Diagnostic algorithm for NCL diseases

Clinical presentation	*Necessary diagnostic tests*	*Possibly affected genes*
Newborn with epilepsy and microcephaly	Enzyme testing for cathepsin D (CtsD) (leucocytes of fibroblasts)	CtsD deficient: *CLN10*
Young child (>6 months) with developmental stillstand or regression and / or newly occuring severe epilepsy of unknown cause	enzyme testing for PPT1 and TPP1 (dry blood spots; confirmation in leucocytes or fibroblasts)	
	PPT1	PPT1 deficient: *CLN1*
	TPP1	TPP1 deficient: *CLN2*
	If PPT1 and TPP1 enzyme activity is normal: Electron microscopic examination (skin biopsy or lymphocytes): If storage material is present: genetic testing.	*CLN5* *CLN6* *CLN7* *CLN8* *CLN14 (KCTD7)*
School child with visual loss and / or dementia and epilepsy	Search for lymphocyte vacuoles (light microscopy of blood smear). If lymphocyte vacuoles are present: genetic testing of the *CLN3* gene	*CLN3*
	If no lymphocyte vacuoles, enzyme testing for PPT1, TPP1 and CtsD (see above)	PPT1 deficient: *CLN1* TPP1 deficient: *CLN2* CtsD deficient: *CLN10*
	If PPT1 and TPP1 enzyme activity is normal: Electron microscopic examination (skin biopsy or lymphocytes). If storage material is present: genetic testing.	*CLN5* *CLN6* *CLN7* *CLN8* *CLN12 (ATP13A2)*
Young adult with non-specific mental, motor or behavioural abnormalities.	Enzyme testing for PPT1, TPP1 and CtsD (see above)	PPT1 deficient: *CLN1* TPP1 deficient: *CLN2* CtsD deficient: *CLN10*
	If PPT1 and TPP1 enzyme activity is normal: Electron microscopic examination (skin biopsy or lymphocytes). If storage material is present: genetic testing (eventually in special cases even without detection of storage material), consider possible mode of inheritance.	If autosomal dominant: *CLN4 (DNAJC5)* If autosomal recessive *:* *CLN6* *CLN11 (GRN)* *CLN13 (CTSF)*