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Uncovering modifier genes for therapeutic target identification in rare diseases: Application of mouse and human genetics

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Understanding phenotypic variability in rare genetic diseases, such as Gaucher disease (GD), is challenging because it is hard to recruit large cohorts of patients with different symptoms to perform association studies. To overcome this problem GD was chemically induced in 15 inbred mouse strains because their SNPs profile is known, followed by GWAS. GD-induced strains mimicked the divergent phenotypes observed in patients, which range from neuropathic disease with short lifespans to others with no evident CNS involvement and longer survival times. GWA analysis identified a small collection of candidate loci underlying the variable strain phenotypes, which allowed us to successfully predict the severity of the disease in other strains upon GD induction and to identify a novel therapy for the neuropathic forms of GD. This strategy, which can be applied for pharmacogenomics studies as well, has several advantages, including 1) Develop new animal models of study the biology of the disease; 2) It is possible to replicate measurements in genetically-identical individuals, minimizing environmental effects; 3) Inbred mouse strains are homozygous for each loci; 3) The SNP profile of each mouse strain is known and freely available; 4) In the validation process in patients, we will be able to reach statistically significant associations by analyzing a reasonable number of patients, since we are focusing on candidate modifier genes rather than interrogating the whole genome blind (due to false discovery rate corrections, FDR). By the end of the talk other approaches that we are currently following to uncover modifier genes and therapeutically relevant pathways will be discussed, including exome sequencing in twins presenting with different disease severity and multi-omics in fibroblasts derived from families of patients with other rare lysosomal diseases presenting significant phenotypic variability.

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