Histopathology and the diagnosis of lysosomal storage disorders – part 2

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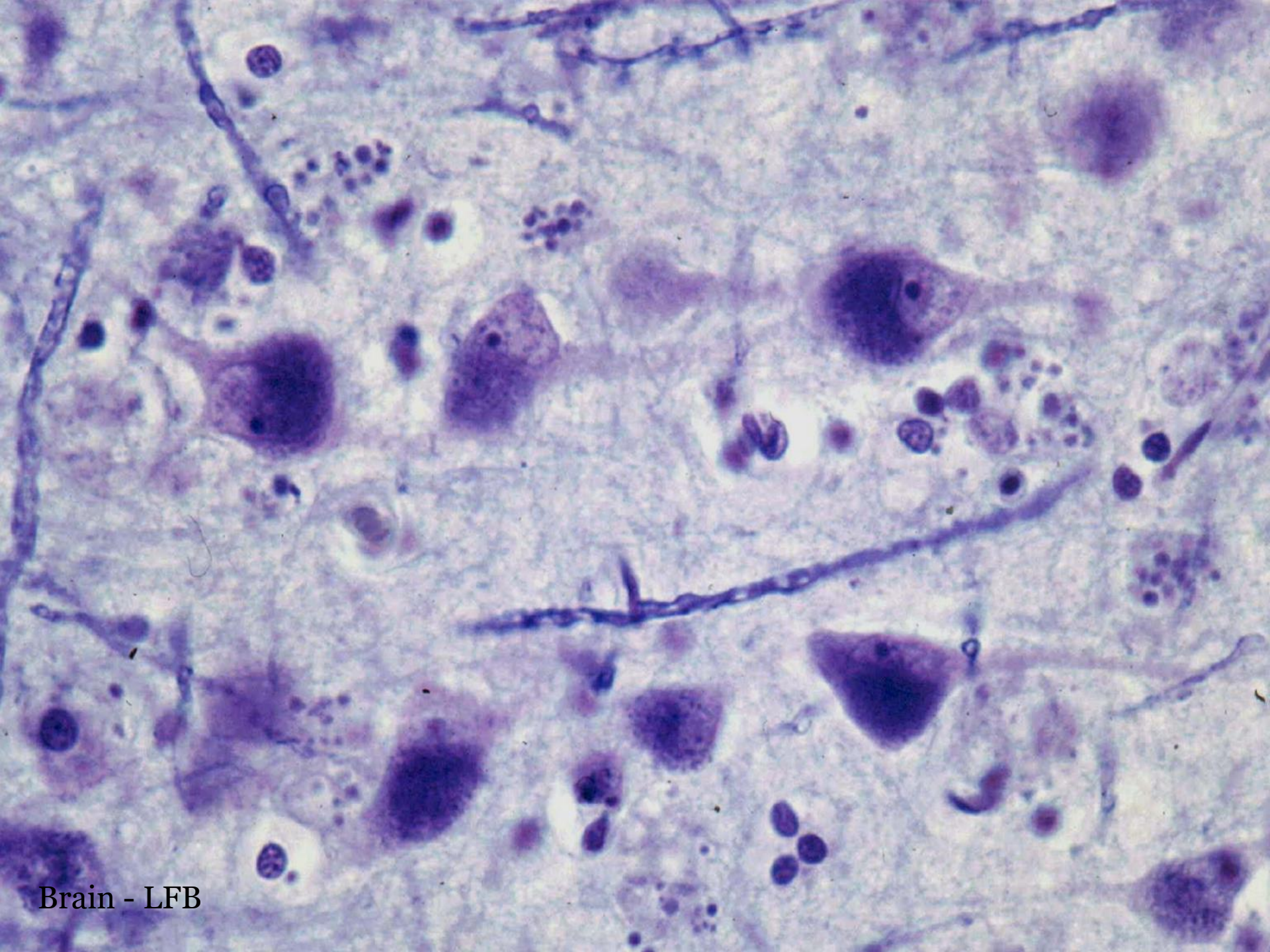
Neuronal Ceroid Lipofuscinosis

- Commonest neurodegenerative disorders of childhood
- Inherited autosomal recessive
- Progressive - visual loss, seizures and dementia
- Proteolipid deposits in lysosomes - neurones & other cell types
- 14 subtypes - based on age at clinical onset & storage inclusion appearance
- Numerous eponyms – Batten's disease

Accurate diagnosis is based on

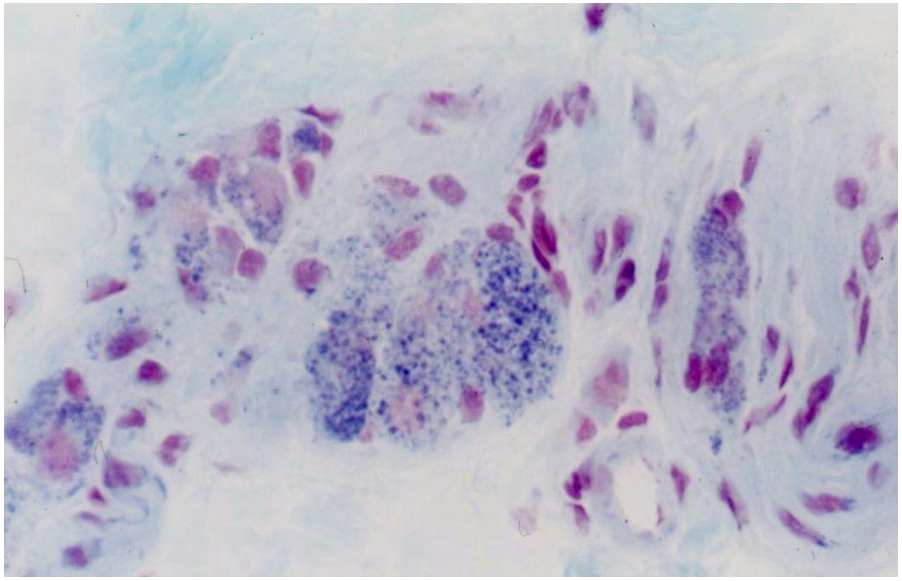
- Clinical presentation
- Age of onset
- Appropriate investigations
  - Electrophysiology (EEG,ERG,VEP)
  - Enzyme assay (PPT, TPP1)
  - Genetic studies
  - Morphological assessment

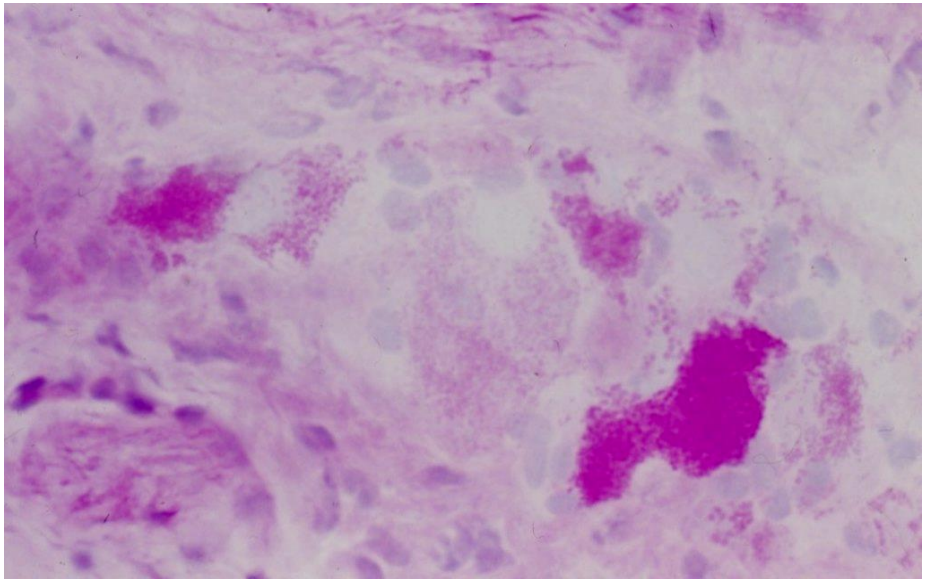

Brain - LFB

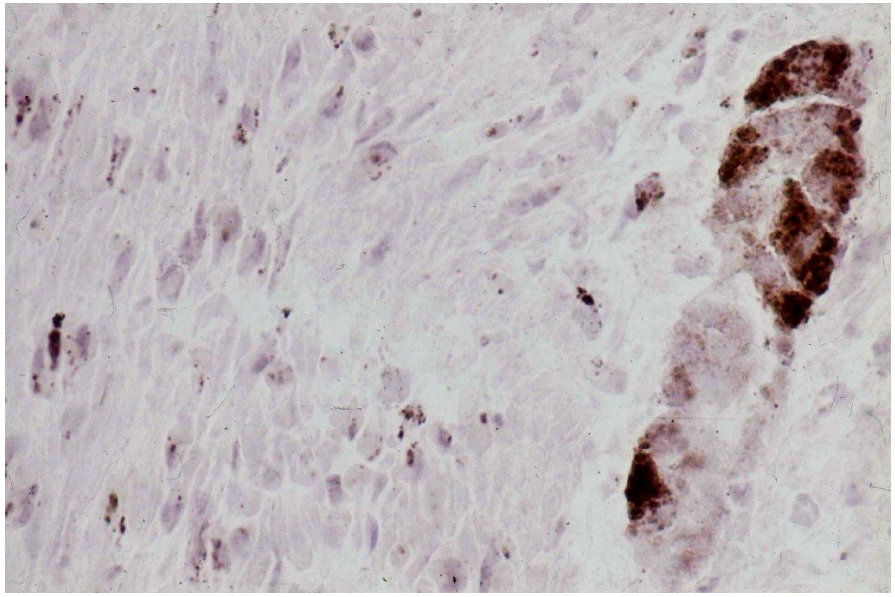
NCL diagnosis - ultrastructure

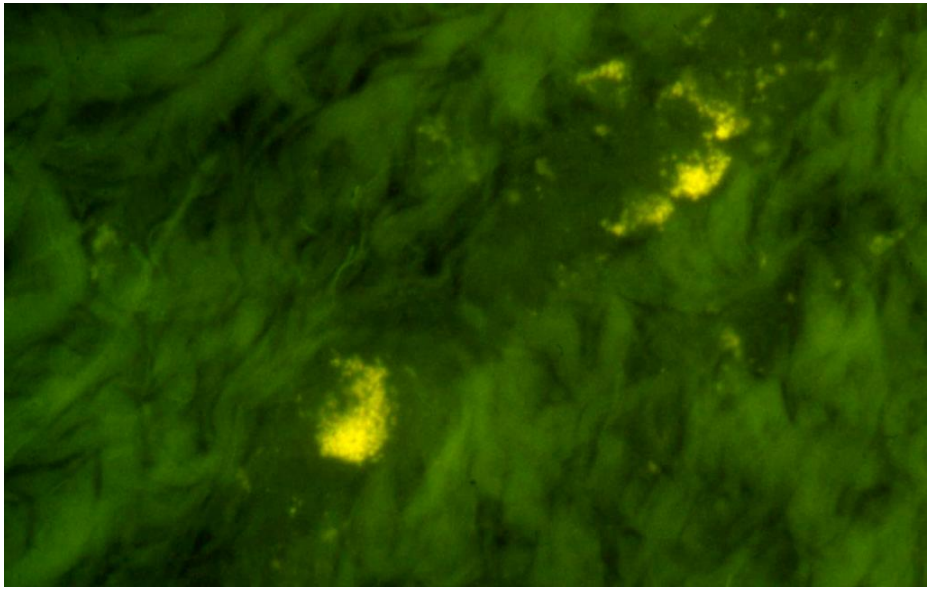
- EM the 'gold standard'
- Numerous tissue sites
  - skin, blood, rectal biopsy
- Retrospective studies
- Correlation with other disciplines for confirmation

Rectal biopsy - neurones







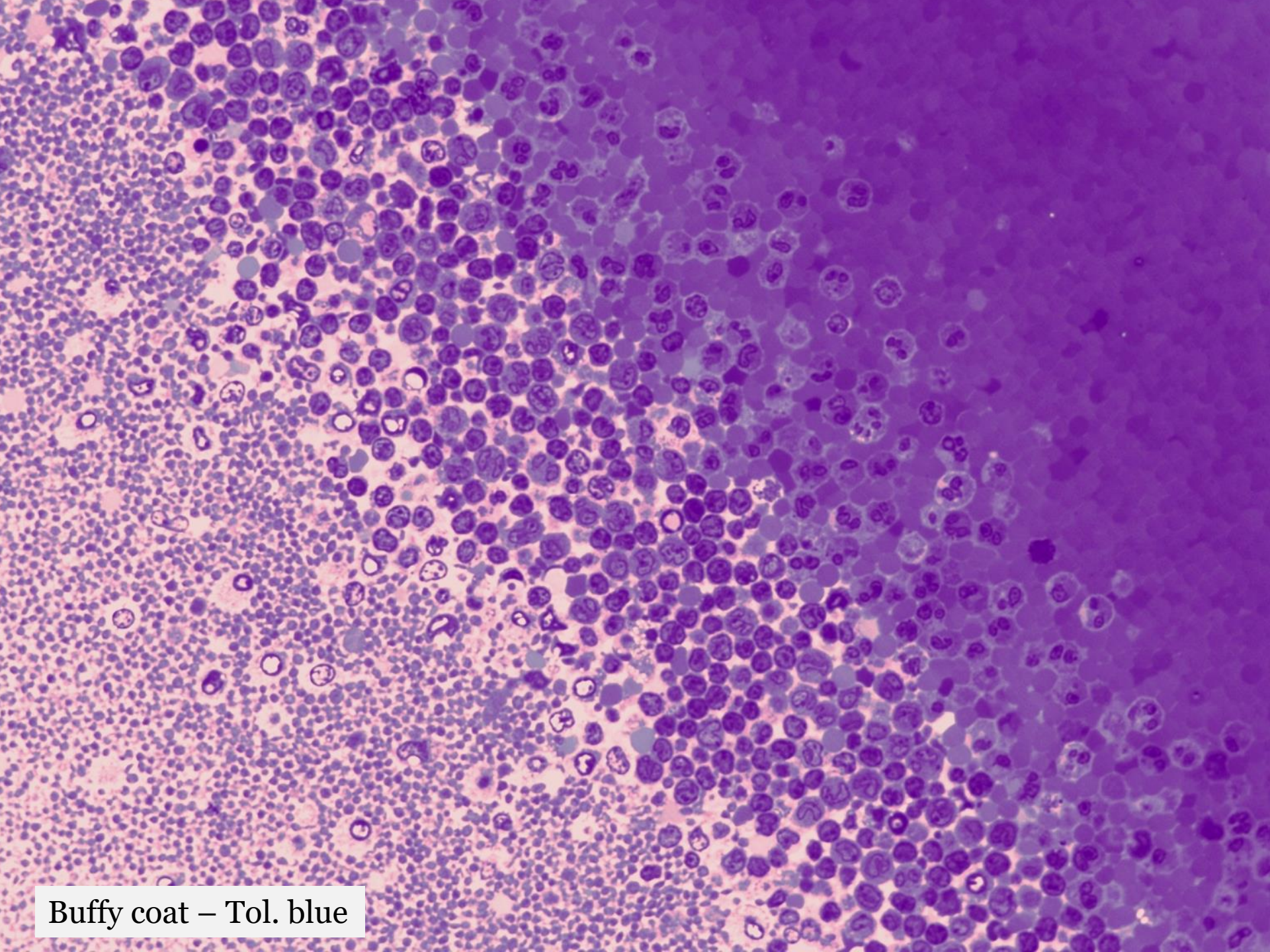


Blood buffy coat

- Blood sample – easily obtained and travels well
- Invaluable for examination of lymphocytes – NCL disease
- Other inherited metabolic conditions – blood/bone marrow
- Other white blood cells & platelet disorders

Buffy coat

- EDTA blood sample – 3 to 5 ml
- Courier to lab or store at 4 C
- Centrifuge & remove supernatant
- Fix in glutaraldehyde
- Process button of cells to EM


Buffy coat – Tol. blue

Batten disease - blood

- CLN 1: Infantile – granular osmiophilic deposits
- CLN 2: Late infantile – curvilinear bodies
- CLN 3: Juvenile – large vacuoles with fingerprint profiles
- CLN 4: Adult form – no data

