
The Competent Lysosome

*Where autophagic failure is a cause of neurodegeneration and where it is a consequence
— a stage-resolved reading of the human evidence in Alzheimer's, Parkinson's,
frontotemporal and Huntington's disease*

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A staged examination of the human Huntington's brain found the autophagy-lysosomal pathway competent in the vulnerable region at the earliest stage tissue permits, and failing only late. That is what a disease clocked by a somatic DNA-repeat expansion should look like. The general claim that clearance failure is the shared upstream mechanism therefore narrows — but not by disease. It narrows to the diseases whose causal genes encode parts of the clearance apparatus, which is a different list.

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Abstract

It is widely proposed that the adult neurodegenerative diseases share a single upstream bottleneck: that failure of the autophagy–lysosomal pathway is the common mechanism, and that the protein which aggregates in each disease is only the local sign of one general breakdown in clearance. The proposal is attractive because it is nearly always confirmed. Every one of these diseases shows autophagic–endolysosomal abnormality somewhere in its course. This paper asks a harder question — not whether the pathway is abnormal, but *when*, and therefore whether the abnormality is a cause or a consequence — and answers it from stage-resolved human tissue rather than from cell and animal models.

The occasion is a result that runs the wrong way. A staged post-mortem study of Huntington’s disease striatum and cortex across Vonsattel grades 2 to 4 found the autophagy–lysosomal pathway *competent* in the vulnerable region at the earliest stage sampled [1]. Upstream markers of induction and autophagosome formation were unchanged; cargo-loaded autophagosomes and cathepsin-positive autolysosomes were both present, so there is no fusion block; cathepsin D and cathepsin B protein and enzymatic activity were unaltered in both regions; lysosomal membrane protein LAMP1 was *elevated*, implying compensatory biogenesis, not collapse. Substrate failure — enlarged, clustered, cargo-laden autolysosomes and lipofuscin — appeared only at grades 3 and 4. The laboratory that produced this result is the laboratory that built the case for early lysosomal failure in Alzheimer’s disease, and it drew the contrast itself.

Three findings follow from taking that result seriously.

First, the widely reported “empty autophagosome” of Huntington’s disease is not confirmed in human brain. The cargo-recognition defect on which the Huntington’s arm of the convergence claim rests was established in cell lines, mouse models and patient fibroblasts and lymphoblasts [2]. In post-mortem human brain, vesicles of that description are present but are attributable in large part to fixation artefact: immunogold labelling decorated their membranes for calnexin, an endoplasmic-reticulum protein, and mitochondria were readily seen inside double-membrane vesicles, so cargo sequestration is not globally impaired [1].

Second, Huntington’s disease runs the other way because its rate-limiting step is not in the cytoplasm. Single-cell measurement of the *HTT* CAG tract alongside genome-wide expression in human striatum shows the repeat expanding somatically from an inherited 40–45 to 100–500 or more, with no detectable cell-autonomous consequence until it passes roughly 150, after which the neuron loses its identity and dies quickly and asynchronously [3]. The genetic modifiers of onset are DNA-maintenance genes, and the onset-determining property is of the uninterrupted DNA repeat rather than of the encoded polyglutamine [4,5]. A disease whose clock is a nuclear DNA process, and whose neurons are unremarkable for most of their lives, is *predicted* to show a competent clearance apparatus in bulk tissue until enough neurons have crossed threshold. The Huntington’s result is not an anomaly to be explained

away; it is what this mechanism entails.

Third, and this is the paper’s substantive proposal, the correct narrowing of the convergence claim is not by disease taxon but by genetic position. Early, causal clearance failure is supported where the primary genetic lesion sits *inside* the endolysosomal system — most cleanly in progranulin-associated frontotemporal degeneration, where a human allelic series runs from childhood lysosomal storage disease at zero functional copies to adult dementia at one, with pre-symptomatic lipofuscin storage detectable in heterozygous carriers [6,7]; strongly in the *GBA1* stratum of Parkinson’s disease, and more weakly in sporadic Parkinson’s disease, where the same enzyme declines with age in people who never develop it [8,9,10]; and strongly for the *endosomal* lesion of Alzheimer’s disease, which precedes amyloid deposition in human tissue [11]. It is not supported where the primary lesion lies elsewhere: Huntington’s disease, and, on present human evidence, sporadic amyotrophic lateral sclerosis. This cuts across the proteinopathy classification. It includes two non-Alzheimer diseases and excludes the primary tauopathies, which have no lysosomal allelic series of the kind *GRN* and *GBA1* provide, and whose granulovacuolar bodies are induced by α -synuclein as readily as by tau [12]. A narrowing to “Alzheimer’s and the tauopathies” would therefore be wrong in both directions.

The paper closes with a graded verdict, eight falsifiable predictions each paired with the experiment that would settle it, and a therapeutic consequence with an unusual property: the sign of the recommended intervention differs between diseases. Stimulating autophagy is a rational early therapy in Huntington’s disease, where the machinery works and the load is clearable, and an irrational one in Alzheimer’s disease at the same nominal stage, where induction is already elevated and the terminal step is the one that has failed [13].

I. Introduction: A Claim That Is Always Confirmed

1.1 The proposition under test

The proposition can be stated in one sentence. Alzheimer’s disease, Parkinson’s disease, frontotemporal degeneration, amyotrophic lateral sclerosis and Huntington’s disease are not five diseases of five proteins but one disease of one system — the autophagy–lysosomal pathway — presenting differently because it fails in different cells. In its most careful published form, the claim is that the post-mitotic and extremely polarised morphology of neurons makes them uniquely vulnerable to autophagic–lysosomal defects, that mutations in the genes regulating this system cause a wide range of neurodegenerative diseases, and that cellular ageing acting on the same system supplies the tipping point at which those diseases emerge in late life [14].

The proposition has real virtues. It is mechanistically specific where the proteinopathy classification is merely descriptive. It explains why aggregates of unrelated proteins accumulate in unrelated cell types under a single kind of stress. It is consistent with the fact that abolishing basal autophagy in mouse neurons produces neurodegeneration and ubiquitinated inclusions with no seeding protein required at all [15,16]. And it gives a therapeutic target that is not a single aggregate.

It also has a structural liability, and the liability is the reason this paper exists. Everything a neuron internalises, condemns, damages or recycles transits the endosomal–lysosomal–autophagic system. A system with that many functions will be found abnormal in any disease that involves cargo, membranes, energy, calcium or trophic support, which is to say in every neurodegenerative disease and in normal ageing. A claim that is confirmed by every dataset one can collect is not thereby strong. It may instead be insufficiently specified.

