# THE ARCHITECTURE OF RESISTANCE

*The Protective Genes and Epigenetic States That Prevent or Delay Alzheimer's Disease*
*— A Strength-Graded Atlas of the Genome's Defences*

*The Icelandic Reprieve · The ε2 Advantage · The Two Spared of Antioquia*
*The Microglial Gain · The Klotho Buffer · The Reversible Ink*

*A Doctoral Synthesis Prepared in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience*

Prepared under the Organic Network Synthesis methodology

**AdultCognitiveDisease.com**

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July 2026

*The defensive counterpart of the corpus's risk atlas. Where The Genetic Architecture of Neurodegeneration maps the alleles that condemn a brain, this volume maps the genes and epigenetic states that reprieve it — and grades every defence, from the Icelandic APP variant to the reversible epigenome, on an explicit scale of evidentiary strength, so that each may be weighed for how much it is known, not merely admired for what it promises.*

*"A lesion tells us only that a pathway can be broken. A reprieve tells us that a pathway can be held — and it tells us so with the one authority human genetics rarely commands: a person in whom the change came first, the outcome after, and time itself forbids the confusion of the two. Every protective allele is an experiment already concluded. The only question it leaves is the pharmacology."*

— ONS Methodology Working Notes, 2026

*For the fortunate few whose genomes ran the trial we could not — and for the ordinary many to whom, one reversible defence at a time, their fortune might yet be lent.*

# THE COLLAPSE CORPUS  THE DEFENSIVE COMPANION

*The Genetic Architecture of Neurodegeneration  (the risk atlas)*

*The Architect's Reprieve  (reelin, the single-gene resilience dive)*

*The Fading Score  (the epigenome as reversible information layer)*

**The Architecture of Resistance ← this volume**

This volume stands to the corpus as the mirror of its genetics of risk. The companion risk atlas catalogues the alleles that bring Alzheimer's disease sooner and to more people; the reelin dive follows one guardian gene in depth; the epigenetic volume reads the disease's reversible information layer. This one reads the whole genome for its *defences* — the substrate-lowering, responder-sharpening, tau-sparing, clock-slowing, and reversible-epigenetic factors by which a brain resists or delays the disease — and grades each on a single scale of strength, so that the atlas of what protects can be held to the same evidentiary standard as the atlas of what harms.

# Contents

# Abstract

Almost the entire genetics of Alzheimer's disease has been written in the language of risk — of the alleles that bring the disease sooner, harder, and to more people. This dissertation reads the same genome in the opposite direction. It asks which genes and which epigenetic states *prevent* the disease or *hold it at bay*, and it grades each of them, explicitly and without flattery, by the strength of the evidence that it does. The premise is that a defence is as informative as a lesion: every allele that protects names a step in the disease that is, in principle, drug-addressable, and does so with the one form of proof the field can rarely obtain — a human being in whom that step was altered and the outcome changed.

The atlas that results has a clear topography. At its established summit sit a small number of factors whose protection is either population-robust or causal-grade in humans: the Icelandic *APP* A673T substitution, which lowers β-secretase cleavage of the amyloid precursor by roughly forty percent and cuts lifetime disease risk several-fold — the strongest single-gene protection known, and the cleanest human vindication of the amyloid hypothesis read forwards; the *APOE* ε2 allele, the common protective counter-weight to ε4, whose homozygotes enjoy an exceptionally low likelihood of Alzheimer's dementia; the *PLCG2* P522R variant, a functional hypermorph of microglial signalling that protects across several dementias and associates with longevity; and the two experiments of nature in the Antioquia kindred — the *APOE3*-Christchurch homozygote and the Reelin-COLBOS man — each of whom resisted an otherwise fully penetrant autosomal-dominant dementia for three decades, and whose protection, now that a 2024 cohort has replicated a milder Christchurch effect in twenty-seven heterozygotes, can no longer be dismissed as an anecdote. Below the summit lie the well-supported common variants — a protective *CD33* allele, an *MS4A* haplotype that raises soluble TREM2, the *KL*-VS klotho variant that buffers the very carriers of ε4 who need it most — and, lower still and frankly graded as emerging, the epigenetic layer: the sirtuins, the restraint of HDAC2, the microRNA control of BACE1, the deceleration of the methylation clock.