Batten disease variants - blood

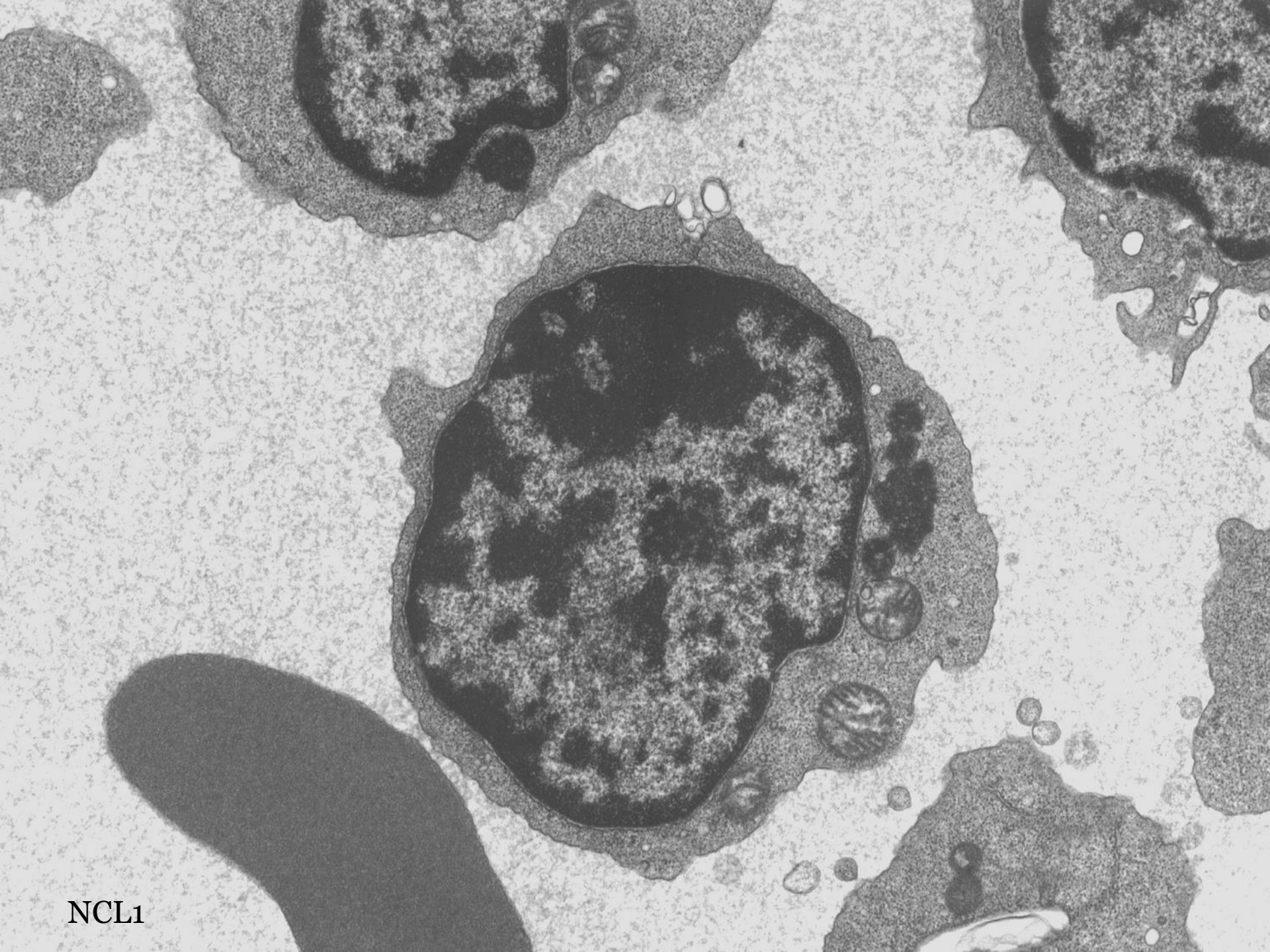
- CLN5: Finnish variant late infantile form – no inclusions reported
- CLN6: Early juvenile/ late infantile variant – very few dense fingerprint inclusions, no vacuolation
- CLN7: Turkish variant – lipopigments with fingerprint profiles
- CLN8: Northern epilepsy – osmiophilic granules

Batten disease variants - blood

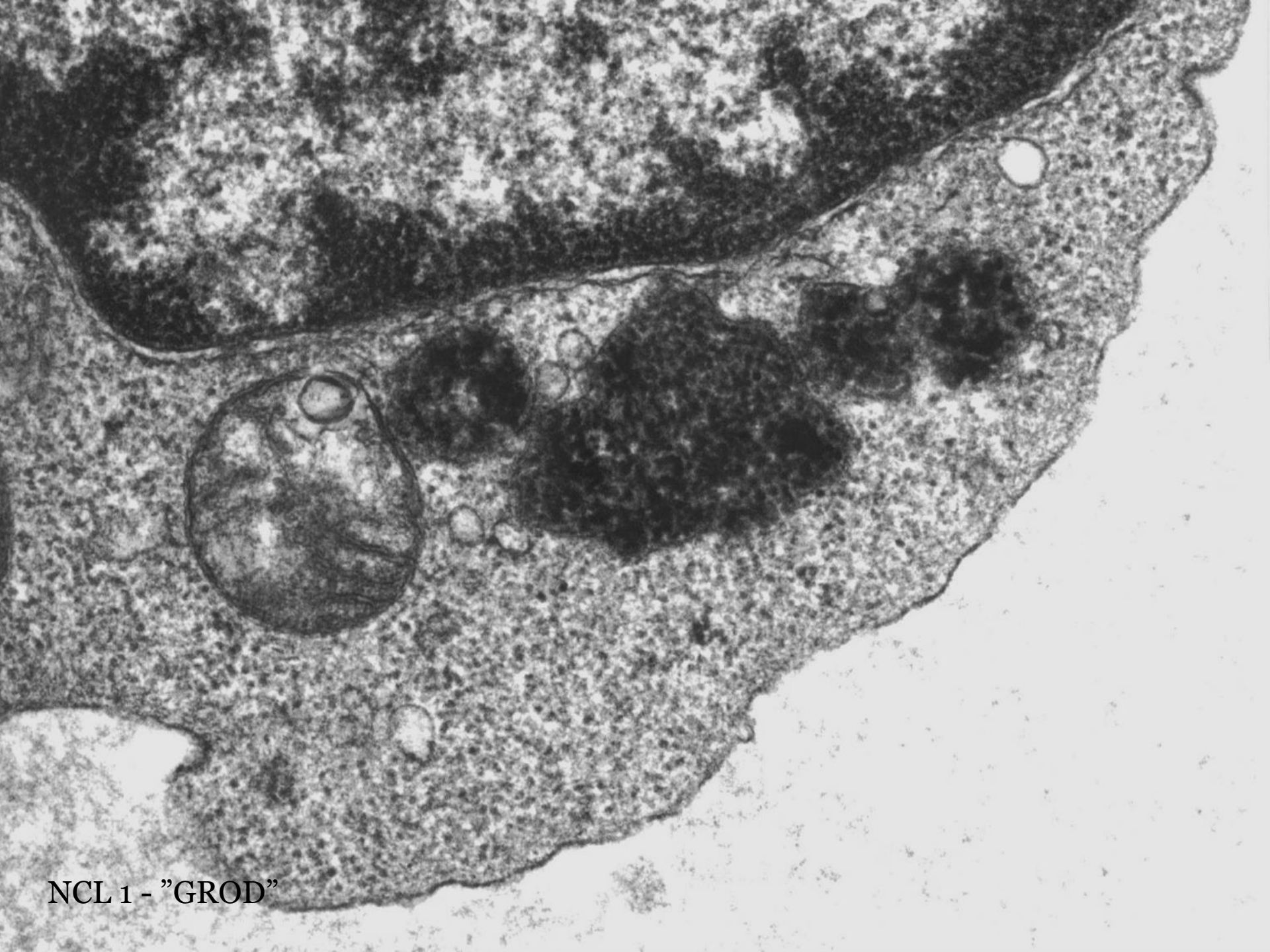
- CLN9: Similar to JNCL but no vacuoles
- CLN10: Cathepsin D gene, congenital, no storage reported
- CLN11: GRN (progranulin) adult onset no data
- CLN12: ATP13A2 mutation with juvenile onset, lipopigment reported
- CLN14: KCTD7 infantile mutation

Infantile NCL

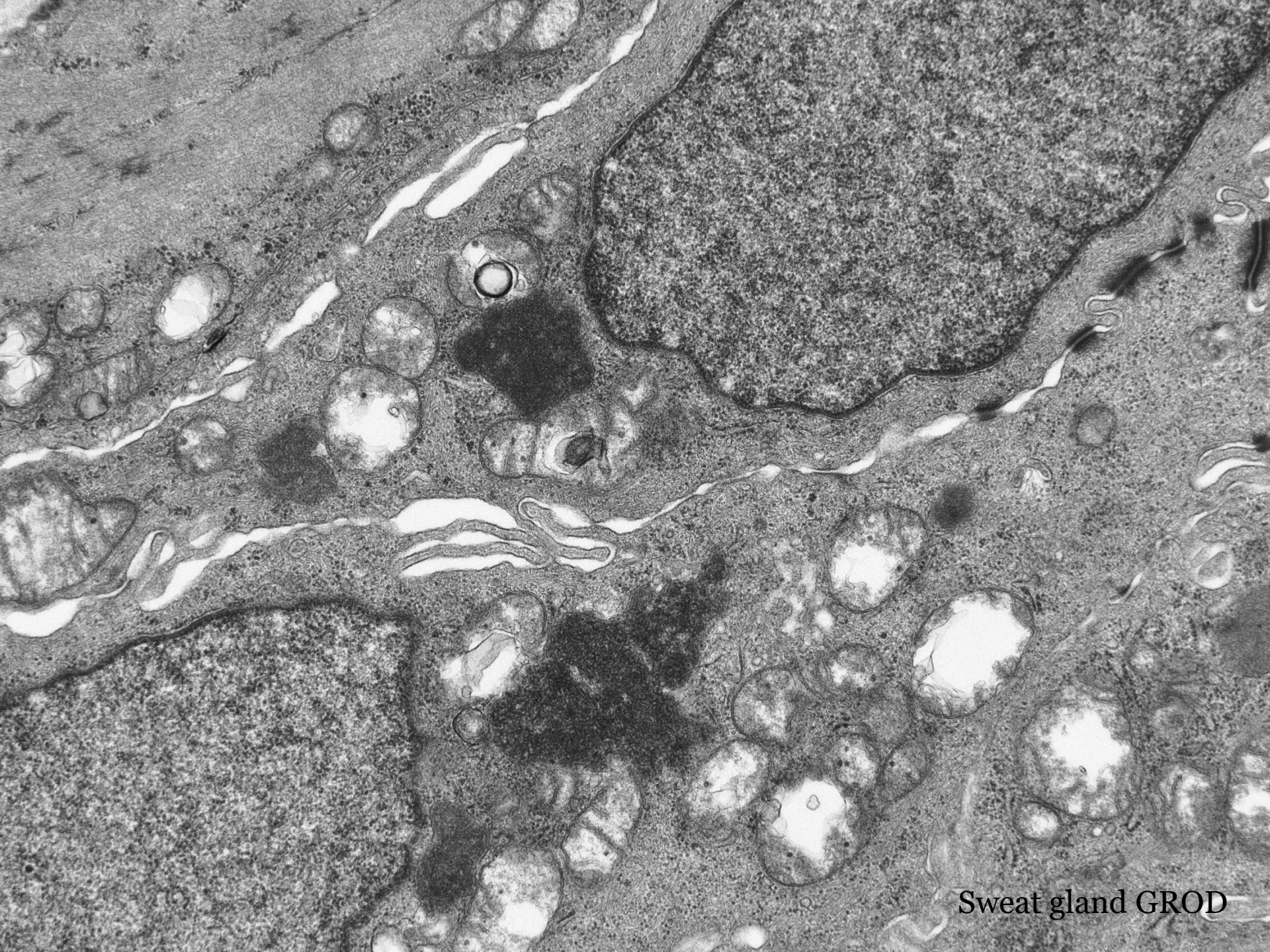
- Mutation in PPT1 gene
- Infantile onset – 6mths to 2 yrs
- Juvenile form
- Rapid progression, FTT, microcephaly, myoclonic jerks
- Life expectancy 5 yrs

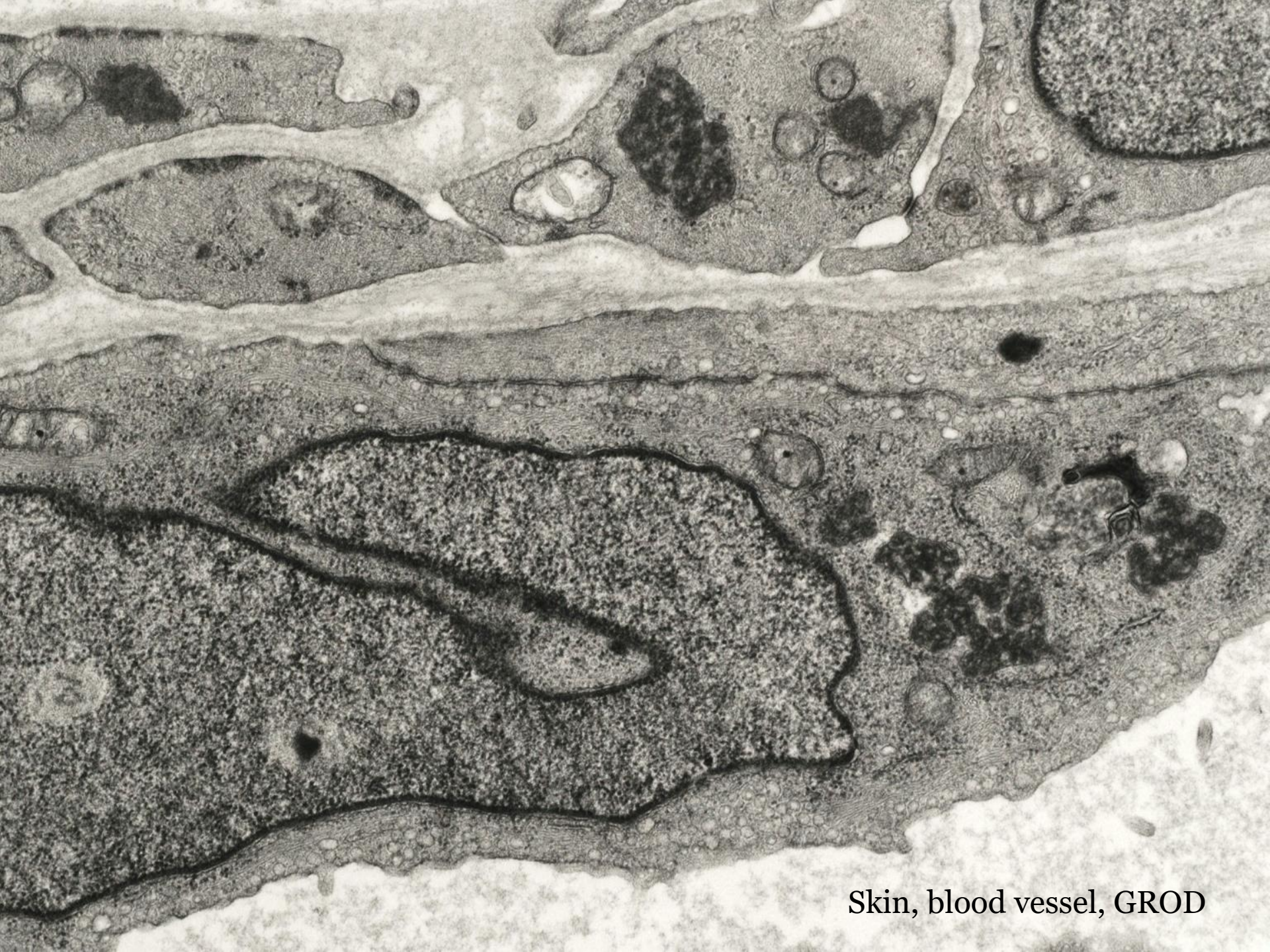


NCL1



NCL 1 - ”GROD”