The way to specify it is temporal. “The pathway is abnormal in disease X” is nearly vacuous. “The pathway is abnormal in disease X *before* the disease’s defining pathology, in the cells that will die, at a stage when the patient is well” is a claim that can fail. The rest of this paper applies that test disease by disease, using human tissue staged by an accepted neuropathological scheme wherever such tissue exists.

1.2 Three claims that are routinely conflated

Careful reading of the convergence literature reveals three distinct propositions travelling under one name.

The co-occurrence claim. Autophagic–endolysosomal abnormality is present in all of these diseases. This is true and essentially uncontested. It is also nearly uninformative, for the reason just given.

The primacy claim. In each disease, the clearance lesion is upstream of and causally prior to the proteinopathy. This is the interesting claim. It is true in some diseases and false in others, and distinguishing them is the work of this paper.

The identity claim. It is the *same* lesion in each disease, differing only in which cell fails. This is the strongest version and it is false as stated. The molecular lesions are not the same: a sorting-receptor deficiency, a hydrolase deficiency, a proton-pump targeting defect and a lysosomal-membrane-protein deficiency are four different failures of one organelle, with different first-affected steps, different compensations, and — the practical consequence — different and in some cases opposite correct interventions.

The three claims have very different evidentiary requirements, and conflating them allows the near-certainty of the first to underwrite the ambition of the third.

1.3 What counts as evidence here

Three methodological commitments constrain what follows.

Human tissue, staged. Cell and animal models establish that a lesion *can* produce a phenotype. They cannot establish that it *does* so in the human disease, still less that it does so first. Where a model result and a human tissue result disagree about the human disease, the human tissue result governs. This rule is applied symmetrically, and it costs the argument as much in Alzheimer’s disease as it does in Huntington’s.

Stage, not severity. The relevant question is always what the pathway looked like at the earliest stage that tissue permits, not what it looks like at autopsy in a person who died of the disease. Terminal neurons are abnormal in every measurable respect. Nothing follows from that.

The whole panel. Autophagy is a sequence — induction, nucleation, cargo capture, autophagosome formation, transport, fusion, acidification, proteolysis, efflux. A study measuring one marker cannot locate the lesion in the sequence, and single markers have generated most of the field’s contradictions. LC3-II rises both when autophagosomes are made faster and when they are cleared more slowly; the two have opposite therapeutic implications. Multiplexed studies that assay the whole sequence in the same tissue are rare and are weighted accordingly here.

2. The Huntington's Result

2.1 What was done

The study that occasions this paper examined striatum (caudate nucleus), prefrontal cortex and cerebellum from patients staged by Vonsattel neuropathological criteria at grades 2, 3 and 4, against matched controls [1]. The Vonsattel scheme grades the spatiotemporal advance of striatal atrophy from grade 0 to grade 4 [17]; grade 2 already carries substantial striatal degeneration, so “early” in this study means early relative to grade 4, not early relative to disease onset. That matters, and it cuts in the direction of strengthening the result rather than weakening it: whatever competence is found at grade 2 is found in a striatum that has already lost a great many neurons. The proteinopathy against which the pathway was assayed is the one described three decades ago in the same tissue: neuronal intranuclear and neuritic inclusions of N-terminal huntingtin, ubiquitin-positive, concentrated in the regions that degenerate [18].

The design assayed the full sequence: transcript levels for induction, transcriptional activators of lysosomal biogenesis, hydrolases and lysosomal membrane proteins; immunoblots for the corresponding proteins, including phospho-p70S6 kinase as a readout of mTOR inhibition, BECN1, ATG5, ATG7 and LC3; enzymatic activity assays for cathepsins D and B; immunohistochemistry and double immunofluorescence for cathepsin D against mutant huntingtin; and electron microscopy, including immunogold, on an exceptionally well-preserved grade 4 case.

2.2 What was found

Induction and autophagosome formation are unchanged. Phospho-p70S6 kinase, BECN1, ATG5, ATG7 and LC3 protein showed no disease-related change in striatum or cortex, consistent with the transcript data. There is no evidence of the compensatory hyper-induction that a blocked pathway would be expected to produce, and no evidence of suppressed induction either.

There is no fusion block. Double-membrane autophagosomes and single-membrane cathepsin-positive autolysosomes coexisted in the perikarya of affected neurons. Mitochondria were seen within double-membrane vesicles. LC3 immunostaining, LC3 puncta number and size distribution, and LC3-II levels gave no indication of impairment at autophagosome formation, autophagosome–lysosome fusion, or autolysosome clearance at grade 2.

Proteolytic capacity is preserved. Cathepsin D and cathepsin B showed no significant alteration in protein level or in enzymatic activity, in either striatum or cortex, across the staged series.

Lysosomal biogenesis is up, not down. LAMP1 protein was elevated in striatum as early as grade 2 — not in cortex — with LAMP1 and LAMP2 transcripts likewise raised. This is the signature of a cell expanding its lysosomal compartment in response to load, which is the opposite of a cell whose lysosomes have been depleted.

Substrate failure is late and regional. Cathepsin D immunohistochemistry was indistinguishable from control at grade 2. At grade 4, cathepsin D-positive granules were grossly enlarged and clustered at one pole of the neuron in a distribution characteristic of lipofuscin, with electron microscopy confirming abundant lipofuscin granules and autophagic vacuole accumulation. The change was more severe in striatum than in cortex, following the regional gradient of the disease. Mutant huntingtin signal within cathepsin D-positive compartments was weak at grade 2 and strong at grade 4.

The biochemistry is regionally selective and tracks the vulnerable region. Fragments of huntingtin, of p62/SQSTM1 and of TRAF6 were elevated roughly fourfold in striatum and not at all in cortex; K48 and K63 ubiquitination rose in striatum. Cerebellum was essentially unchanged throughout.

2.3 The authors' own reading

The paper's conclusion is explicit: the pathway is competent in early-stage disease, failure of the lysosomal clearance step emerges mainly at advanced stages, and therefore stimulating autophagic flux is a rational intervention in Huntington's disease *provided it is applied early*, when the clearance machinery still works. The contrast with Alzheimer's disease — where, on this group's account, impaired flux emerges pre-symptomatically as a direct consequence of disease genetics acting on autolysosomal proteolytic efficacy — is drawn by the authors themselves.

This is worth pausing on. The result is not a hostile finding produced by a rival programme. It is a narrowing published by the laboratory with the largest stake in the broad version of the claim, in the disease where the broad version was weakest.

2.4 What the result does not show

Three limits must be stated, because the argument that follows depends on not overreading it.