Two principles organize the whole. The first is that protection is upstream-heavy and tau-sparing: the strongest defences either make less toxic substrate or, having failed to stop the amyloid, still spare the tau — a pattern that repeatedly identifies tau, not amyloid, as the proximate executioner, and the amyloid-generating and tau-releasing steps as the two most protectable joints of the disease. The second is that the genome's defences are the mirror of its risks: the same loci recur — *APOE*, the *TREM2–PLCG2* axis, *CD33*, reelin — with the arrow reversed, so that risk and protection are not two catalogues but one dial read from opposite ends. From this follows the therapeutic ambition that closes the dissertation: to phenocopy the fortunate. We grade, for each defence, how far that ambition is already justified, name for each the experiment that would settle it, and insist throughout on the distinction that most of the literature blurs — between the fixed defences written into the germline, which teach us where to aim, and the reversible defences of the epigenome, which are the only ones we might yet learn to

install.

# I. The Inverse Question

The genetics of Alzheimer's disease is, overwhelmingly, a literature of accusation. It names the alleles that condemn: the autosomal-dominant mutations in *APP*, *PSEN1*, and *PSEN2* that guarantee an early dementia; the *APOE* ε4 allele that, in double dose, has lately been reclassified as a near-Mendelian form of the disease in its own right (Fortea and colleagues, 2024); the lengthening roster of common variants — in the microglial genes, the endocytic genes, the immune genes — each of which nudges the odds a little further toward ruin. This is the architecture of neurodegeneration, and it has been mapped, in a companion volume to this one, in exhaustive detail. The present dissertation is written to map its shadow: the architecture of *resistance*, the far smaller and far less studied set of genes and epigenetic states that do the opposite — that prevent the disease, delay it, or hold a brain intact against a burden of pathology that should by every rule have destroyed it.

The choice to study protection rather than risk is not a rhetorical inversion but a methodological one, and it rests on a simple asymmetry of evidence. A risk allele tells us that a pathway, when broken, permits the disease; it is consistent with that pathway being causal, but also with its being a bystander swept up in the wreckage. A protective allele tells us something stronger and rarer. When a fixed genetic change is present from conception and the disease that should have come does not, the change has run a controlled experiment across a human lifetime, with the confound of reverse causation excluded by the arrow of time itself: the allele preceded the outcome, and nothing the disease did could have installed it. Protection, in short, is the closest thing human genetics offers to a proof of mechanism. Each protective variant is a natural clinical trial of a target, already concluded, its result written in a phenotype. To catalogue these variants and grade them is therefore not an exercise in optimism. It is the most efficient available route to the list of steps in Alzheimer's disease that are worth a drug.

There is a second reason to prefer the inverse question, and it is therapeutic. The history of Alzheimer's drug development is a history of trying to remove things — to clear amyloid, to inhibit a secretase, to quiet a kinase — and its most instructive failures, examined in Section XI, came precisely from removing too much of something the brain also needed. The protective alleles suggest a different grammar. They do not, for the most part, abolish a pathway; they tune it. The Icelandic *APP* variant does not delete β-secretase cleavage but lowers it by a fraction. The *PLCG2* protective variant does not silence microglia but sharpens them. The klotho variant does not rebuild the brain but raises, by a modest increment, a hormone the brain already makes. The fortunate are not fortunate because they lack a disease pathway; they are fortunate because they carry a slightly better-set version of a pathway everyone carries. That is a far more tractable thing to imitate with a

molecule than the wholesale removal of a protein, and it reframes the therapeutic project from subtraction to calibration.

This dissertation is organized as a graded atlas. After establishing, in Section II, a grammar of what "protection" can mean and an explicit scale on which to weigh it, we proceed layer by layer through the genome's defences — the reduction of the toxic substrate (Section III), the fortification of the cellular responder (Section IV), the resistance and resilience variants that act downstream on the diseased brain itself (Section V), the modifiers that slow the clock of ageing on which the disease depends (Section VI), and the reversible defences of the epigenome (Section VII) — before assembling every factor into a single strength-graded ledger (Section VIII), drawing out the two principles the defences share (Section IX), and turning at last to the therapeutic corollary that animates the whole: whether, and how far, we can learn to phenocopy the fortunate (Sections X through XII).