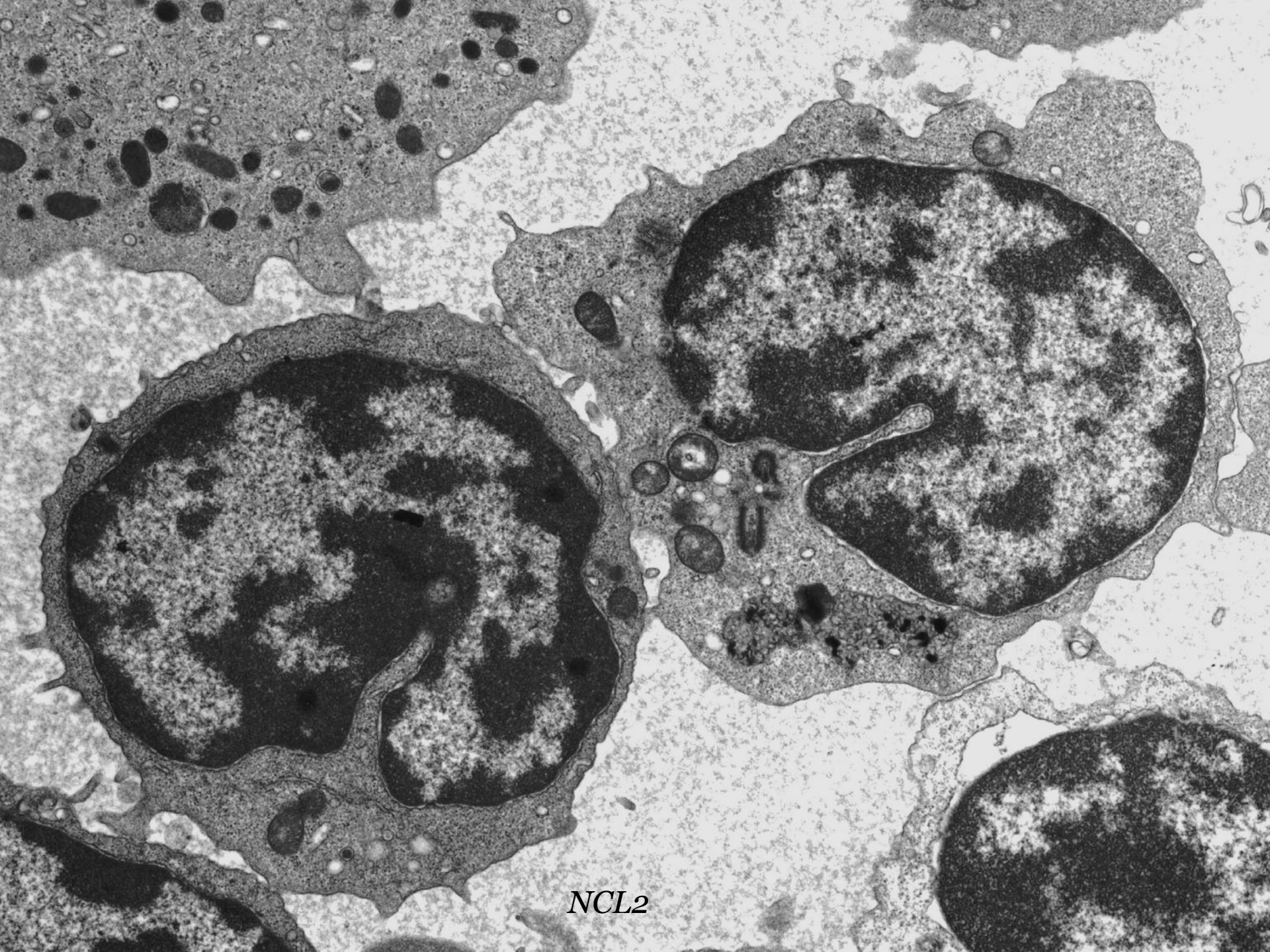

Sweat gland GROD



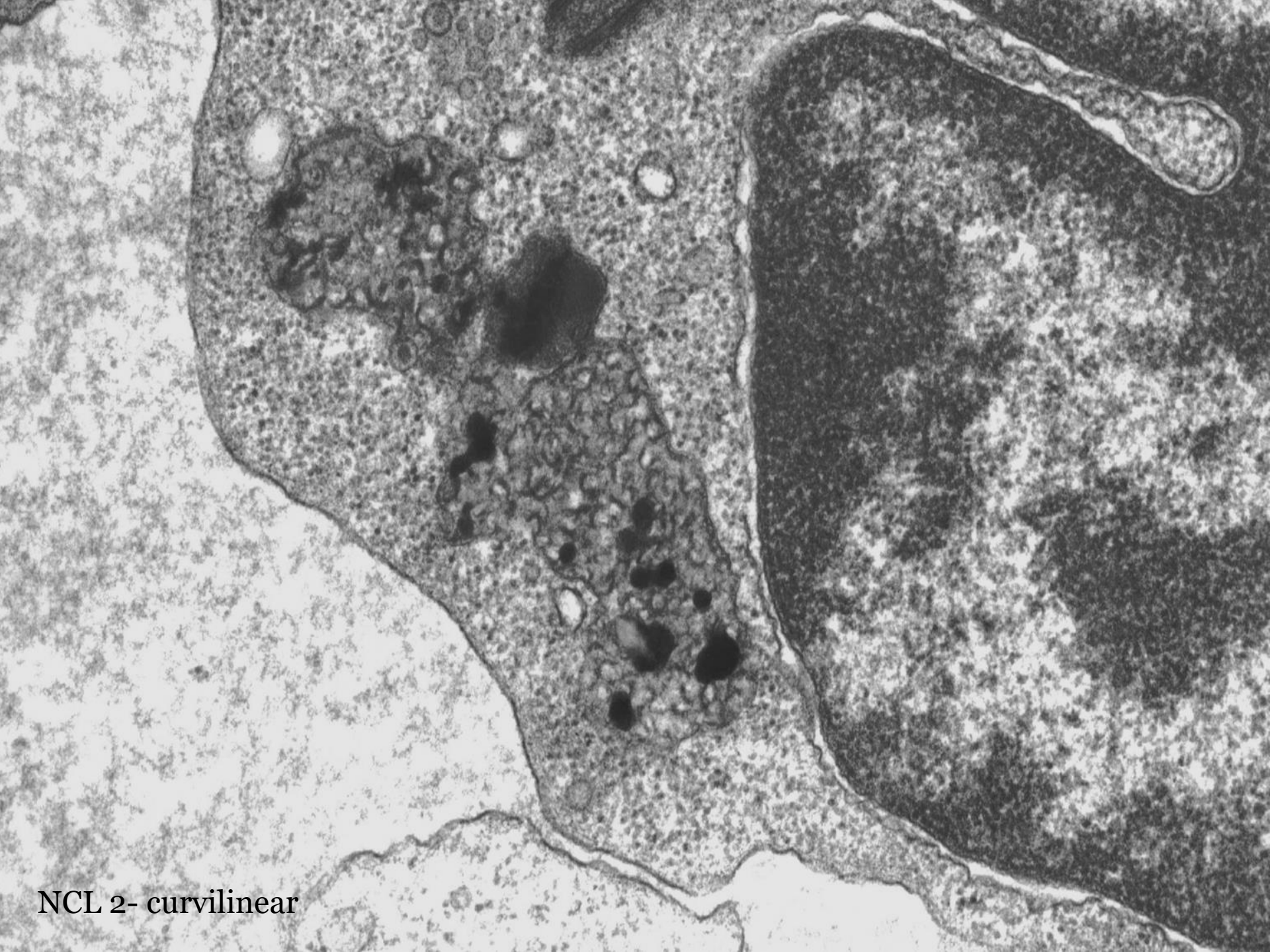
Skin, blood vessel, GROD

Late infantile NCL

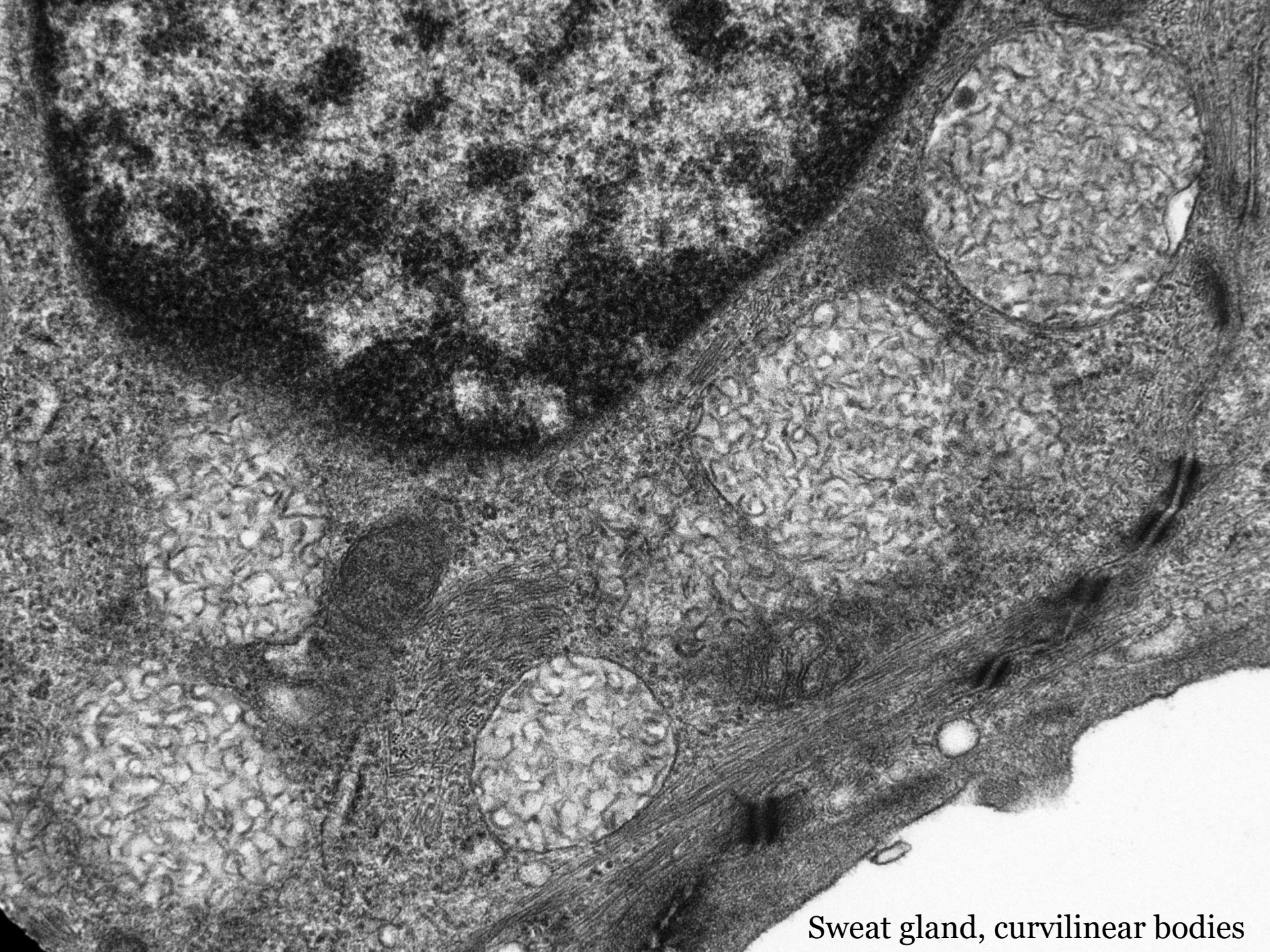
- Mutation in TPP1 gene
- Symptoms appear 2-4 yrs
- Epilepsy, regression of development, myotonic ataxia
- Visual impairment 4-6 yrs
- Life expectancy 6 yrs to early teens