It does not show that clearance is *irrelevant* in Huntington's disease. Mutant huntingtin is a substrate of this pathway in human brain — that is one of the study's positive findings — and clearance capacity plausibly sets how long a neuron tolerates a given repeat length. What it shows is that clearance is not the *rate-limiting* lesion at the stages sampled.

It does not sample pre-manifest disease. No grade 0 or grade 1 tissue was examined. A deficit could exist earlier and be masked later by compensatory biogenesis, though this would require the

deficit to be present before grade 2, absent at grade 2, and present again at grade 4, which is not a parsimonious course.

Its ultrastructural claims rest heavily on one exceptionally preserved grade 4 case, the other cases being of insufficient quality for quantitative electron microscopy. The immunoblot, transcript, enzymology and light-microscopic findings do not have this limitation; the electron-microscopic ones do.

3. The Claim the Result Displaces

3.1 The empty autophagosome

The Huntington's arm of the convergence claim has rested for fifteen years on a single, influential mechanism: that autophagic vacuoles in Huntington's disease form at normal or increased rates but fail to recognise and engulf cytosolic cargo, so that the pathway runs while clearing nothing. The original report established this in cell models, mouse models and cells from patients, showing autophagic vacuoles with markedly reduced luminal content, and proposed inefficient cargo engulfment as the primary defect [2]. The result was rigorous, and the phenotype is real in those systems.

The imagery that grew around it — trucks that arrive empty, an engine revving in neutral, an energetically ruinous futile cycle — is not, however, the finding. It is an extrapolation of the finding to a level of organisation the experiments did not reach: the neuron in the human brain.

3.2 Why the human brain does not confirm it

The staged human study looked for exactly this phenotype and reported what it found with unusual care [1]. Clusters of vesicles with minimal luminal content were present. But the same pattern was frequently seen in fresh post-mortem brain from Alzheimer's cases in the same laboratory's other material, and was *not* seen in biopsied — as opposed to post-mortem — brain from Alzheimer's patients, which points to fixation and post-mortem change rather than disease. Immunogold labelling for calnexin significantly decorated these vesicular membranes, identifying much of the population as swollen, vacuolised endoplasmic reticulum. Artefactual vacuolisation of lipid within lipofuscin granules produces a similar appearance. And against a general failure of cargo capture stands the direct observation of mitochondria inside double-membrane vesicles: sequestration of at least that cargo is unimpeded.

The authors decline to go further than the evidence allows, stating that their study neither supports the presence of empty autophagosomes in human brain nor refutes their existence in cells. That is the correct position. But the asymmetry matters for the convergence claim: a mechanism that has been demonstrated in models and *not* demonstrated in human brain cannot carry the weight of a claim about what human disease fundamentally is.

3.3 The compounding error

There is a second, subtler problem with the way the cargo-recognition result has been deployed. In the standard synthesis, Huntington's disease contributes a distinct "choke point" — cargo loading — to a list on which Alzheimer's contributes acidification, Parkinson's contributes mitophagy and ALS/FTD contributes trafficking. The distinctness of the choke points is presented as evidence for the generality of the convergence: different entry lanes, one collapse.

But this construction has the logic backwards. If each disease fails at a different step, then the diseases do not share a mechanism; they share an organelle. Sharing an organelle is the co-occurrence claim, not the identity claim. The rhetorical force of "one mechanism, many diseases" is borrowed from the identity claim while the evidence supports only the co-occurrence claim, and the list of distinct choke points is what makes the borrowing visible.

4. Why Huntington's Disease Runs the Other Way

4.1 The clock is in the nucleus

The strongest reason to expect the Huntington's result is not in the autophagy literature at all. It is in the genetics, and it has become sharp only in the last two years.

Huntington's disease is caused by an inherited CAG expansion in *HTT*, conventionally 40–50 repeats. Single-cell measurement of that repeat alongside genome-wide RNA expression in human striatum shows that the repeat is not static. In striatal projection neurons it expands somatically across the lifespan, from the inherited 40–45 to 100, 200, 500 and beyond. Crucially, expansion from 40 to about 150 has no apparent cell-autonomous effect: those neurons are transcriptionally unremarkable. Past roughly 150, the neuron loses first the positive and then the negative features of its identity, de-represses senescence and apoptosis programmes, and is lost. The authors' summary is that at any one time most neurons in a Huntington's brain carry an innocuous but unstable gene, and that pathogenesis is a DNA process for almost all of a neuron's life [3].

A preprint from the same group extends this to cortex across twelve areas and more than 130,000 nuclei, reporting the same approximately 150-repeat toxicity threshold in cortical projection neurons of all types, with up to fiftyfold variation between pyramidal subtypes in the probability of reaching it within a human lifespan [19]. This is a preprint and is graded accordingly, but its convergence with the striatal result is notable: cortical and striatal degeneration appear to be the same cell-autonomous sequence running at different rates, rather than one being secondary to the other.

4.2 The human genetics names DNA repair, not clearance

This is corroborated from an entirely independent direction. Genome-wide association studies of age at onset in Huntington’s disease find modifiers at DNA-maintenance loci — *MSH3*, *FANL*, *PMS1*, *PMS2*, *MLH1*, *LIG1* [20]. The decisive observation came when the *HTT* repeat was sequenced rather than sized: alleles carrying glutamine-encoding CAA interruptions, which yield the same polyglutamine protein but a shorter uninterrupted DNA tract, behave as shorter alleles. Onset is set by a property of the uninterrupted DNA repeat, not by the length of the encoded polyglutamine, and shows no significant association with *HTT* expression quantitative trait loci [4]. The most recent modifier analysis separates genetic modification of somatic expansion itself from modification of clinical trajectory and identifies *MSH3*, *PMS2* and *FANL* as shared modifiers of both, while also finding a synonymous *HTT* variant that hastens motor onset without increasing somatic expansion — a reminder that the DNA account is not the whole account [5]. Proof of principle for intervention on the DNA arm exists: antisense suppression of *MSH3* stalls CAG expansion in patient-derived striatal neurons [21]. The inherited repeat itself behaves in a fully dominant fashion with respect to onset, the normal allele contributing nothing — which is what one expects if the pathogenic variable is a property of the expanded tract rather than a dosage of protein [22].

Set beside this, the absence of any endolysosomal gene among the Huntington’s modifiers is itself a datum. In a disease where the clearance apparatus was rate-limiting, common variation in that apparatus would be expected to modify onset. It does not.

4.3 The Huntington’s result is what this mechanism predicts

Put the two together and the staged tissue findings cease to be surprising.

