

***Drosophila melanogaster* Lacking the Lysosomal Enzyme Palmitoyl-Protein Thioesterase 1 Accumulate Aberrant Ultrastructural Deposits in the Form of Lamellar Cytoplasmic Bodies**

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The gene *PPT1* encodes the lysosomal enzyme palmitoyl-protein thioesterase 1 (Ppt1), which cleaves long-chain fatty acids from acylated proteins. Mutations in the human *PPT1* gene cause the pediatric neurodegenerative disease infantile neuronal ceroid lipofuscinosis (INCL) [1]. INCL is characterized by the accumulation of granular osmiophilic deposits (GROD) in all cells and the extensive death of cortical neurons [2]. It is not known how the loss of Ppt1 causes neurodegeneration or GROD formation. *Drosophila melanogaster* has been a useful model system for studying numerous genetic neurodegenerative diseases, and *Drosophila* has a functional *PPT1* ortholog (*Ppt1*), so it was hypothesized that *Drosophila* could provide a useful model to study the etiology of INCL [3-4].

A chromosomal deletion was generated, *Df(1)446-20*, which removes *Ppt1*, in addition to three neighboring genes [4]. Flies carrying the *Df(1)446-20* deletion lack Ppt1 enzyme activity, yet are viable, fertile, and have no obvious signs of neurodegeneration. They do, however, accumulate aberrant ultrastructural deposits named lamellar cytoplasmic bodies (LCBs). In contrast to the GROD that accumulates in human disease, which is granular and amorphous in structure, LCBs are lamellar and spherical in structure and more closely resemble the deposits seen in Tay-Sachs disease [5]. Two major types of LCBs have been observed in *Df(1)446-20* fly tissues. One type, found predominantly in females, consist of tightly packed concentric layers of material often surrounding a granular core (Fig. 1). The other type, found predominantly in males, consists of stacked layers of material often separated from one another to form prominent gaps (Fig. 2). LCBs were detected in multiple *Drosophila* tissues but were enriched in both frequency and size in the adult brain. This contrasts with GROD in humans, which is abundant in all tissues.

The LCB phenotype could be rescued in the brains of transgenic *Df(1)446-20* flies by expressing a *Ppt1* cDNA transgene in the central nervous system. In addition, suppressing Ppt1 enzyme activity by expressing a *Ppt1* RNAi construct in otherwise wildtype flies resulted in the formation of LCBs. These observations suggest that the LCB phenotype is caused by the loss of *Ppt1*, specifically, and not by the loss of any of the other three genes removed by the *Df(1)446-20* deletion.

Although LCBs do not resemble GROD, the fact that the loss of Ppt1 enzyme activity in both flies and humans results in the abnormal accumulation of material suggests that a common cellular mechanism is disrupted in both organisms. Understanding the mechanism involved in LCB

formation in flies may provide clues to how and why GROD accumulates in human INCL patients, and may ultimately provide insights into INCL etiology.

References

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- [6] This work was supported by a grant from the National Institute of Neurological Disorders and Stroke to R.L.G.

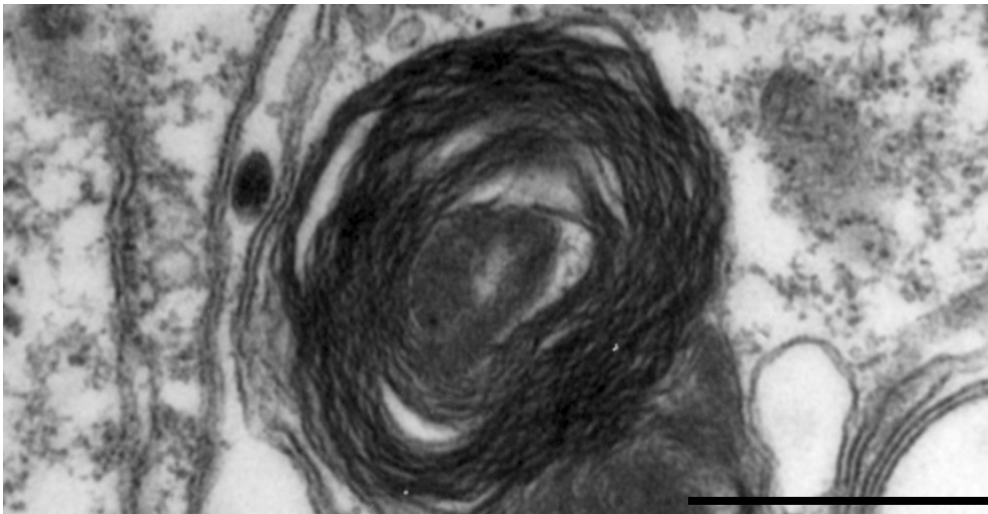


Fig. 1. Lamellar cytoplasmic body in the brain of a female *Df(1)446-20* fly. Note concentric layers surrounding a granular core. Scale bar = 1 μ m.

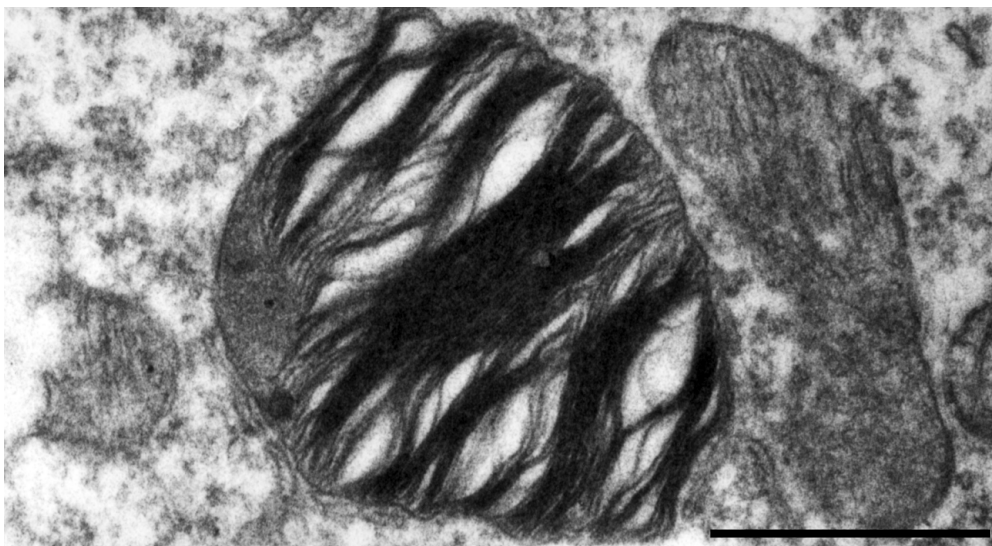


Fig. 2. Lamellar cytoplasmic body in the brain of a male *Df(1)446-20* fly. Note stacked layers with frequent separations. Scale bar = 1 μ m.