> *The disease has been read for forty years as a list of the ways a brain can be condemned. This dissertation reads the same genome for the ways a brain has been reprieved — and asks, of each reprieve, exactly how much we know.*

# II. A Grammar of Protection — and the Scale on Which It Is Weighed

Before cataloguing the defences one must be precise about what a defence is, because the word "protective" conceals at least two different biological claims, and the confusion between them has muddled the resilience literature for a decade.

### Resistance and resilience are not the same thing

The distinction, sharpened by the investigators of the Antioquia kindred, is between *resistance* and *resilience*. A factor confers **resistance** when it prevents the pathology from accumulating — fewer plaques, less tau, a lighter burden of the disease's physical lesions. A factor confers **resilience** when it preserves cognition *despite* the pathology — the lesions accumulate, but the mind does not fail on schedule. The two are mechanistically distinct and they live at different points in the causal chain. Resistance acts upstream, on the production or clearance of the toxic species; resilience acts downstream, on the capacity of the neural tissue to tolerate a given insult. A drug modelled on a resistance factor would aim to lower amyloid; a drug modelled on a resilience factor would aim to protect the synapse while amyloid ran on. Much of the argument of this dissertation turns on keeping the two apart, because the most illuminating protective variants — the Christchurch and COLBOS cases — are resilience factors that let amyloid accumulate almost unchecked and spared the tau and the cognition downstream, which is why they point so insistently at tau rather than amyloid as the disease's proximate executioner.

## Five layers at which a genome can defend a brain

Across both categories, the defences distribute among five biological layers, and this dissertation is structured around them. **First, the substrate layer:** reduce the amount of toxic material made in the first place — the domain of *APP* A673T and, in part, *APOE* ε2. **Second, the handling and clearance layer:** dispose of the material more efficiently once made — the domain of the lipid- and endosome-handling genes. **Third, the responder layer:** equip the brain's innate-immune cells, the microglia, to contain and clear the pathology rather than to inflame around it — the domain of the *TREM2–PLCG2* axis, *CD33*, and *MS4A*. **Fourth, the target layer:** harden the neuron and the synapse themselves against a given burden — the domain of reelin, and of the resilience variants. **Fifth, the tempo layer:** slow the biological ageing on which the disease is scaffolded — the domain of klotho and the sirtuins, and the reversible domain of the epigenetic clock. A protective factor is best understood not in isolation but by the layer at which it acts, because the layer determines both the therapeutic strategy it implies and the window in which that strategy could work.

## The grading scale

The discipline of this atlas is that no factor is asserted to protect without a grade attached, and the grade is assigned on an explicit, four-tier scale defined once, here, and applied uniformly in the ledger of Section VIII.

| Tier | Name | The bar it must clear |
|---|---|---|
| **I** | Established | Human evidence, either population-robust (replicated genetic association with a stable effect size) or causal-grade (a fixed variant that changed a human disease course), *and* a mechanism at least partly worked out. |
| **II** | Well-supported | Robust human genetic association with the protective direction secure, but mechanism incomplete or the effect conditional on context (e.g. present only in a subgroup). |
| **III** | Emerging | Mechanistically compelling and directionally supported, but the human protective evidence is thin, indirect, or largely inferred from animal and cellular models. |
| **IV** | Conjectural | Plausible and worth stating, but resting on correlation vulnerable to reverse causation, on model systems alone, or on evidence that has since been contradicted or withdrawn. |

Two orthogonal flags are carried alongside the tier because they matter for both honesty and therapy. A **double-edged** flag (a dagger, †) marks a factor whose protection against Alzheimer's disease is bought at a cost elsewhere — the clearest case being *APOE* ε2, which lowers Alzheimer's risk while raising the risk of the cerebral amyloid angiopathy that causes lobar haemorrhage. And an **installability** flag distinguishes the **fixed** defences (●), written into the germline and unmodifiable after conception, from the **reversible** defences (○) of the epigenome, which are in principle installable in a person who was not born with them. The distinction is the hinge of the therapeutic argument: the fixed defences tell us where to aim; only the reversible defences can be aimed at directly.