NCL2



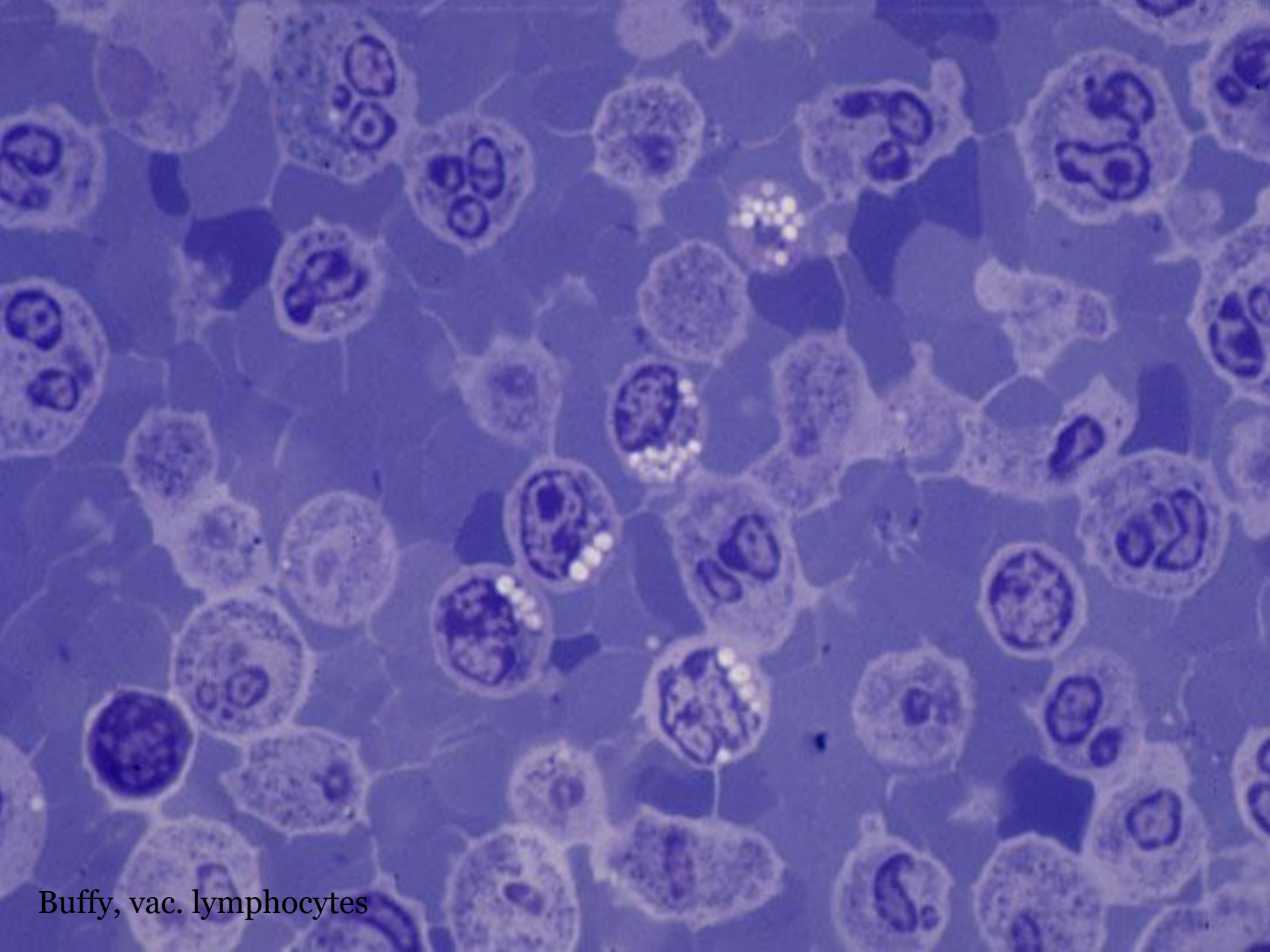
NCL 2- curvilinear



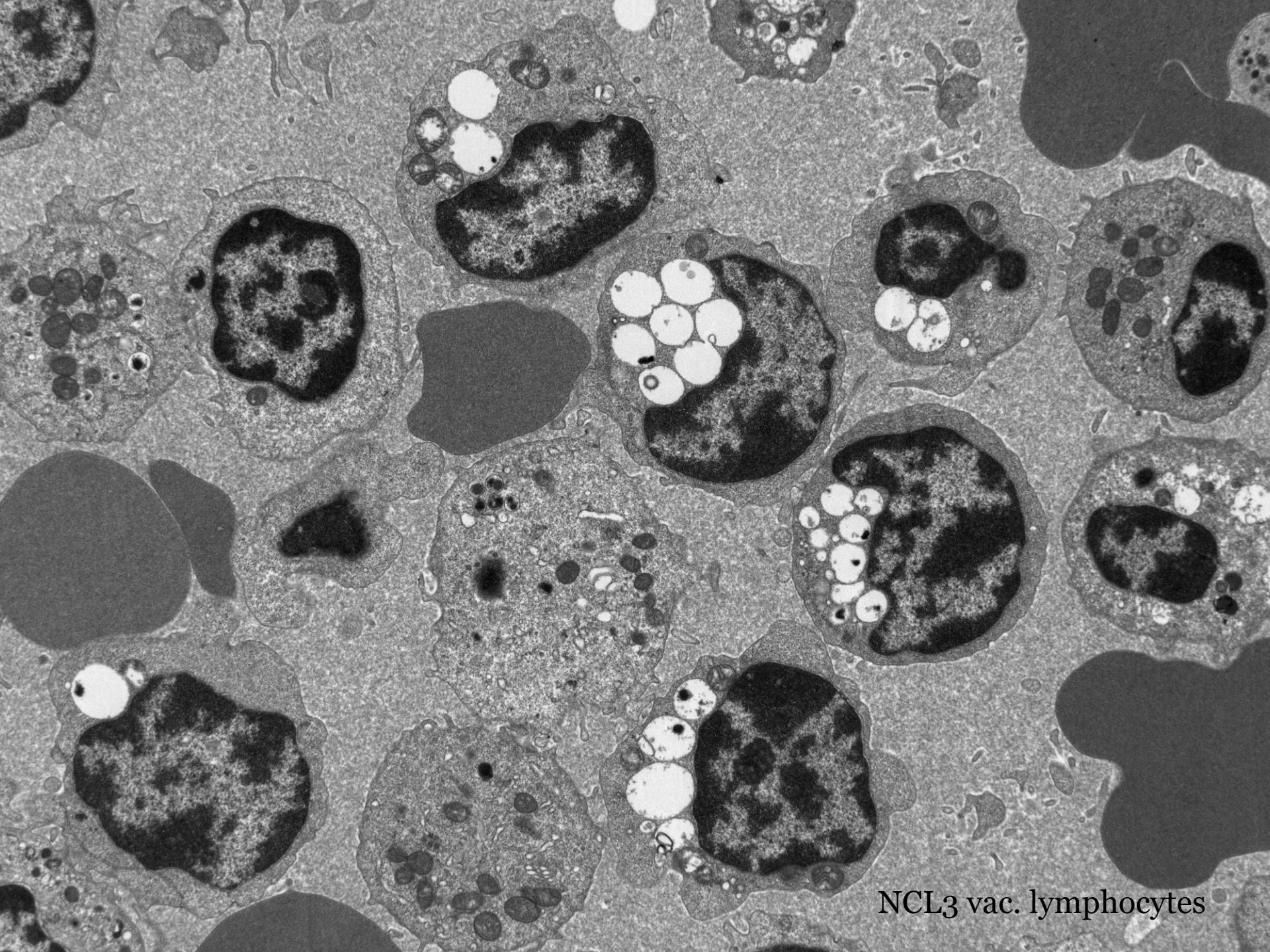
Sweat gland, curvilinear bodies

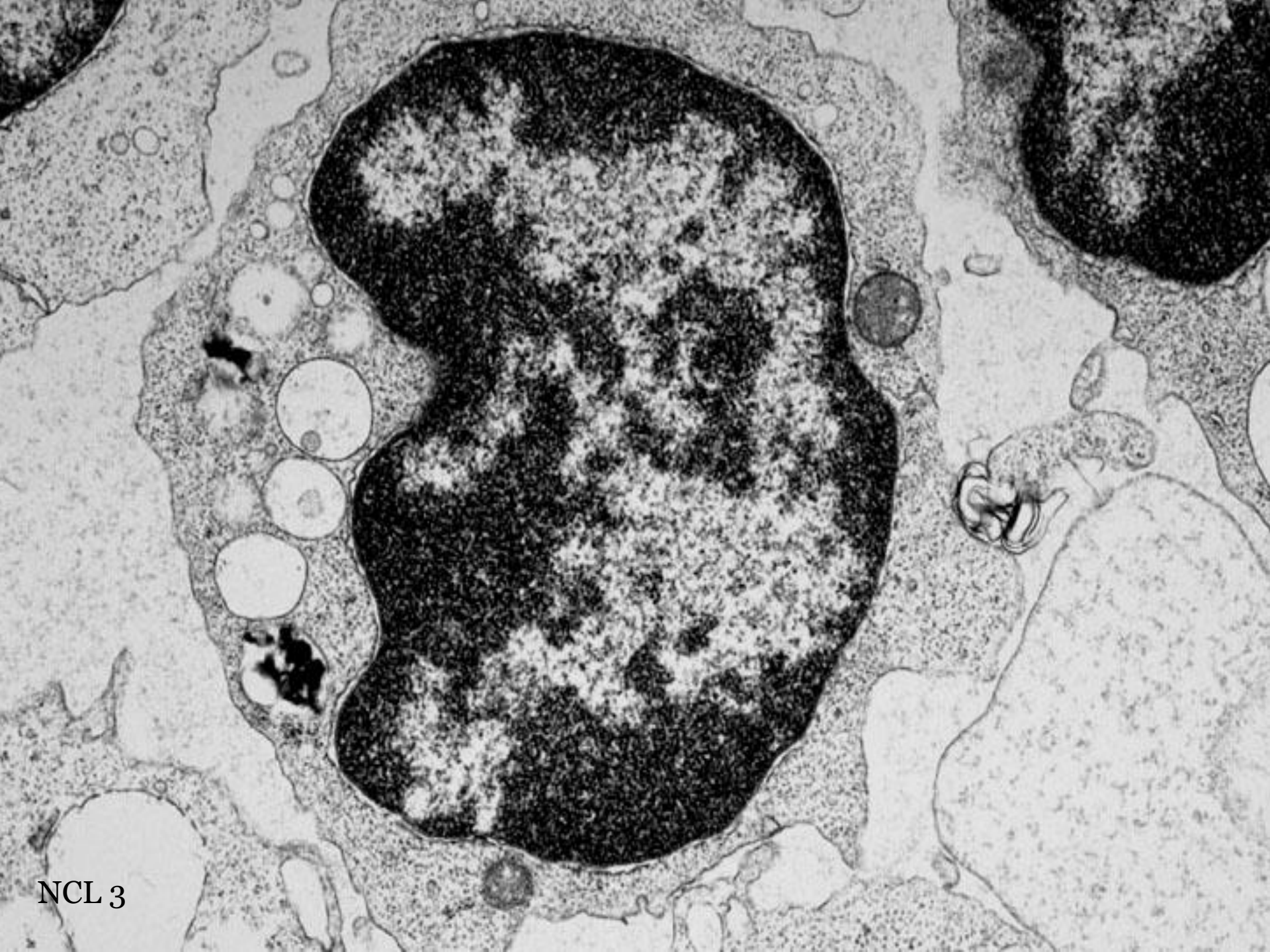
Juvenile NCL

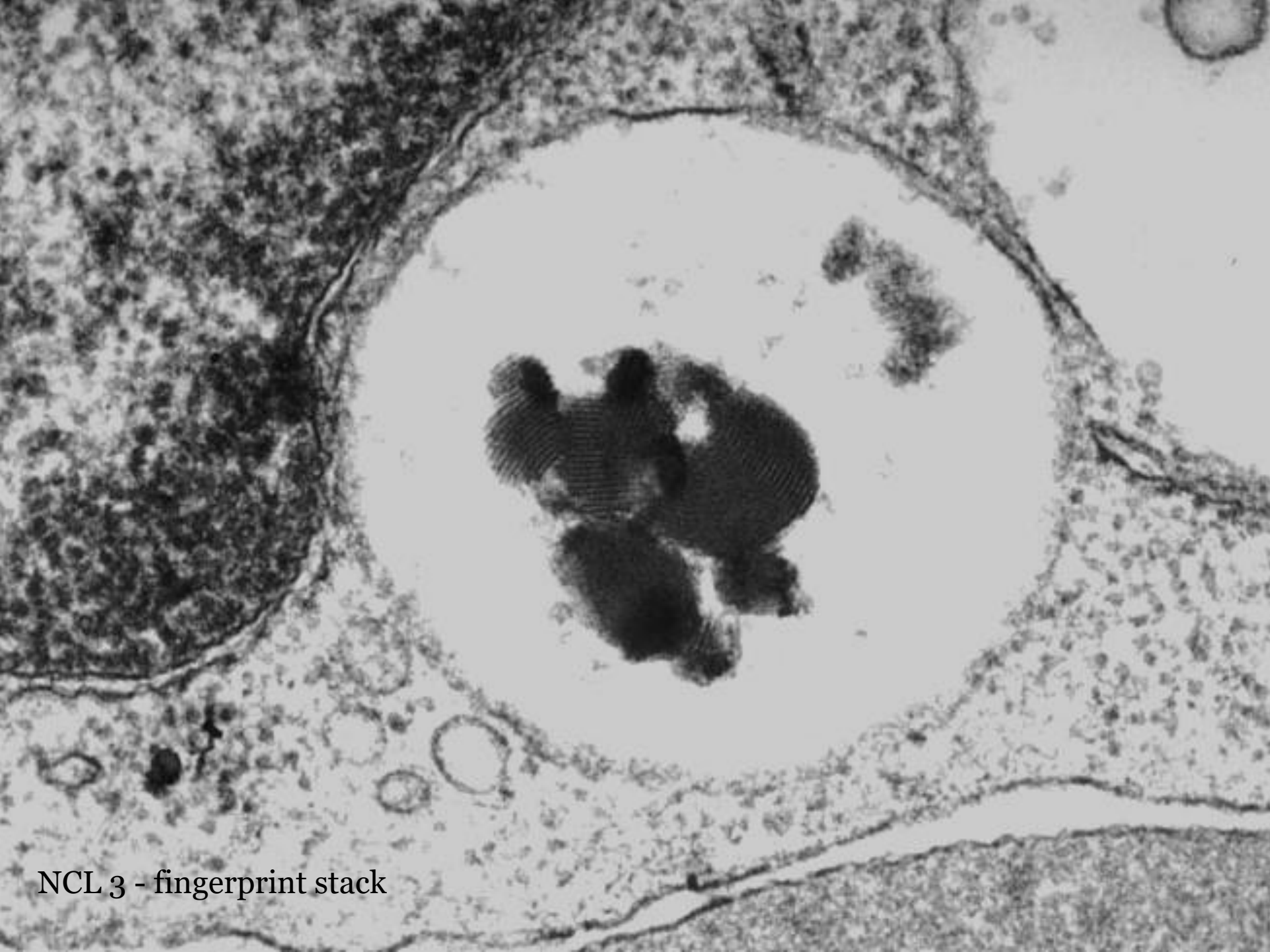
- Onset 4-10 yrs
- Rapid visual loss
- Epilepsy with generalised tonic-clonic seizures
- Life expectancy late teen to 30's
- Vacuolated lymphocytes