If a neuron is unremarkable until its own repeat crosses about 150, and then dies within a short window, then bulk tissue from a given disease grade is a mixture: a large majority of neurons below threshold, functioning normally, and a minority above it, in rapid decline. At grade 2 the above-threshold fraction is small, and bulk transcript, immunoblot and enzymology measurements — all dominated by the majority population — will read as normal. At grades 3 and 4 the fraction has grown, the debris of the dying has accumulated, and bulk measures record enlarged cathepsin D-positive granules, lipofuscin, and substrate build-up. This is precisely the reported pattern, including its regional gradient: striatum ahead of cortex, cerebellum unchanged, in the order of the neuronal populations’ probabilities of reaching threshold.

The elevated LAMP1 at grade 2 fits too. A cell handling an increasing but still manageable burden of an aggregation-prone fragment expands its lysosomal compartment. That is a load response, not a lesion.

The proposition can be stated generally. **In a disease whose rate-limiting step is a slow, cell-autonomous, nuclear process with a sharp toxicity threshold, staged bulk tissue will necessarily show late clearance pathology, and the lateness is evidence about the position of the clearance step in the causal chain rather than about its importance.**

4.4 The alternatives, and why they do not fit

Four alternative readings deserve explicit disposal.

The deficit is there but masked by compensation. Possible in principle. But compensation that fully normalises transcript, protein, enzymology and morphology at grade 2, in a striatum that has already lost substantial numbers of neurons, and then fails completely by grade 4, is a strong claim requiring its own evidence. None is offered anywhere in the literature.

Bulk tissue dilutes a neuronal signal with glia. True and acknowledged by the study's authors as a caveat for the immunoblot data. It does not dispose of the result, because the immunohistochemical and ultrastructural data are cell-resolved and agree with the bulk data: individual neurons at grade 2 have normal-appearing cathepsin D puncta.

Post-mortem interval degrades the measurement. This would predict noise, and would degrade cases and controls alike. It does not predict the specific, ordered, regionally graded pattern actually observed.

Grade 2 is not early enough. This is the one serious objection, and it is a reason for the prediction in §10.1 rather than a reason to discount the finding. Note, though, that the objection has to be made carefully: the claim under test is that clearance failure is *upstream*, and a lesion that only appears after substantial striatal neuron loss is not upstream of that loss whatever else it is.

5. Alzheimer's Disease: The Lesion Inside the Machine

If Huntington's disease is the case where the clearance lesion is downstream, Alzheimer's disease is meant to be the case where it is upstream. The evidence is good, but it is not uniformly good, and the parts that are weakest are the parts most often cited.

5.1 What human tissue actually shows, and when

The endosomal evidence is the strongest and the earliest. Neurons in vulnerable regions of the sporadic Alzheimer brain show enlarged early endosomes and up-regulated endocytic machinery, and this is present *before* β -amyloid deposition, including in Down syndrome brain before the appearance of plaques [11]. This is a genuine pre-pathological human finding of the kind the primacy claim requires, and it is the single most load-bearing observation in the Alzheimer arm of the convergence argument.

Autophagic vacuoles accumulate massively in dystrophic neurites in Alzheimer cortex, with immature forms predominating, in a pattern indicating impaired maturation and transport rather than impaired formation [23]. In primary neurons the same configuration was shown to arise from a defect in autophagosome clearance rather than from excess induction, which is the interpretive key to the human morphology [24]. Beclin 1, required for autophagosome nucleation, is reduced in affected regions early in the disease [25].

The most informative human study, because it assayed the whole sequence in one identified cell population, laser-captured CA1 pyramidal neurons from early and late-stage Alzheimer cases and controls [13]. Its findings deserve quoting against the usual summary. Autophagy-related genes were *up*-regulated from early stages, with increased autophagosome formation and increased lysosomal biogenesis through the MiTF/TFE transcription factors. Autophagic sequestration was competent and up-regulated. Autophagosome-lysosome fusion was not evidently altered. Flux was nonetheless progressively impeded, and the impediment was at substrate clearance.

That should be read carefully, because at the level of induction, sequestration and fusion, human Alzheimer CA1 neurons and human Huntington striatal neurons look alike. The difference between the diseases is not that one has a broken pathway and the other an intact one. It is *where in the sequence* the deficit sits and *at what stage* it appears: in Alzheimer's the substrate-clearance deficit is detectable at early Braak stages [26], whereas in Huntington's the equivalent deficit is absent at Vonsattel grade 2 and present at grades 3–4.

5.2 The genetics puts the lesion inside the pathway

Autosomal-dominant Alzheimer's disease is caused by mutations in *APP* and in the presenilins — genes whose products are, respectively, a cargo of the endosomal system and a component of the membranes that system is built from. Isogenic human induced pluripotent stem-cell neurons carrying a large panel of *APP* and *PSEN1* mutations converge on the same endosomal enlargement, and the mediator is the β -C-terminal fragment of APP rather than A β itself [27]. On the sporadic side, the risk gene *SORL1* encodes a sorting receptor of the retromer-dependent endosomal route, and its depletion in human neurons produces early-endosome enlargement — the defining cytopathology — in a manner independent of amyloidogenic APP processing, and selectively in neurons rather than microglia [28]. The largest Alzheimer genome-wide association study to date reports risk loci enriched in endocytosis, intracellular trafficking and protein degradation pathways alongside immunity and lipid handling [29].

This is what “the lesion is inside the machine” means concretely. It is not that the machine is stressed. It is that the genes whose variation causes and modifies the disease encode parts of the machine.

5.3 Two complications the standard account omits

The mechanism of the lysosomal defect is disputed, and the dispute is unresolved.

The influential account is that presenilin 1 holoprotein is required for N-glycosylation and lysosomal delivery of the V0a1 subunit of the vacuolar ATPase, so that presenilin loss or familial mutation de-acidifies the autolysosome and disables cathepsin activation [30]. A subsequent study reported that N-glycosylation is not required for V0a1 targeting or function in vitro or in *Drosophila*, that lysosomal acidification is not compromised in presenilin-deficient cells, and that the endolysosomal phenotype is instead attributable to altered lysosomal calcium storage and release impairing fusion [31]; a contemporaneous commentary set out the conflict without resolving it [32]. Fourteen years later there is no consensus experiment. The convergence literature has largely proceeded as though the acidification account were settled. It is not, and the significance is direct: if the defect is in calcium-dependent fusion rather than in the proton pump, then re-acidification is the wrong therapeutic target.

Human neuropathology separates the *APP* and presenilin lesions. Endocytic pathway abnormalities are present in Alzheimer's disease caused by certain *APP* mutations and are *absent* in disease caused by presenilin mutations, which was the basis for the proposal that these are distinct cellular routes to the same phenotype [33]. The presenilin–vacuolar ATPase story and the endosomal-enlargement story are therefore not one story, and the human tissue says so.