With the grammar and the scale in place, we turn to the defences themselves, beginning at the layer where protection is both strongest and simplest — the reduction of the substrate.

# III. The Substrate Defence — Making Less of the Poison

The most decisive way to protect a brain from a toxic peptide is to make less of it, and the two strongest protective factors in all of Alzheimer's genetics both act, in whole or in part, at this layer. One of them is the single most important protective variant ever found.

### The Icelandic reprieve: APP A673T

In 2012, sequencing the genomes of nearly eighteen hundred Icelanders, Jonsson and colleagues found a coding change in the amyloid precursor protein that did what every other *APP* mutation known to medicine did in reverse. The autosomal-dominant *APP* mutations that cause early-onset Alzheimer's disease cluster around the sites where the precursor is cut — at the β-secretase site, where the Swedish mutation enhances cleavage and floods the brain with amyloid; at the γ-secretase site, where the London mutation shifts the product toward the aggregation-prone Aβ42; within the peptide itself, where the Arctic mutation makes the fragment assemble faster. The Icelandic variant, A673T, sat at the same β-secretase site — a single alanine-to-threonine substitution two residues into the amyloid sequence — and it lowered the cleavage. In vitro, cells carrying A673T produced roughly forty percent less of the amyloidogenic peptides. In the population, the carriers were markedly protected: the variant conferred an odds ratio for Alzheimer's disease on the order of 0.2, a roughly five-fold reduction in lifetime risk, and — the detail that lifts it above every other protective allele — it protected the carriers against ordinary, age-related cognitive decline as well, in elderly people who did not have and would never develop the disease (Jonsson and colleagues, 2012).

The importance of A673T is difficult to overstate, and it is threefold. First, as protection: a several-fold reduction in lifetime risk from a single common-mechanism change is the largest protective effect of any known *APP* variant and among the largest of any locus. Second, as proof: A673T is the cleanest piece of human evidence, read forwards rather than backwards, that the amyloid cascade is causal. Every pathogenic *APP* mutation increases amyloid production and causes the disease; this one variant decreases amyloid production and prevents it — same protein, same enzyme, same biochemical step, opposite direction, opposite outcome. If the amyloid hypothesis needed a controlled human experiment, A673T is it. Third, as a target: because the variant works by lowering β-secretase cleavage, it identifies partial BACE1 inhibition as a strategy with a human proof-of-concept already in hand — a promise that, as Section XI recounts, the clinic then spent a decade learning how to break.

The mirror of A673T deserves a sentence, because it demonstrates that the same codon can be read in either direction. A different substitution at the very same residue, A673V, does the opposite: it *causes* early-onset Alzheimer's disease. But it does so only in the homozygous state — a recessive dementia — because a single copy, mixed with wild-type peptide, actually *destabilizes* the aggregates and inhibits amyloid formation, a dominant-negative effect that renders the heterozygote unaffected (Di Fede and colleagues, 2009). Residue 673 of the amyloid precursor is thus a hinge on which the disease turns both ways: threonine protects, valine condemns, and the difference is a matter of how the mutant peptide keeps company with the normal one. No single locus states the amyloid hypothesis's logic more economically.

We grade A673T at **Tier I**, the ledger's most secure entry: a replicated, population-scale human protective effect with a worked-out biochemical mechanism and a coherent dose–response across the whole *APP* mutational spectrum. It is a fixed defence — the fortunate are born to it — and its therapeutic lesson is the sharpest in the atlas.

