Genomic Approach to Rare Heterogeneous Neurological Disorders

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Positional cloning of Mendelian disorders has led to the identification of >3000 genes involved in these disorders. However, the etiology of many rare disorders remains unknown because the disorder is so heterogeneous that many families carry essentially private mutations, but each family is usually not large enough to permit unambiguous gene mapping. The past years have seen an unprecedented growth in ~omics technologies. We will show successful gene identification by combinations of linkage, microarray expression and massively parallel next generation sequencing (NGS) in four examples.

DIAPH3 as the mutant gene in a rare form of deafness was differentially expressed in lymphoblastoid cell lines (LCLs) and mapped under the linkage peak. We identified a novel dominant myopathy and a dominant ataxia gene by combining linkage analysis with next generation sequencing. In a consanguineous family with only two affected DNA samples available, the culprit gene was identified by homozygosity mapping and next generation sequencing. Aberrant splicing shown in LCLs provided crucial confirmation, in addition to recapitulation of the phenotype in cellular or animal models.

While our successes so far used familial cases with at least two affected subjects, most present as single cases. To move from family linkage to gene identification in singletons, we are now adding bioinformatic analysis of pathways from large-scale genomic data and the literature, using machine-learning generated networks in mouse and humans that are expert curated for relevance for ataxia,