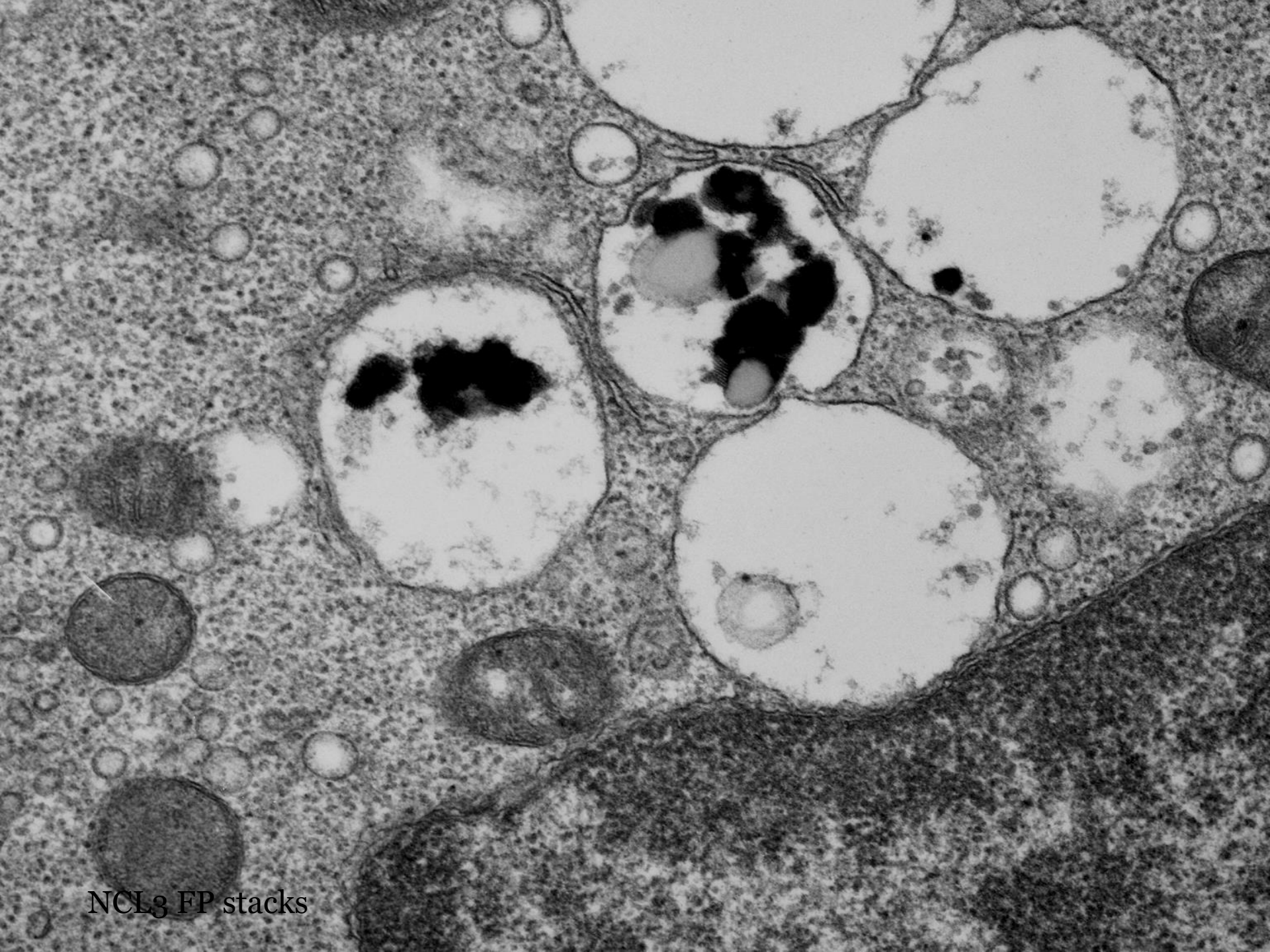
Buffy, vac. lymphocytes

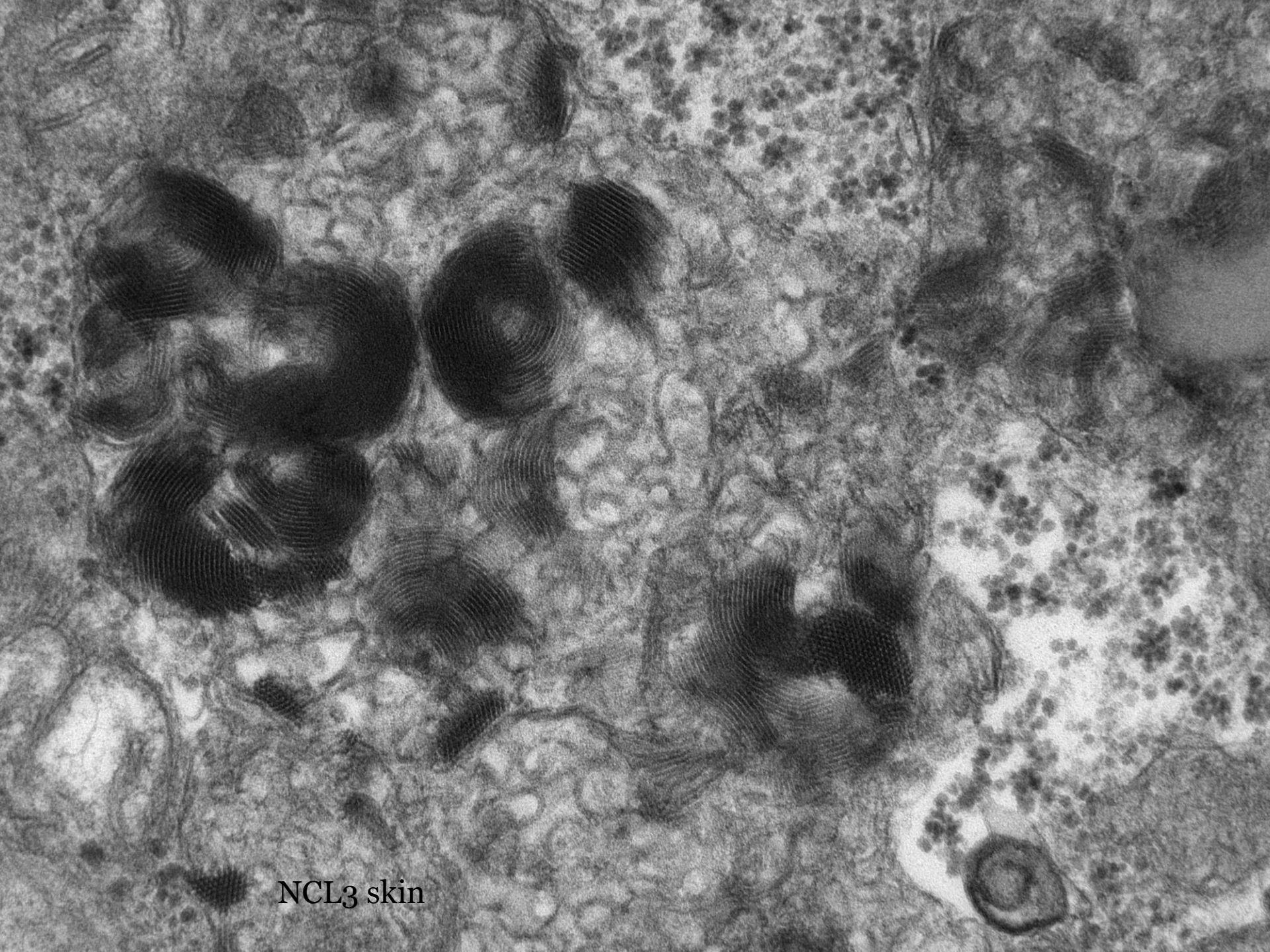

NCL3 vac. lymphocytes


NCL 3



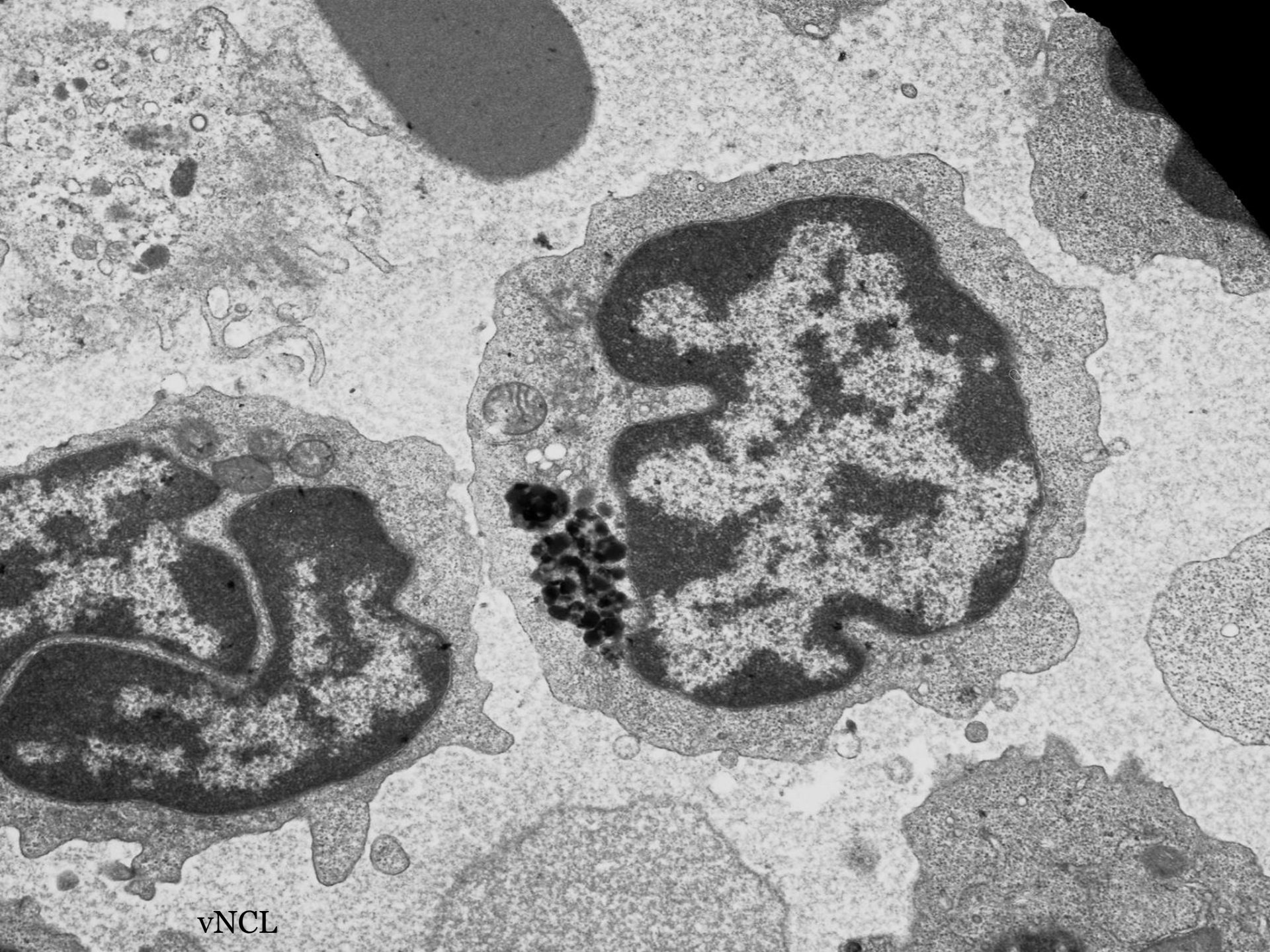
NCL 3 - fingerprint stack

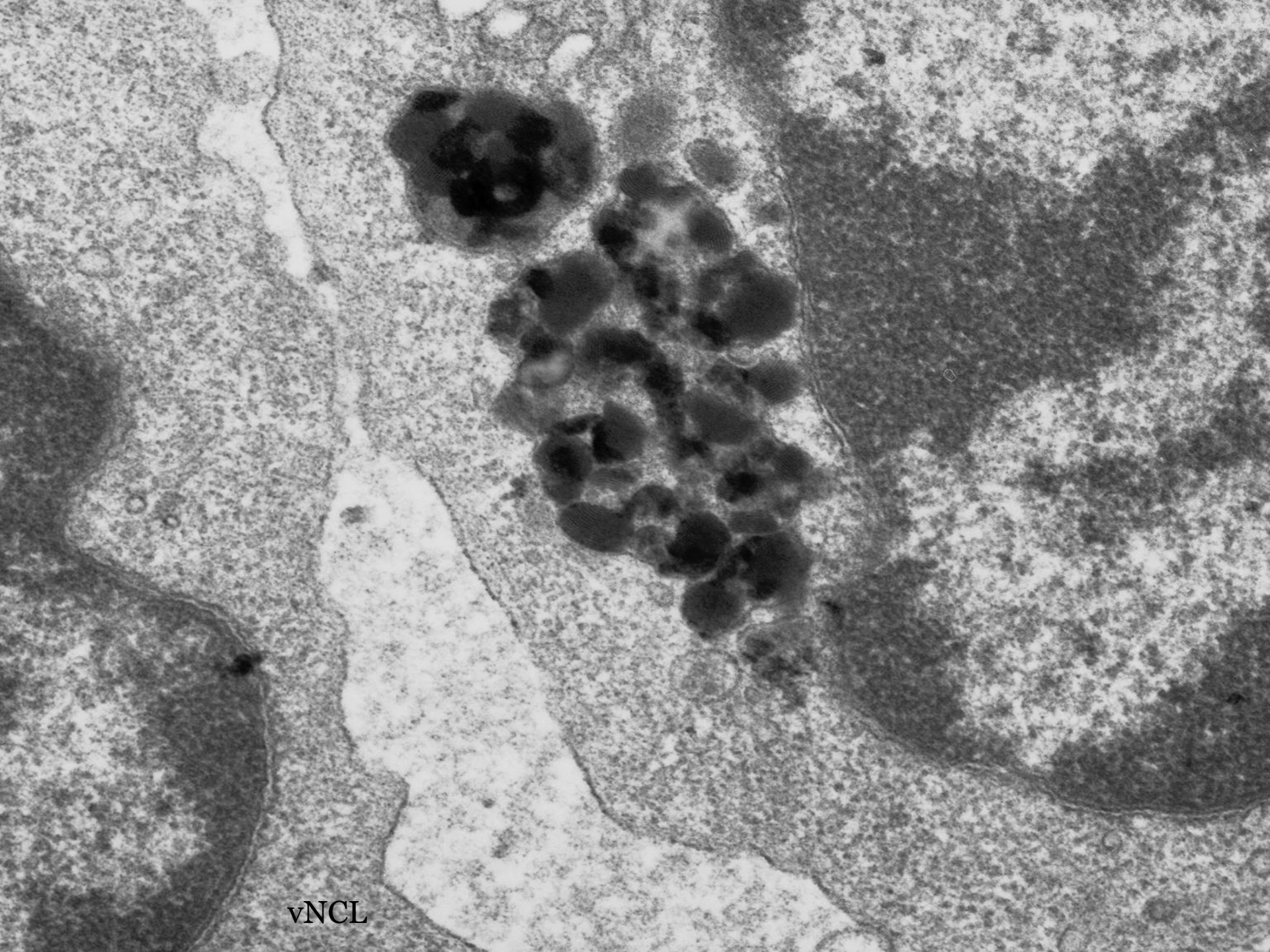

NCL3 FP stacks

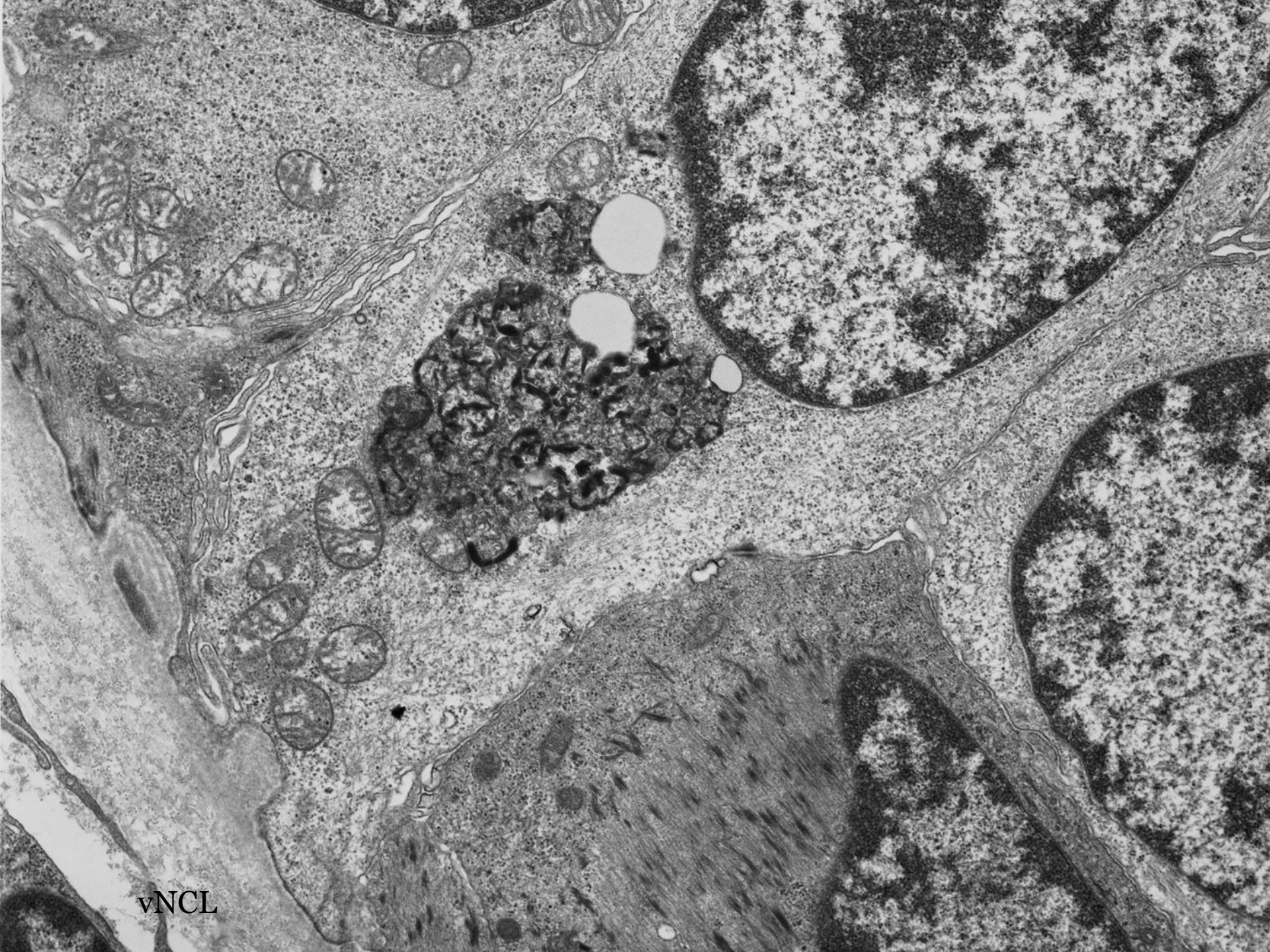

NCL3 skin

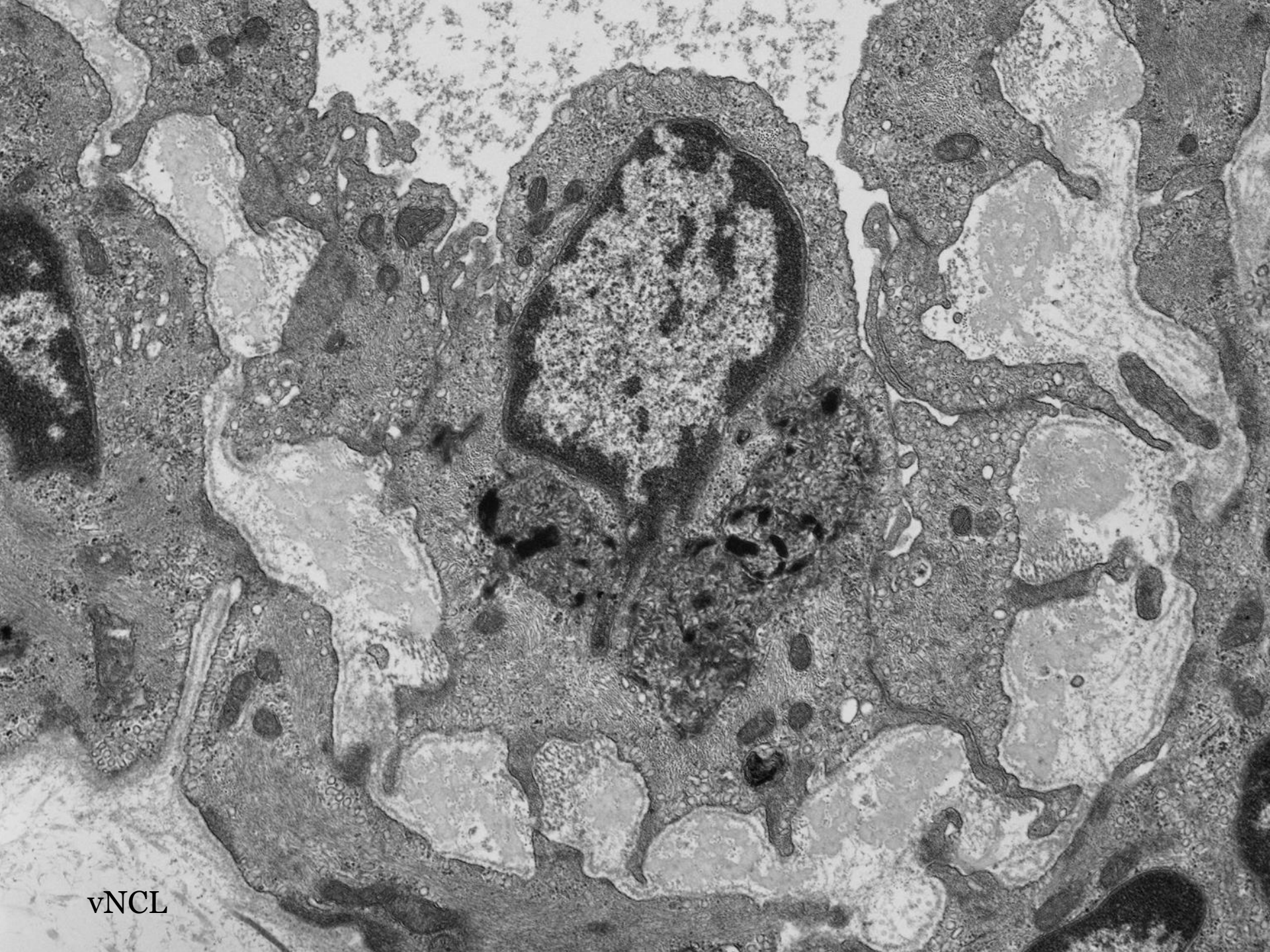
Variant NCL

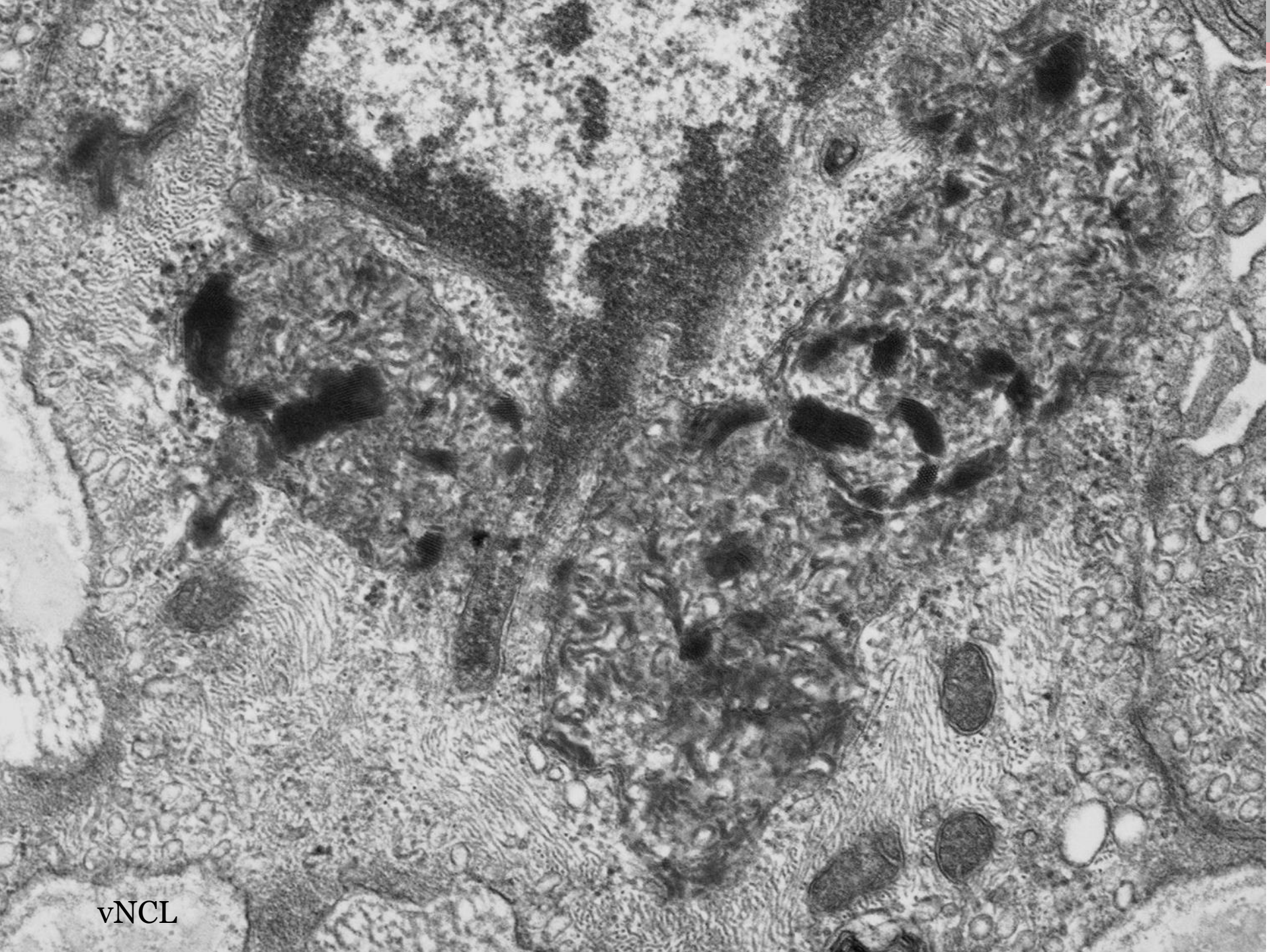
- Numerous genes identified
- Progression of disease may be variable
- All clinical symptoms described previously may be present
- Genetic testing essential


