Genetic modifier approaches and experiences in Charcot-Marie-Tooth disease (CMT)

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The discovery of disease genes for HSP, CMT and related disorders has progressed dramatically in recent years. With the now broadly available technologies of exome and genome sequencing new challenges can be approached. As is known for a long time, patients even with the same causative mutation, do not always express the same phenotypic details, such as age of onset, severity, additional symptoms. This variability in phenotypic expression is either due to environmental influences, genetics, or both. With standardized phenotypic assessments and long term follow up it is now increasingly possible to study the genetic contributions to phenotypic variability. In this presentation I show early data from CMT and other studies in this area. The principle approaches will be discussed, including association studies, extreme phenotype statistics, and large family based strategies. These type of studies are still challenging and depend largely on excellent clinical work. The follow up of any findings in mechanistic studies is key but poorly worked out. Yet, if successful, the identified genetic alleles may well provide superior targets for pharmacological intervention.