The acidification evidence in human brain is thinner than the citation pattern suggests. The demonstration that autolysosomal acidification declines before extracellular

amyloid deposition, with lowered vacuolar ATPase activity and the accumulation of A β within de-acidified autolysosomes into the perikaryal rosettes named PANTHOS, is a study of five mouse models; the human contribution is that the PANTHOS pattern is also present in Alzheimer brains [34]. That presence is real and important. It is not a stage-resolved human measurement of lysosomal pH, and no such measurement exists, because pH cannot be measured in fixed post-mortem tissue. The proposition that lysosomal de-acidification is early *in the human disease* is an inference from mouse timing plus human end-point morphology. Restoring lysosomal proteolysis in an Alzheimer mouse ameliorates amyloid pathology and cognitive deficits, which supports causality in the model [35].

5.4 The Alzheimer verdict

The primacy claim holds for Alzheimer's disease at the *endosomal* level: early-endosome abnormality precedes amyloid deposition in human tissue, and the causal and risk genetics encode endosomal machinery. It holds more weakly at the *lysosomal-proteolytic* level: the deficit is demonstrated in human tissue at early Braak stages by the whole-panel CA1 study, but the specific acidification mechanism is contested and its human timing is inferred rather than measured.

That is a defensible, well-evidenced, and considerably more modest claim than "Alzheimer's disease is autophagic collapse."

6. Parkinson's Disease: A Partly Inside Lesion

6.1 The genetics is strong

Heterozygous mutation in *GBA1*, encoding the lysosomal hydrolase glucocerebrosidase, is the most common known genetic risk factor for Parkinson's disease, with an odds ratio above five in a 5,691-patient multicentre analysis and earlier age at onset in carriers [36]. Homozygous mutation causes Gaucher disease, a lysosomal storage disorder. That allelic structure — storage disease at two hits, neurodegeneration at one — is the same structure that makes the progranulin case so strong in §7, and it is strong evidence that the lysosome is upstream rather than downstream in the *GBA1* stratum.

6.2 The tissue evidence is genuinely mixed

Two human post-mortem results point in opposite directions, and the field usually cites only one of them.

Pointing to primacy: glucocerebrosidase protein and enzyme activity are selectively reduced *in the early stages* of sporadic Parkinson's disease, in regions showing raised α -synuclein but limited inclusion formation, with associated reduction in chaperone-mediated autophagy and altered sphingolipid handling [8]. "Early" here is defined by the α -synuclein staging scheme in which the pathology ascends from medulla and olfactory structures through pons and midbrain to neocortex [37], so the regional dissociation is interpretable. The staging and the regional dissociation are exactly what the primacy claim needs. Independent measurement confirms reduced glucocerebrosidase activity in substantia nigra in both *GBA1*-carrier and sporadic Parkinson's disease, greatest in the nigra [9].

Pointing to consequence: in nigral neurons, LAMP1, cathepsin D, HSC70 and 20S proteasome immunoreactivity are reduced in Parkinson's disease relative to controls, but the reduction is *significantly greater in the neurons that contain α -synuclein inclusions*, and in aged control brain, non-aggregated α -synuclein is present with no difference in these markers [38]. Lysosomal depletion in Parkinson tissue and models has also been attributed to lysosomal membrane permeabilisation secondary to mitochondrially derived reactive oxygen species — that is, to a lesion upstream of the lysosome rather than in it [39]. Chaperone-mediated autophagy markers are likewise reduced in Parkinson substantia nigra [40].

6.3 The complication that should change the reading

Glucocerebrosidase activity declines progressively with normal ageing in substantia nigra and putamen of healthy controls, reaching levels comparable to those in *GBA1*-mutation-carrier patients [10].

This is the most important single fact in this section, and it generalises beyond Parkinson's disease. If the lysosomal deficit that is proposed as the cause of a disease is also present in people who do not have the disease, then that deficit is not sufficient, and its role is to lower a threshold rather than to initiate. The same reading applies to the discovery that filaments of the lysosomal membrane protein TMEM106B form in an age-dependent manner in the brains of older individuals with normal neurology as well as across tauopathies, synucleinopathies, amyloidoses and TDP-43 proteinopathies, with no clear relationship between fold and disease [41,42].

A declining lysosome is a property of the ageing human brain. That is a background condition against which diseases occur, and mistaking a background condition for a mechanism is the specific error the convergence claim is prone to.

6.4 The Parkinson verdict

Primacy is well supported in the *GBA1* stratum, where the genetics places the lesion inside the lysosome and the enzymology finds it reduced early and regionally. It is supported more weakly in sporadic disease, where the best tissue evidence finds the deficit tracking inclusion formation rather than preceding it, and where the age-related decline of the same enzyme in unaffected people argues for a threshold effect rather than an initiating lesion.

7. Frontotemporal Degeneration: The Strongest Human Case

The cleanest human evidence for early, causal lysosomal failure in an adult neurodegenerative disease is not in Alzheimer's disease. It is in progranulin-associated frontotemporal degeneration, and it takes the form of an allelic series that functions as a natural human experiment.

Heterozygous loss-of-function mutation in *GRN* causes frontotemporal dementia with TDP-43 pathology in adults. Homozygous loss of the same gene causes neuronal ceroid lipofuscinosis, a classical lysosomal storage disease of childhood [7]. One gene, two doses, two diseases, both of them disorders of the lysosome.

The question that arrangement raises is whether the adult disease shares the child's mechanism or merely the child's gene. It has been answered directly in human carriers. Non-invasive retinal imaging in heterozygous *GRN* mutation carriers detects lipofuscinosis *before dementia onset*; post-mortem cortex from heterozygous carriers shows increased lipofuscin and intracellular storage material of the ceroid-lipofuscinosis type; lymphoblasts from carriers accumulate the same storage material, which is rescued by normalising progranulin expression; and fibroblasts from carriers show impaired lysosomal protease activity [6].

Every element the primacy claim requires is present here and present in humans: a defined genetic lesion inside the lysosome, a measurable lysosomal phenotype in living pre-symptomatic carriers, a dose-response across the allelic series, and rescue by restoring the missing protein.

The genetic modifier of this disease is also lysosomal. Common variation at *TMEM106B*, encoding a lysosomal type II transmembrane protein, is the strongest known risk locus for frontotemporal lobar degeneration with TDP-43 inclusions and modifies risk in *GRN* mutation carriers specifically [43]. Two independent genes, both lysosomal, one causal and one modifying, in the same disease.