vNCL


vNCL

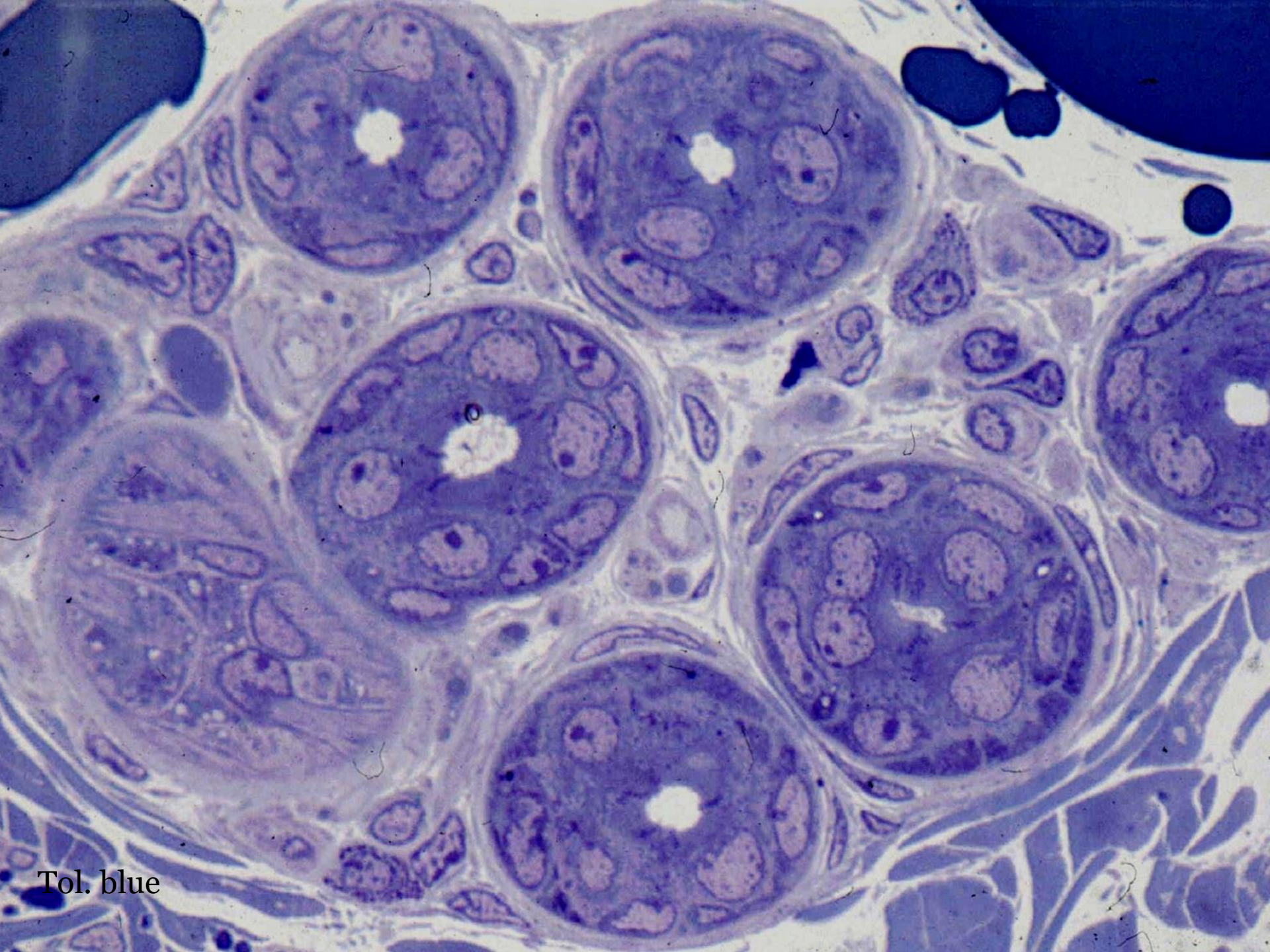

vNCL

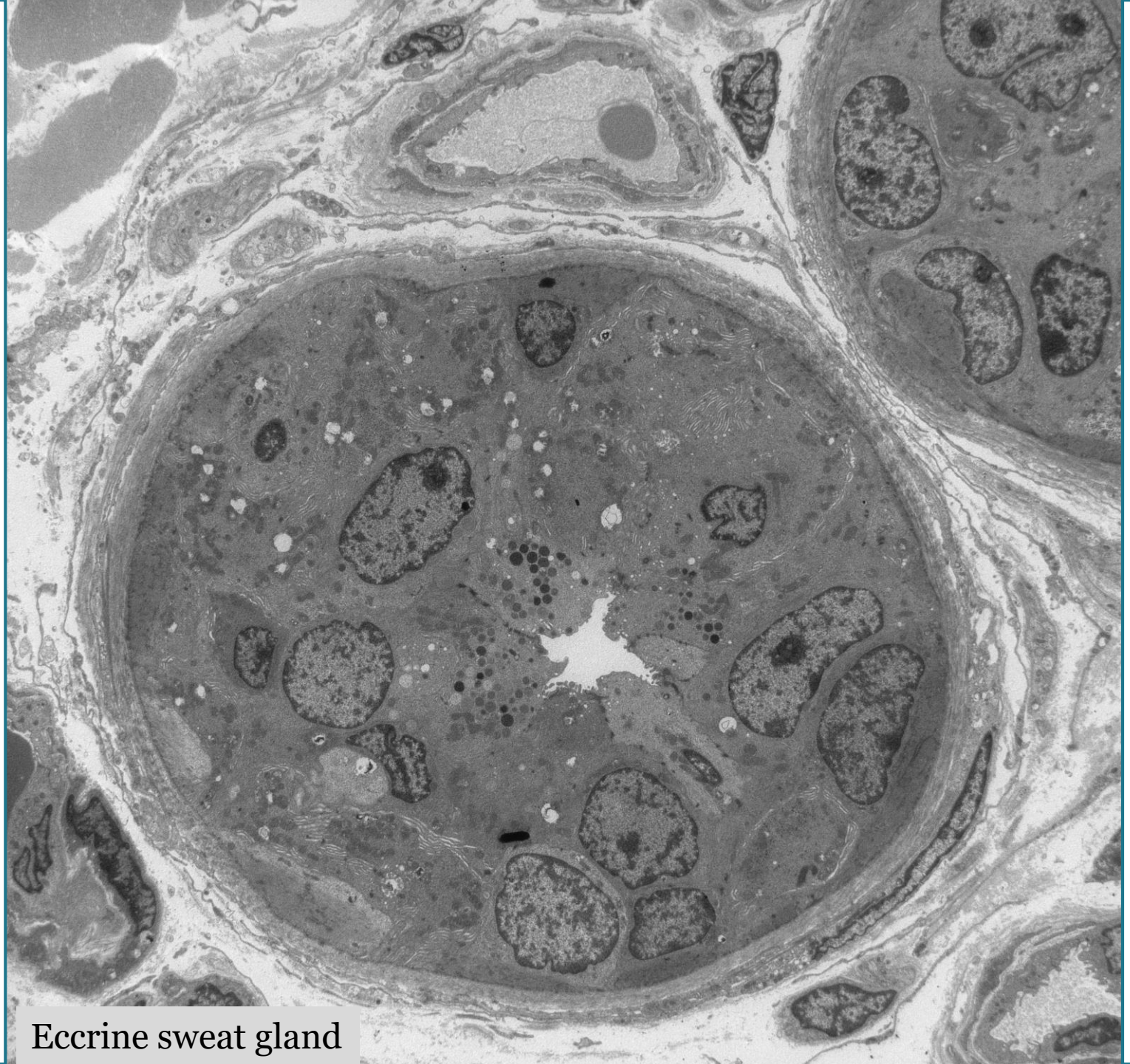

vNCL


vNCL

Skin

- NCL's
- Neuroaxonal dystrophy
- Lafora disease
- Other storage conditions
- Other pathology – LCH, EB, collagen disorders

