MaPping by Linkage Exclusion), accelerates the scanning of genotype data for regions that can be excluded from linkage to recessive disease loci in consanguineous families. Genome-wide SNP genotypes are first obtained only in parents and unaffected offspring. Through a series of steps designed to eliminate regions not compatible with linkage, SAMPLE presents a nonparametric graphical summary of the remaining regions of possible linkage. The results delineate a smaller set of possible linkage regions, which then can be examined by genotyping affected offspring DNA. SAMPLE will undoubtedly facilitate the identification of candidate gene regions in rare recessive disorders for which affected DNA is difficult to obtain.

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Toward Understanding the Molecular Basis of Ovarian Cancer

The genome of an ovarian tumor typically represents a culmination of somatically acquired, poorly understood genomic aberrations that functionally alter genes which contribute to tumorigenesis. Because the changes vary numerically and structurally, the evolution of the ovarian tumor in familial and sporadic ovarian cancer (OvCa) can appear stochastic in nature. It is a major challenge to identify the key recurrent copy number alterations (RCNAs) and to differentiate tumorigenic causal genes and their pathways from other non-contributory genes or bystanders.

Leunen et al. (*Hum Mutat 30:1693–1702, 2009*) provide a unique comparison of BRCA1-related and sporadic OvCa, using array-CGH and pathway analysis to identify RCNAs and candidate oncogenic pathways that may underlie the disease for different clinical groups. They observe that the type, number and length of RCNA differ between the genomes of *BRCA1*-related and sporadic tumors, as might be expected due to differences in genetic origin. Furthermore, pathways affected by RCNAs, such as those involving ESR1, also differ between the two groups, providing impetus for further investigation.

Studies of DNA aberrations in familial and sporadic forms of ovarian cancer, such as that by Leunen et al. could potentially lead to the discovery of OvCa-causing genes and hence to therapeutic targets. For example, the identification of *ERBB2* (*HER2*) amplification in a significant proportion of breast cancers led to the development of Trastuzumab as an effective therapy that targets the amplified gene. Profiling studies with larger cohorts are now required to extend the important findings of Leunen et al. in order to provide further insight into the mechanisms by which ovarian cancer develops and to identify new candidate targets for therapy.

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