The *C9orf72* hexanucleotide expansion, the most common genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis [44], also has a lysosomal mechanism: the C9orf72 protein binds SMCR8, localises to lysosomes, and its loss produces swollen lysosomes and impaired amino-acid regulation of mTORC1 [45]. This is cell-biological rather than human-tissue evidence, and stage-resolved human material for *C9orf72* carriers is not available, so it is graded lower than the progranulin case despite the mechanism being clear.

8. Amyotrophic Lateral Sclerosis: The Weakest Case

The convergence claim assigns ALS a “cargo recognition and logistics” choke point on the strength of *SQSTM1*, *OPTN*, *TBK1*, *VCP* and *C9orf72* genetics — all of which do implicate the autophagic route, and none of which has been examined in staged human tissue in the way Huntington’s disease now has.

The human neuropathology that exists is late and is compatible with either reading. In lumbar spinal cord from nineteen sporadic ALS cases, autophagic features were found by electron microscopy in the cytoplasm of normal-appearing motor neurons and more frequently in degenerated ones, in association with the characteristic inclusions, and were absent from control anterior horn neurons [46]. The authors’ conclusion is that autophagy is activated and up-regulated in ALS motor neurons — which is an observation of response, not of failure, and which does not distinguish a protective reaction from a stalled pathway.

Stated plainly: there is no stage-resolved human evidence that clearance failure precedes motor neuron degeneration in sporadic ALS. The disease’s inclusion in the convergence claim rests on genetics in familial forms plus model work, and should be graded accordingly.

9. The Discriminator

9.1 A rule of genetic position

Assemble the four diseases and one pattern organises them, and it is not the pattern the convergence claim proposes.

Table 1 — Where the primary genetic lesion sits, and when clearance fails in human tissue

Disease	Principal causal / risk genes	Lesion inside the clearance system?	Earliest human evidence of clearance failure	Reading
FTD with <i>GRN</i> mutation	<i>GRN</i> ; modifier <i>TMEM106B</i>	Yes — lysosomal protein; lysosomal modifier	Pre-symptomatic lipofuscin storage in living heterozygous carriers; storage material in carrier cortex and lymphoblasts	Cause
Alzheimer's disease	<i>APP</i> , <i>PSEN1/2</i> , <i>SORL1</i> ; GWAS loci in endocytosis and trafficking	Yes — cargo, membrane component, sorting receptor	Early-endosome enlargement before amyloid deposition; substrate-clearance deficit in CA1 at early Braak stage	Cause at the endosome; probable cause at the lysosome, mechanism disputed
Parkinson's disease, <i>GBA1</i> stratum	<i>GBA1</i> ; also <i>LRRK2</i> , <i>VPS35</i> , <i>ATP13A2</i>	Yes — lysosomal hydrolase	Reduced glucocerebrosidase in early-stage regions with raised α -synuclein and limited inclusions	Cause in the <i>GBA1</i> stratum; threshold-setter in sporadic disease
Amyotrophic lateral sclerosis, sporadic	<i>SQSTM1</i> , <i>OPTN</i> , <i>TBK1</i> , <i>VCP</i> , <i>C9orf72</i> in familial forms	Partly — autophagy receptors and adaptors	None stage-resolved; autophagic features in motor neurons at autopsy	Undetermined
Huntington's disease	<i>HTT</i> CAG repeat; modifiers <i>MSH3</i> , <i>FAN1</i> , <i>PMS1/2</i> , <i>MLH1</i> , <i>LIG1</i>	No — a nuclear DNA-repeat process; modifiers are DNA-repair genes	Absent at Vonsattel grade 2; present at grades 3–4	Consequence

The rule the table states is this. **Early, causal clearance failure is found where the genetics places the primary lesion inside the endolysosomal system, and not elsewhere.** The

predictive variable is not which protein aggregates, nor which cell dies, nor which clinical syndrome results. It is whether the gene that causes the disease encodes a part of the clearance apparatus.

9.2 Why “Alzheimer’s and the tauopathies” is the wrong narrowing

The natural first attempt at narrowing the convergence claim is to restrict it to Alzheimer’s disease and the tauopathies, on the grounds that the Alzheimer evidence is the best and that tau is the shared lesion. The rule above says this is wrong in both directions.

It is wrong to exclude *GRN*-associated frontotemporal degeneration and *GBA1*-associated Parkinson’s disease, whose human evidence for early lysosomal causation is, in the progranulin case, better than the Alzheimer evidence. Both are non-Alzheimer, non-tau diseases with lysosomal genes.

It is wrong to include the primary tauopathies, though this requires care. No endolysosomal gene *causes* progressive supranuclear palsy, corticobasal degeneration or Pick’s disease; *MAPT* encodes a microtubule-associated protein, and tau’s relation to the lysosome is that of a substrate. The honest qualification is that the trafficking system is not absent from the risk genetics: the progressive supranuclear palsy association study that identified *MOBP* and *EIF2AK3* also identified *STX6*, a SNARE acting at the Golgi–endosomal interface [47]. But a risk variant in a trafficking SNARE is a different kind of evidence from an allelic series running to a lysosomal storage disease, which is what *GRN* and *GBA1* provide and what no tauopathy has. And the apparent lysosomal signature of tauopathy — granulovacuolar degeneration bodies, which are proteolytically active lysosomes induced by tau pathology — is not tau-specific: the same structures are induced by α -synuclein, in primary neurons and in human Parkinson tissue [12]. A marker induced by two unrelated aggregating proteins is a marker of the cellular response to aggregation, not of a tau-specific lesion.

And the Alzheimer case itself does not rest on tau. It rests on *APP*, the presenilins and *SORL1* — genes of amyloid precursor trafficking. Narrowing the convergence claim to “Alzheimer’s and the tauopathies” would therefore keep the diseases whose genetics does not support it and drop the diseases whose genetics does.

9.3 The three-tier reading the evidence actually supports

What survives is a layered account rather than a single claim.

Tier one — universal, and non-specific. Lysosomal capacity declines with age in the human brain. Glucocerebrosidase activity falls in normal nigra and putamen to levels seen in mutation carriers [10]; filaments of a lysosomal membrane protein accumulate age-dependently in neurologically normal brains [41]. This is real, it is general, and it is a background condition. It explains why these diseases are diseases of ageing. It does not explain why a given person gets a

given one of them.

Tier two — causal and early, in the diseases of the clearance genes. Where the primary lesion is inside the system, the pathway fails first and the proteinopathy follows. The progranulin case is the cleanest; the Alzheimer endosomal case is strong; the *GBA1* case is strong within its stratum.

Tier three — late and consequential, elsewhere. Where the primary lesion is elsewhere, clearance pathology appears when the affected neurons are already dying, and represents overload and debris rather than initiation. Huntington's disease is the demonstrated instance. Sporadic ALS is, on present evidence, undetermined, and the honest expectation is that many sporadic proteinopathies will sort into this tier when they are examined with the whole panel at stage.