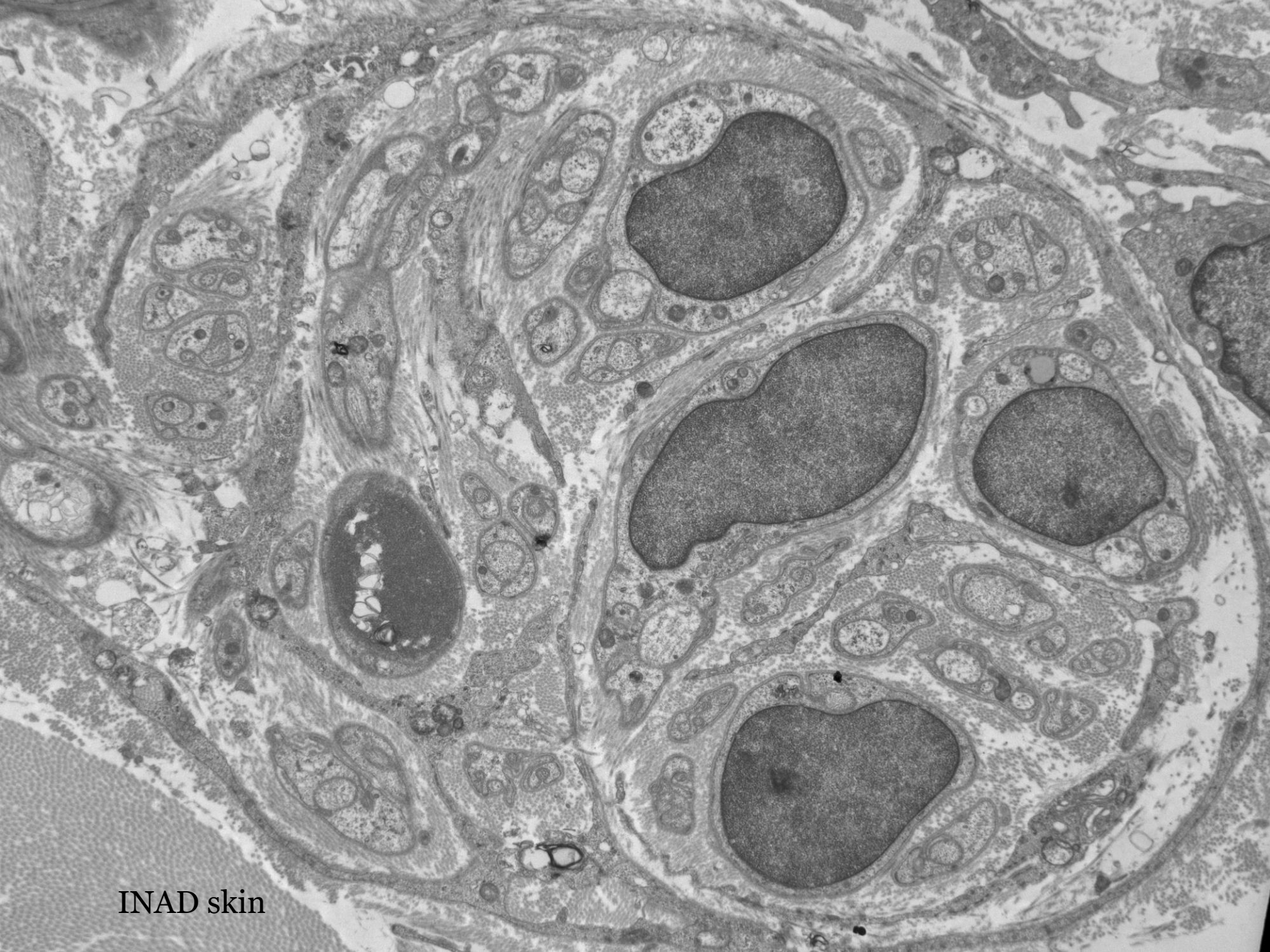

Tol. blue

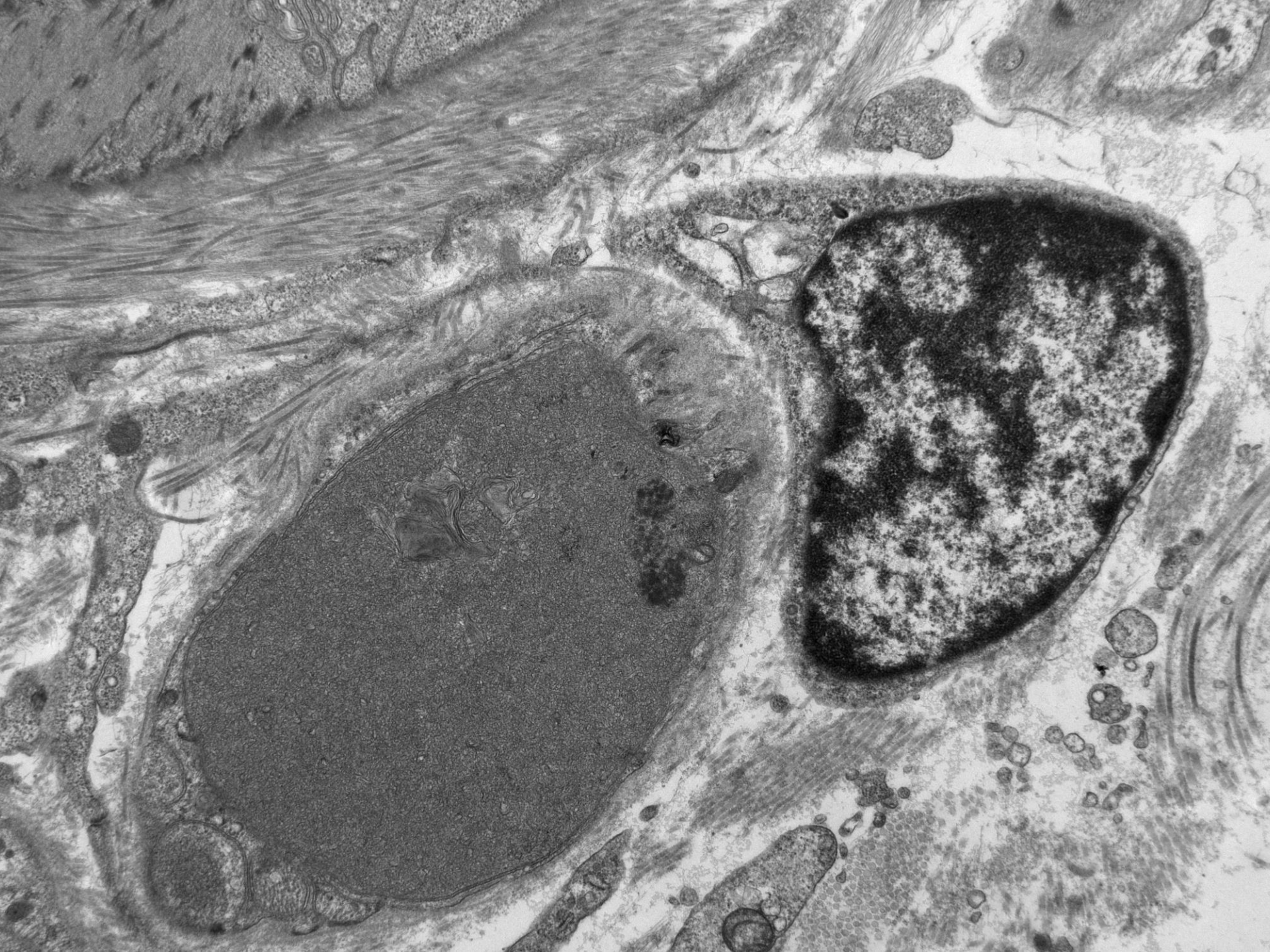


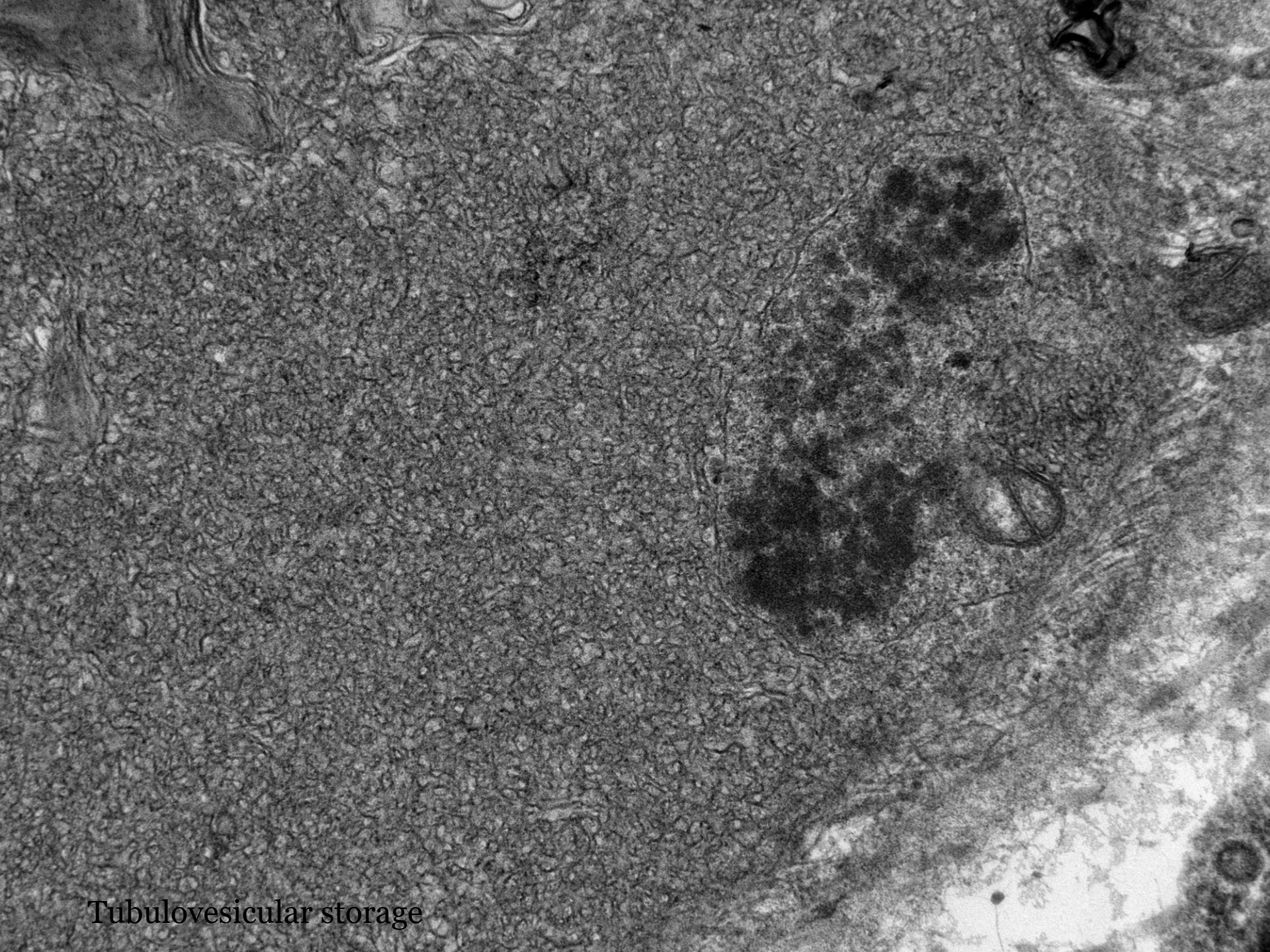
Eccrine sweat gland

Infantile neuroaxonal dystrophy

- AR inheritance in infancy
- Progressive
- Characterised by – weakness, spasticity, cerebellar signs, deafness & visual impairment, cognitive decline
- Late infantile and juvenile forms
- Mutations in PLA2G6


INAD skin

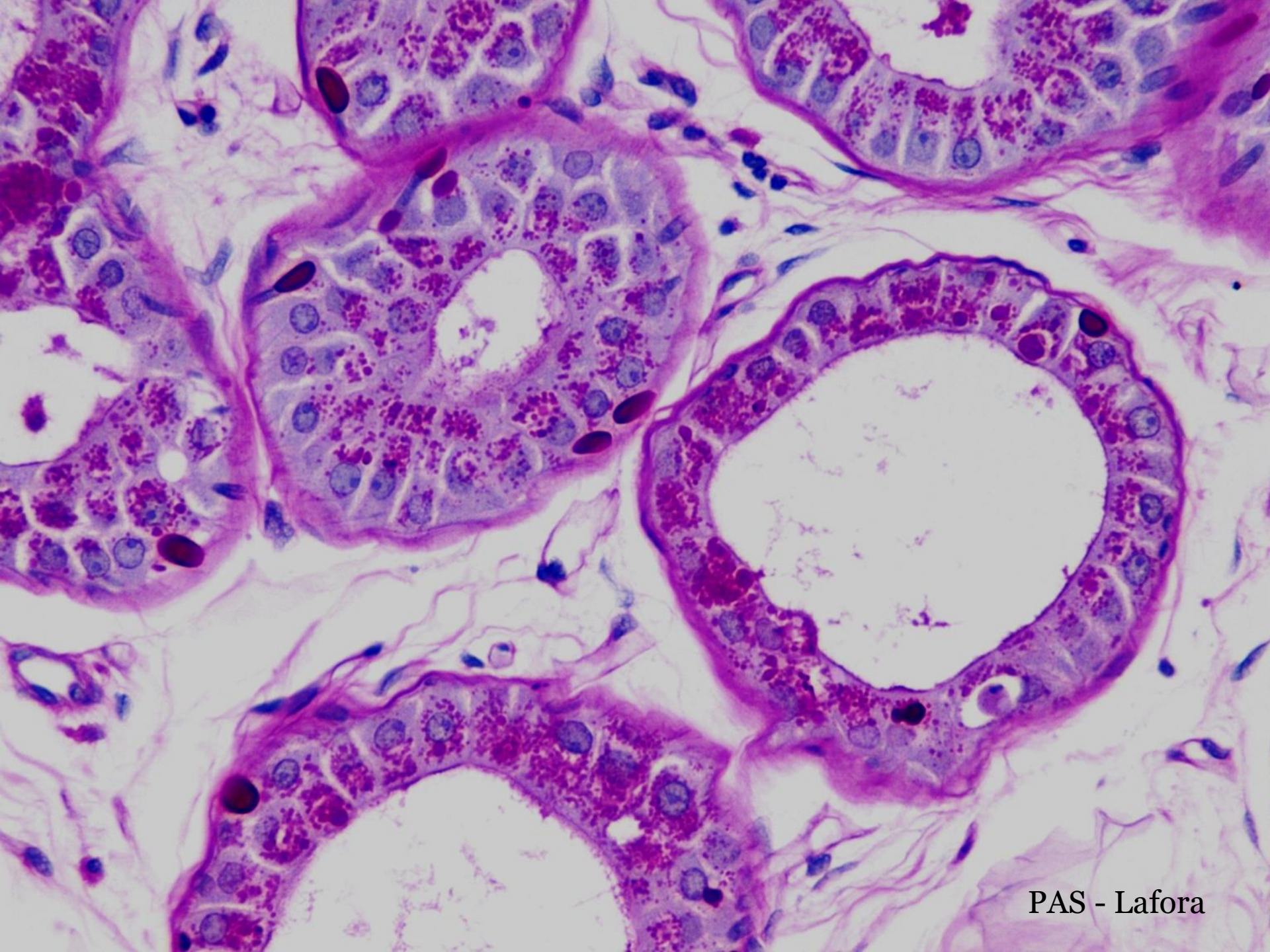


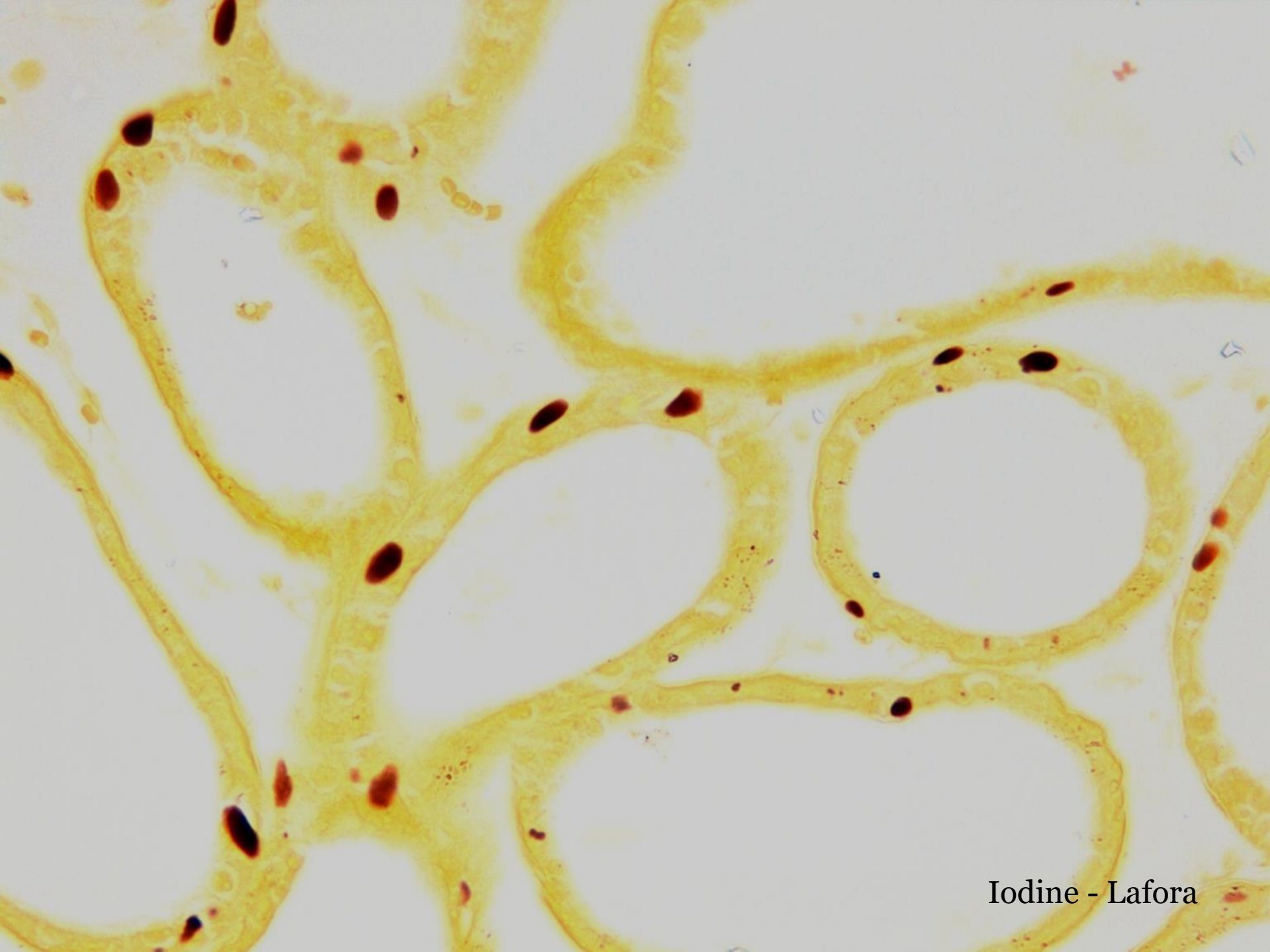


Tubulovesicular storage

Lafora body disease

- Progressive myoclonic epilepsy
- Polyglucosan bodies – Lafora
- Onset in late childhood/early adolescence
- Myoclonus, seizures and visual problems
- Neurological deficit – cerebellar degeneration, dementia, pyramidal tract signs
- EMP2A and EMP2B genes associated


PAS - Lafora


Iodine - Lafora

Lafora inclusion body

Skin LSD EM

- Mucopolysaccharidoses - vacuolation of ESG, granular storage
- Oligosaccharidoses - Fucosidosis, Mannosidosis, Sialidosis – vacuoles, lamellar storage
- GSD2 – lysosomal glycogen
- Sphingolipidoses - Fabrys, MLD, Krabbe – characteristic storage material

Prenatal diagnosis

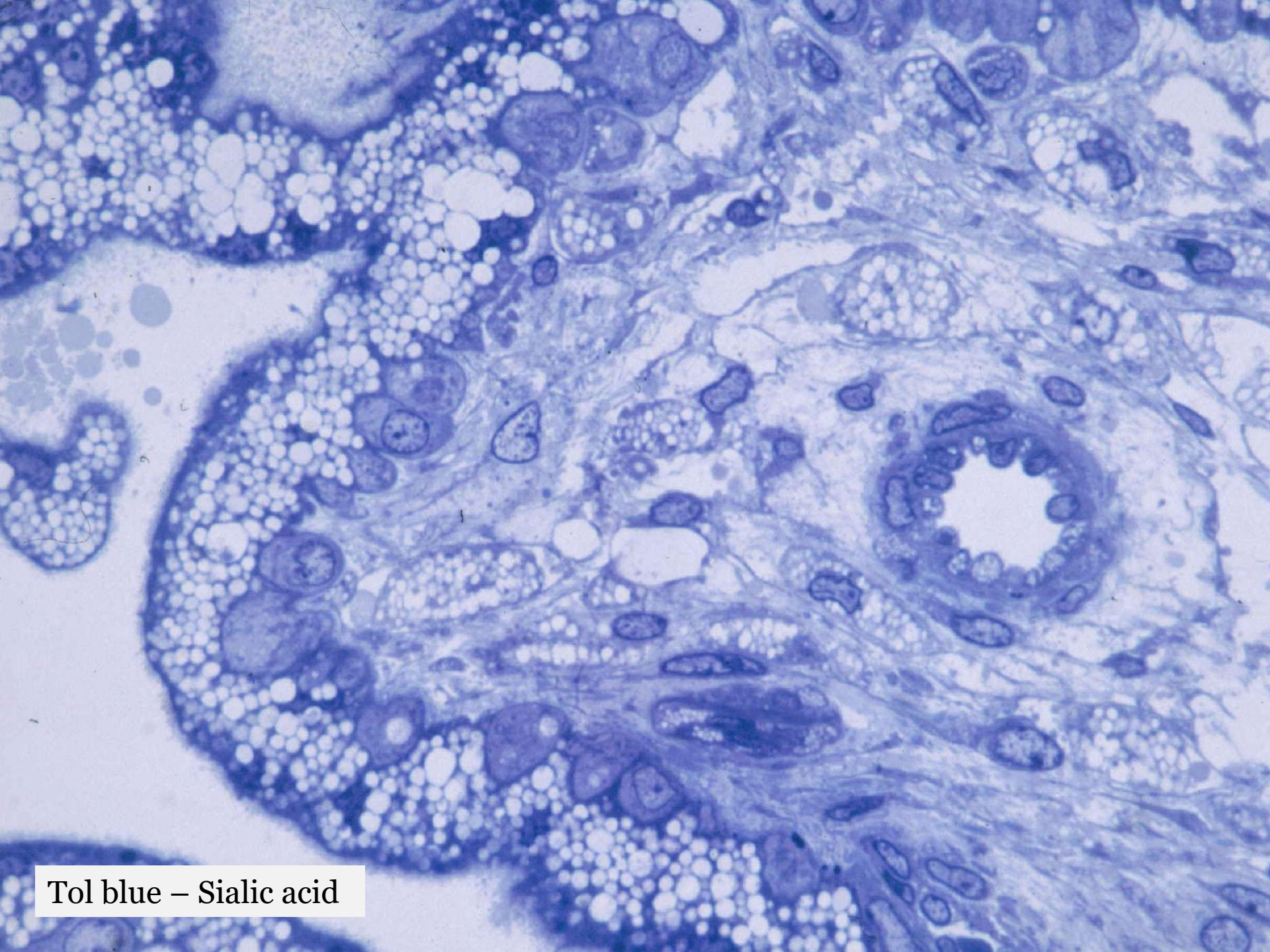
Cellular pathology support:

