

Satellite Symposium: Genetics in Neuronal Ceroid Lipofuscinosis (initiated and supported by the NCL-Foundation)

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Abstract: New insights into the neurobiology of Batten disease

The neuronal ceroid lipofuscinoses (NCLs or Batten disease) are a group of at least nine fatal monogenetic storage disorders, mostly affecting children. Although the genetic basis of most forms of NCL have been identified, very little is known about how mutations in these genes lead to the devastating effects upon the affected individual. To help understand the events that happen in each form of NCL, a variety of mutant mouse models are available. We have been characterizing the progressive pathogenesis of each form of NCL, obtaining detailed pathological landmarks of disease progression. These analyses have revealed a series of unexpected findings.

The characteristic intralysosomal accumulation of autofluorescent lipopigments that occurs in the NCLs does not appear to be central to the disease process, with no direct correlation to neurodegenerative or reactive events during disease progression. Moreover, although the NCL brain exhibits widespread neurodegeneration at autopsy, this neuronal loss actually displays remarkable selectivity. Surprisingly, although neuron loss is profound in the cortex, this appears to take place only after the loss of subpopulations of thalamic neurons that relay information of different sensory modalities to the cortex. Indeed, the thalamus appears to be a particular pathological target in multiple forms of NCL, displaying an early localized astrogliosis, followed by successive waves of neuronal loss and finally microglial activation. The early activation of reactive cell types serves as an accurate predictor of subsequent neuronal loss and appears to be already underway prenatally. There is also evidence for progressive reorganization of synapses during the early stages of pathogenesis, localized effects that may be mediated via astrocytes.

Such detailed landmarks of disease progression can also be used to judge the efficacy of therapeutic approaches, including stem cell and gene transfer strategies. Indeed, data of this type is likely to prove essential for the effective targeting and delivery of these potential therapies for these profoundly disabling disorders.

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Abstract: Cathepsin D deficiency cause a novel neurodegenerative disease of childhood

Cathepsin D is a ubiquitously expressed lysosomal aspartyl protease that is involved in various biological processes such as proteolytic degradation, cell invasion and apoptosis. In mice and Sheep cathepsin D deficiency is known to cause fatal neurodegenerative diseases. Here we report on a so far undescribed neurodegenerative disorder in humans that manifests in childhood and is also associated with cathepsin D deficiency. Two missense mutations in the human *CatD* gene, F229I and W383C, were identified and cause markedly reduced proteolytic activity and diminished amount of cathepsin D in patient fibroblasts. Expression of human wild-type and mutant cathepsin D in cathepsin *-/-* mouse fibroblasts revealed a residual activity for mutant F229I and an almost complete loss of proteolytic function for mutant W383C. The latter mutant also showed a disturbed posttranslational processing to mature peptidase forms and an intracellular mistargeting to non-lysosomal compartments. Kinetic analyses of mutant F229I expressed in cathepsin D *-/-* mouse fibroblasts showed a reduction of maximal enzyme velocity leading to decreased proteolytic activity. Furthermore, the functional importance of F229I is strengthened by the strict conservation of this residue among members of the pepsin family of peptidases. The structural effects of cathepsin C mutants were anticipated by computer modeling suggesting larger structural alterations for W383C than for F229I. The level of residual proteolytic activity in distinct cathepsin D mutants is likely to determine the clinical phenotype of this neurodegenerative disease.

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Abstract: In the hunt for the “true” CLN7 gene

The Turkish variant of LINCL (vLINCL-Turk) has been thought to be a distinct clinical and genetic entity (CLN7). We previously showed that in a subset of vLINCL-Turk patients mutations in either the CLN8 or the CLN6 genes underlie the disease phenotype. In consanguineous Turkish families with no linkage to known NCL loci we performed a genome-wide scan using 378 microsatellite markers (modified Applied Biosystems LMS-2/MD10 set, Finnish Genome Center, University of Helsinki), but found no single genomic region showing overlapping homozygosity in all families. Instead, several homozygous regions were observed in a subset of the families suggesting genetic heterogeneity and the existence of more than one NCL-causing, novel genes in the Turkish patients. In order to increase the informativity of the analysis, we undertook a genome-wide scan with Affymetrix's GeneChip 50K SNP array. Analysis of this high-density genotyping dataset with the GENEHUNTER MAPMAKER/HOMOZ application revealed three loci with HLOD scores of over 2. We are currently in the process of analyzing one of these promising regions in more detail in order to identify a putative novel NCL gene.