The general form is that the endolysosomal system is a **convergence point**, which the co-occurrence data amply demonstrate, and is an **origin** only in the subset of diseases whose genetics put it there. Those are different roles, and the phrase “one mechanism, many diseases” conflates them.

10. Therapeutic Consequence: The Sign Differs Between Diseases

The practical reason this distinction is worth the trouble is that it inverts a therapeutic recommendation.

In Huntington’s disease, stimulate the pathway, and do it early. The machinery is competent at the stages examined, mutant huntingtin is a genuine substrate of it in human brain, and the burden is in principle clearable. This is the conclusion the staged human study itself draws, and it is consistent with the long record of benefit from mTOR inhibition and mTOR-independent autophagy induction in polyglutamine models [48]. The window is bounded: once enough striatal neurons have crossed the repeat threshold, the pathway is carrying debris from dying cells and induction has less to offer.

In Alzheimer’s disease, do not. Induction is *already* elevated in human CA1 neurons from early stages; autophagosome formation and lysosomal biogenesis are both up; and the impediment is downstream, at substrate clearance [13]. Adding induction to a pathway whose terminal step has failed increases the population of undegraded vesicles, which is the mechanism by which neuritic dystrophy propagates. The rational Alzheimer intervention is repair of the terminal step, and the relevant caution is that its molecular identity is disputed (§5.3): re-acidification is right if the vacuolar ATPase account holds and wrong if the lysosomal-calcium account does.

Where the lesion is a specific missing protein, replace it. Progranulin replacement in *GRN* carriers, glucocerebrosidase chaperones or substrate reduction in *GBA1* carriers. These follow from the tier-two reading and require no general theory of convergence at all.

Where the lesion is upstream of the pathway, treat upstream. Suppression of somatic CAG expansion, for which antisense reduction of *MSH3* is a demonstrated approach in patient-derived neurons [21], acts on the rate-limiting step in Huntington’s disease. It is not in competition with early autophagy induction; the two act at different points and the convergence framing obscures that they could be combined.

The point of general interest is that a single mechanistic claim, applied across diseases, generated a single therapeutic recommendation — boost clearance — in diseases where the correct sign of the intervention differs. That is the cost of a theory that is always confirmed.

II. Strength of Evidence

Each claim below is graded by the strongest evidence that supports it, with the kind of evidence named.

Table 2 — Graded claims

Claim	Grade	Basis
Autophagic–endolysosomal abnormality is present at some stage in AD, PD, FTD, ALS and HD	Established	Convergent human tissue across all five diseases; uncontested
Lysosomal capacity declines with normal human brain ageing	Established	Glucocerebrosidase activity falls with age in normal nigra and putamen; age-dependent TMEM106B filaments in neurologically normal brains
The autophagy–lysosomal pathway is competent in human HD striatum at Vonsattel grade 2 and fails at grades 3–4	Strong	Multiplexed human study: transcripts, immunoblots, cathepsin activity, immunohistochemistry, electron microscopy, staged, two regions plus cerebellum control
HD pathogenesis is rate-limited by somatic CAG expansion past a ~150-repeat threshold, not by clearance	Strong	Single-cell repeat sizing with paired transcriptomes in human striatum; modifier GWAS naming DNA-maintenance genes; CAA-interruption result
The “empty autophagosome” of HD is not demonstrated in human brain	Moderate	Vesicles of that appearance decorate for calnexin and are absent from biopsied material; authors decline to affirm or refute their existence
Early-endosome abnormality precedes amyloid deposition in human AD tissue	Strong	Sporadic AD and Down syndrome cortex before plaque formation; corroborated by isogenic human neuron panels and <i>SORL1</i> depletion
Substrate-clearance failure is present in human AD CA1 neurons at early Braak stage	Strong	Whole-sequence assay in laser-captured CA1 neurons, early and late stage, with controls
Autolysosomal de-acidification is an early event in the human AD brain	Moderate	Timing established in five mouse models; human contribution is end-point morphology; lysosomal pH not measurable post mortem

Claim	Grade	Basis
The presenilin–vacuolar ATPase mechanism of AD lysosomal failure	Contested	Primary report and a direct rebuttal both stand; no resolving experiment in fourteen years; human neuropathology separates <i>APP</i> from presenilin endocytic phenotypes
Lysosomal failure is causal and pre-symptomatic in <i>GRN</i>-associated FTD	Strong	Human allelic series from storage disease to dementia; storage material and impaired protease activity in living heterozygous carriers; rescue by restoring progranulin
Lysosomal failure is causal in the <i>GBA1</i> Parkinson stratum	Strong	Odds ratio above five in 5,691 patients; enzyme deficit greatest in nigra; homozygous state is a storage disease
Lysosomal failure is causal in sporadic Parkinson’s disease	Moderate	Early regional glucocerebrosidase deficit supports it; marker loss tracking inclusions and age-matched decline in controls argue for a threshold effect
Clearance failure precedes degeneration in sporadic ALS	Weak	No stage-resolved human data; autopsy findings show activation, not failure; genetics is familial
Early causal clearance failure occurs where and only where the primary genetic lesion lies inside the endolysosomal system	Proposed	The organising claim of this paper. Consistent with five diseases; it is a rule inferred from five instances and is stated to be falsifiable by the tests in §12
Autophagy induction is beneficial early in HD and harmful at the equivalent stage in AD	Proposed	Follows from the staged tissue findings in each disease; no head-to-head trial or tissue comparison exists

12. Predictions

Each prediction names the experiment that would settle it and the result that would refute the argument.

12.1 Pre-manifest Huntington’s tissue will show no clearance deficit. Run the same multiplexed panel — induction markers, cathepsin activity, LAMP1/2, cathepsin D immunohistochemistry, ultrastructure — on caudate from Vonsattel grade 0 and grade 1 cases and from pre-manifest carriers who died of other causes. *Prediction: indistinguishable from control, with the possible exception of raised LAMP1 as a load response. Refuting result: a substrate-clearance deficit present at grade 0–1 and absent at grade 2, which would restore the primacy claim in HD and force the artefact reading of §3.2 to be reconsidered.*

12.2 Within Huntington’s striatum, clearance pathology will segregate by repeat length, not by disease grade. Combine single-nucleus *HTT* CAG sizing with single-nucleus measurement of lysosomal and autophagic transcripts in the same nuclei. *Prediction: autophagy–lysosomal transcript changes appear only in the stratum above roughly 150 repeats, and a grade 4 nucleus below threshold looks like a control nucleus. Refuting result: clearance changes distributed across repeat lengths and tracking grade, which would make clearance a tissue-level rather than a cell-autonomous consequence and would reopen a non-cell-autonomous causal role.*

12.3 The head-to-head has never been run and will separate the diseases. Apply one protocol, in one laboratory, to Braak I–II entorhinal cortex and Vonsattel grade 2 caudate, with matched post-mortem intervals. *Prediction: the Alzheimer tissue shows a substrate-clearance deficit at its early stage and the Huntington tissue does not. Refuting result: both competent, which would remove the Alzheimer primacy claim as well; or both deficient, which would restore the general convergence claim.* This is the single most decisive available experiment, and it requires no new technique.