- Various tissue types – blood, skin, muscle
- Chorionic villous sample
- In conjunction with enzymology or genetics
- Index case a prerequisite

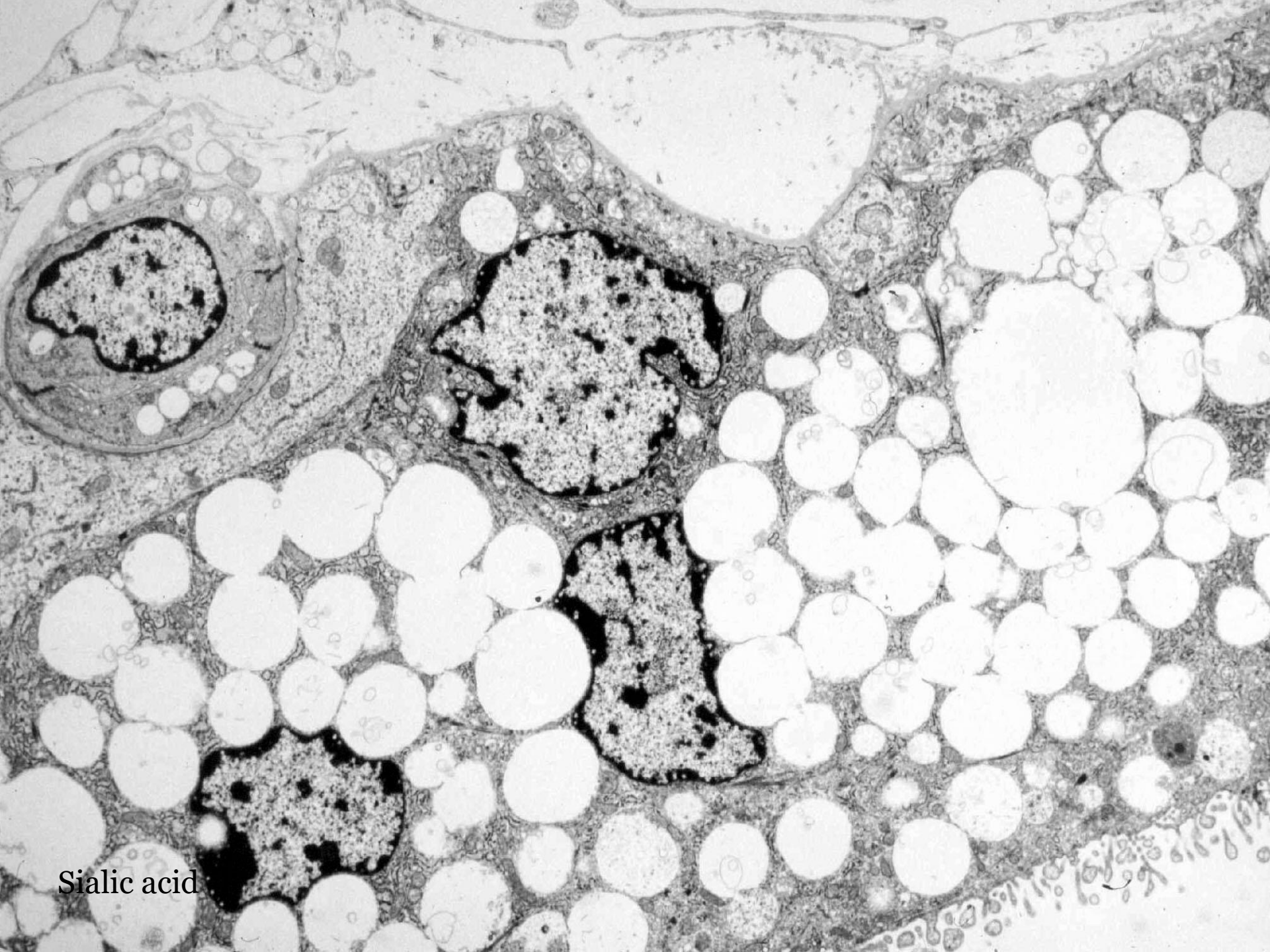
Chorionic villous sample

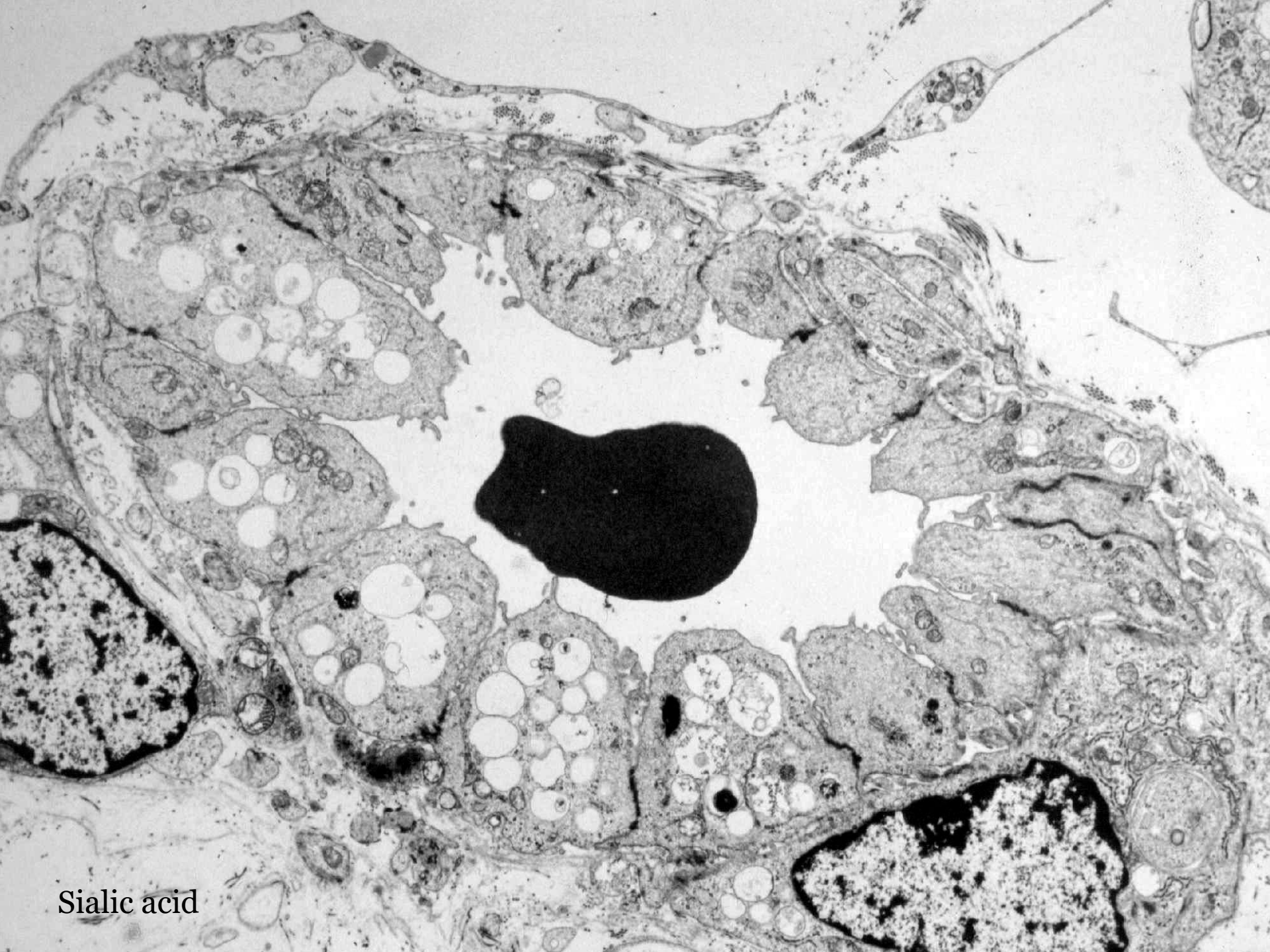
Disorders showing prominent trophoblast vacuolation:

- GM1 gangliosidosis
- Infantile sialic acid storage disease
- I cell disease
- Sialidosis



Tol blue – Sialic acid


Sialic acid

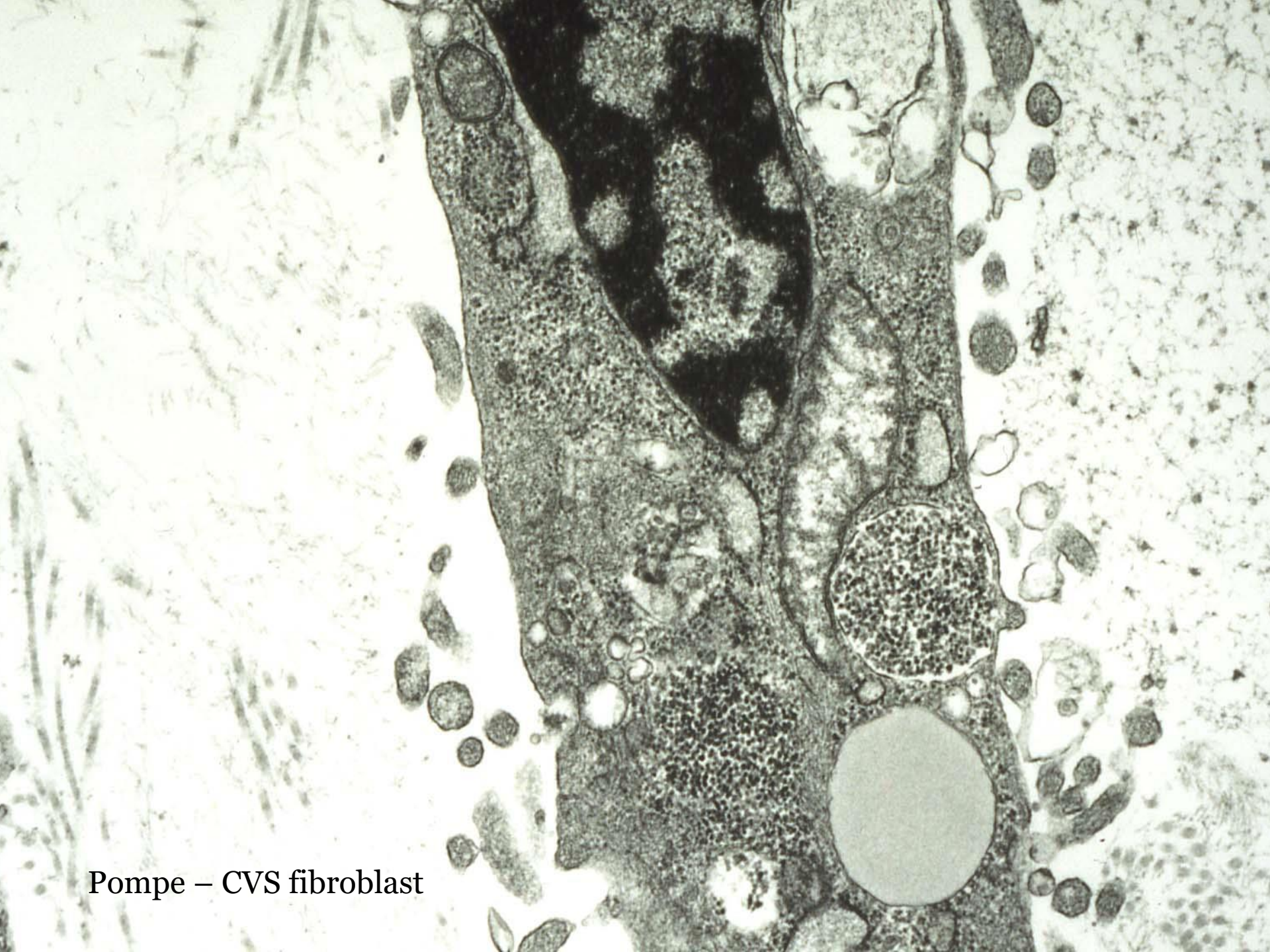


Sialic acid

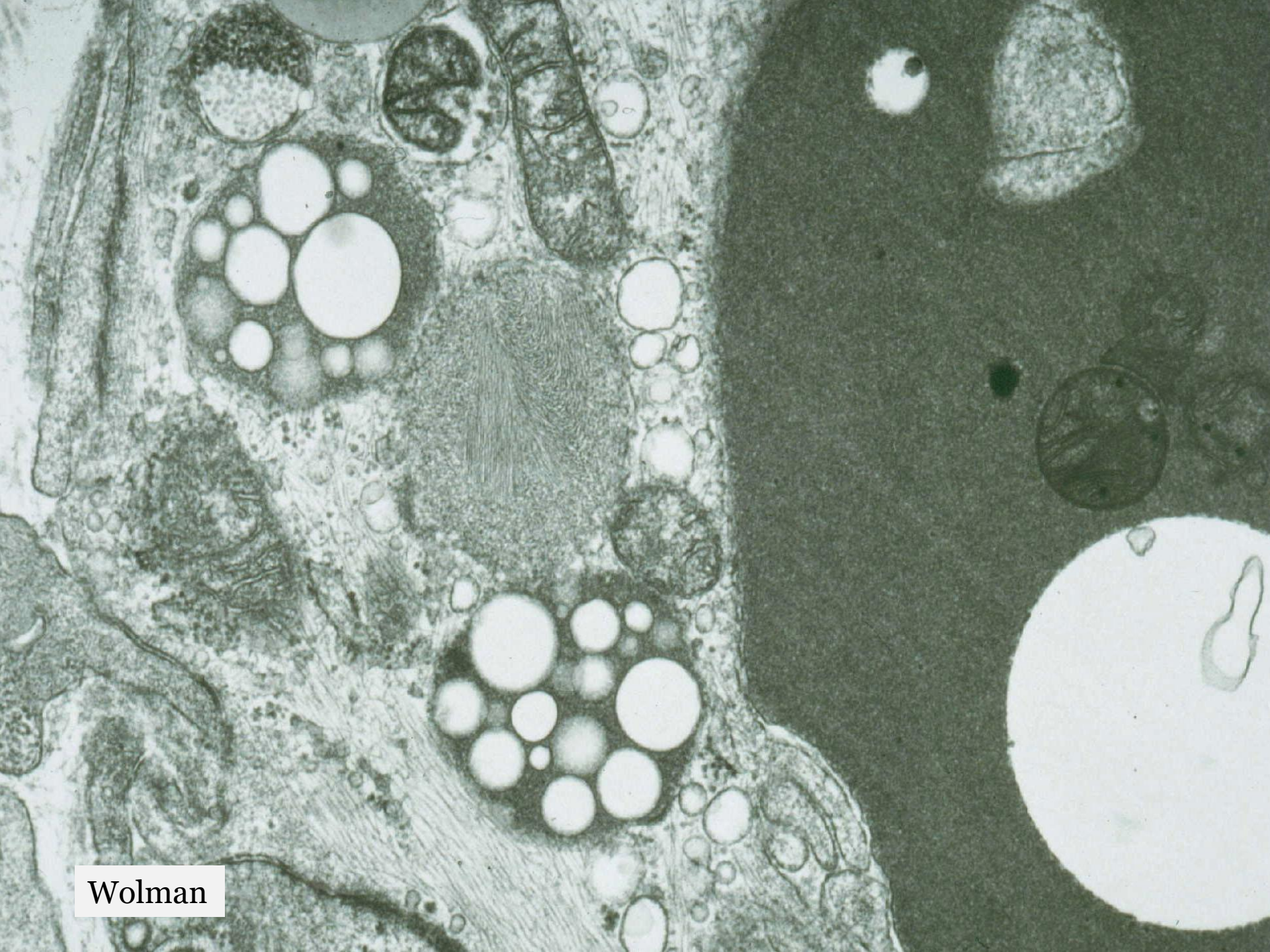
CVS – specific storage inclusions

Detected mainly in endothelial cells:

- Pompe – glycogen storage disease II
- Neuronal ceroid lipofuscinosis
- Wolman – lipid storage disease
- Niemann-Pick type A



Pompe – CVS fibroblast


Wolman

CVS – disorders with no EM changes

- Gaucher
- Fabry
- Krabbe & metachromatic leucodystrophy
- GM2 gangliosidosis
- Cystinosis
- Mucolipidosis IV

Therapies for LSD's

- Bone marrow transplant
- Enzyme replacement therapy
- Substrate reduction therapy
- Stem cells
- Chemical chaperone therapy
- Gene therapy

Thank you