12.4 The genetic-position rule is testable across diseases now. For each neurodegenerative disease with both a genome-wide association study and staged neuropathology, compute the proportion of genome-wide-significant loci mapping to endolysosomal genes, and rank diseases by the stage at which clearance pathology first appears in human tissue. *Prediction: the two rank orders correlate. Refuting result: no correlation, or a disease with no endolysosomal genetics showing clearance failure at its earliest stage.*

12.5 Somatic-expansion suppression will not change early clearance markers, and will prevent late ones. In a model permitting both measurements, suppress *MSH3* and assay the autophagy–lysosomal panel over time. *Prediction: no effect on early markers, because they are*

already normal, and prevention of the late deficit, because the neurons never cross threshold. Refuting result: early clearance markers change on MSH3 suppression, which would place clearance in the causal chain after all.

12.6 Autophagy induction will have opposite signs in the two diseases. *Prediction: an autophagy-inducing agent trialled in early Huntington's disease shows benefit on the substrate measures, and the same agent at the equivalent stage of Alzheimer's disease shows null or worsening on the same measures. Refuting result: benefit in both, which would indicate that the Alzheimer terminal-step deficit is not rate-limiting in life.*

12.7 Pre-symptomatic lysosomal storage predicts conversion in progranulin carriers. Follow heterozygous *GRN* carriers prospectively with retinal imaging. *Prediction: the magnitude or rate of change of retinal lipofuscinosis predicts time to symptom onset. Refuting result: no relation between storage burden and conversion, which would demote the storage phenotype from cause to correlate even in the disease where the case is strongest.*

12.8 Sporadic ALS will sort into tier three. Apply the whole panel to spinal cord from cases staged by TDP-43 distribution. *Prediction: clearance competent at the earliest stage, failing where TDP-43 pathology is established — that is, the Huntington pattern rather than the Alzheimer pattern. Refuting result: early clearance failure in sporadic ALS, which would extend tier two to a disease whose principal genetics is not clearly inside the pathway and would weaken the genetic-position rule.*

13. Limitations

Post-mortem tissue cannot measure flux. Every human result in this paper is a snapshot of a steady state. Autophagic flux is a rate, and rates are inferred from marker configurations, not observed. The inference is strongest when the whole sequence is assayed at once, which is why those studies carry the argument, but it remains an inference.

Lysosomal pH cannot be measured in fixed human tissue. The claim that autolysosomes de-acidify early in the human Alzheimer brain therefore cannot currently be tested in the human brain. This is a structural limit, not an oversight, and it means the Alzheimer arm of the argument has a gap at exactly the point that is most often asserted most confidently.

The Huntington result has not been replicated. It is one study, from one laboratory, on one staged series. Its internal consistency across five independent methods is considerable, and its concordance with independent genetics is the reason it is graded strong here; but replication in a second cohort has not occurred.

No pre-manifest Huntington's tissue was examined, and the earliest stage available is already one of substantial striatal degeneration. §12.1 exists because of this.

Bulk tissue mixes cell types. The immunoblot and transcript data in every disease discussed are dominated by whichever population is most abundant, and glial autophagy can mask neuronal change. Cell-resolved data agree with bulk data in the Huntington study, which is reassuring, but this caveat applies throughout the field.

Genome-wide association loci are not genes. The claim that Alzheimer risk loci are enriched in endolysosomal pathways depends on locus-to-gene assignment, which is uncertain at many loci. The genetic-position rule inherits this uncertainty.

The rule is inferred from five diseases. A regularity across five instances, chosen because they are the instances with the best data, is a hypothesis and is graded as one. §12.4 is the test that would move it.

Selection of the literature. Human tissue studies with staging and multiplexed panels are rare, and weighting them heavily means weighting a small number of studies heavily. Where a single study carries a claim, this is stated in Table 2.

14. Conclusions

A staged examination of the human Huntington’s brain found the autophagy–lysosomal pathway competent in the vulnerable region at the earliest stage tissue permits, with failure emerging only late and regionally. The finding is not a curiosity. It is the predicted behaviour of a disease whose rate-limiting step is a somatic DNA-repeat expansion in the neuron’s own nucleus, silent until it crosses a threshold and then rapidly lethal — a mechanism established independently, by single-cell repeat sizing and by modifier genetics that names DNA-maintenance genes and no clearance genes at all.

The general claim that convergent autophagic collapse is the shared upstream mechanism of adult neurodegeneration therefore requires narrowing. But the narrowing that the evidence supports is not by disease taxon. It is by genetic position. Early, causal clearance failure is found where the genes that cause the disease encode parts of the clearance apparatus — most cleanly in progranulin-associated frontotemporal degeneration, where the human allelic series runs from childhood lysosomal storage to adult dementia and heterozygous carriers store lipofuscin before they are ill; strongly for the endosomal lesion of Alzheimer’s disease, whose causal and risk genes are genes of endosomal trafficking; strongly within the *GBA1* stratum of Parkinson’s disease. It is not found where the primary lesion lies elsewhere.

That narrowing crosses the proteinopathy classification in both directions. It admits two non-Alzheimer diseases and excludes the primary tauopathies, which have no lysosomal allelic series of the kind progranulin and glucocerebrosidase provide, and whose apparent lysosomal signature is induced as readily by α -synuclein as by tau. A narrowing to “Alzheimer’s disease and the tauopathies” would keep the wrong diseases and drop the right ones.

Between these two roles sits a third fact that is easily mistaken for the mechanism: the lysosome of the ageing human brain declines in every person, to levels that in the *GBA1* case are indistinguishable from those in mutation carriers. That decline is why these are diseases of late life. It is not why any of them is the disease it is.

The practical consequence is a change of sign. Stimulating autophagy is a rational early intervention in Huntington’s disease, where the machinery works and the load is clearable, and an irrational one at the corresponding stage of Alzheimer’s disease, where induction is already raised and the failure is at the end of the line. A theory that is confirmed by every dataset cannot tell those two situations apart. A theory that specifies *when* can.

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