## The common counter-weight: APOE ε2

If A673T is the rarest and strongest protective allele, *APOE* ε2 is the most common and the most consequential at the population scale. The *APOE* gene carries three alleles distinguished by two amino-acid positions — ε2, ε3, and ε4 — and their effects on Alzheimer's risk span nearly two orders of magnitude, the widest range of any common locus in the disease. Against the ε3/ε3 reference, the canonical meta-analysis of Farrer and colleagues (1997) placed a single ε4 allele at an odds ratio near 3 and the ε4/ε4 homozygote near 15; the ε2 allele ran the other way, the ε2/ε3 genotype sitting at an odds ratio near 0.6. Each ε2 allele delays the median age of onset by several years, precisely as each ε4 allele advances it. And the protection deepens with dose in a way that has only recently been quantified at scale: in a neuropathologically confirmed series of more than five thousand brains, Reiman and colleagues (2020) found that *APOE* ε2 homozygotes carry an *exceptionally* low likelihood of Alzheimer's dementia — the lowest-risk common genotype yet described, its odds against the ε4/ε4 homozygote separated by a chasm. The same study made a methodological point that bears on every effect size in this atlas: the *APOE* dose effects, both protective and harmful, were substantially stronger when measured against autopsy-confirmed diagnosis than against clinical diagnosis alone, a reminder that genetic protection is systematically underestimated by studies that cannot see the pathology.

The mechanism of ε2 protection is multiple and only partly resolved, which is why it sits, on mechanism, a notch below the biochemical clarity of A673T. Apolipoprotein E is the brain's principal lipid-transport protein, secreted mostly by astrocytes, and the three isoforms differ in how they bind lipid, how they engage the lipoprotein receptors, how they are cleared, and how they influence the aggregation and clearance of amyloid. The ε2 isoform lipidates more favourably, seeds amyloid less avidly, and appears to support the clearance of the peptide and the maintenance of the

synapse where ε4 impairs all three. Because *APOE* touches the disease at several layers at once — substrate handling, microglial state, and the synaptic matrix — its protection is not cleanly assignable to a single step, and we place it, honestly, at the substrate-and-handling layer while noting that its reach extends further. What is not in doubt is the direction and the magnitude, both replicated across three decades and every major cohort.

*APOE* ε2 also carries the atlas's clearest **double-edged** flag. The same ε2 biology that protects the parenchyma against Alzheimer's disease predisposes the cerebral vasculature to amyloid angiopathy, and in the setting of lobar intracerebral haemorrhage the ε2 allele is associated with larger haematomas, higher mortality, and worse functional outcome — each copy adding measurably to the bleed (Biffi and colleagues, 2011). The lesson is general and worth stating early: a factor that protects one compartment may imperil another, and an honest atlas of defence must grade the cost alongside the benefit. We grade *APOE* ε2 at **Tier I** for its protection against Alzheimer's disease — population-robust, replicated, dose-dependent — with the double-edged flag raised and the mechanism marked as incompletely resolved.

# IV. The Responder Defence — Sharpening the Microglion

The second layer of defence does not touch the amyloid directly but the cell that is supposed to deal with it. Microglia, the brain's resident immune cells, surround plaques, take up amyloid, and — when they work — contain the pathology; when they fail, they inflame around it and accelerate the injury. A striking fraction of the common protective genetics of Alzheimer's disease acts here, and the pattern it forms is unusually coherent: nearly every one of these variants makes the microglion a better clearer and a worse inflamer. The axis is best introduced through its most famous risk gene, because the protective variants are legible only against it.

### The axis defined by its loss: TREM2

TREM2 is a microglial surface receptor that senses lipids and damaged material, licenses the cell to proliferate, migrate to plaques, and adopt the "disease-associated" state in which it walls off and processes amyloid. Its importance was established, as so often, by a loss-of-function experiment written into a human population: the rare R47H variant, reported simultaneously by Guerreiro and colleagues (2013) and Jonsson and colleagues (2013), impairs the receptor's ligand binding and roughly triples the risk of Alzheimer's disease — an odds ratio near 2.9, approaching that of an *APOE* ε4 allele. R47H is not itself protective; it is the opposite. But it defines the axis, because it demonstrates that the microglial containment response is causally load-bearing: cripple it, and the disease comes. Everything protective in this section works by strengthening the same response that R47H weakens, and the therapeutic programme it has spawned — agonist antibodies that push TREM2 signalling upward, one of which reduced plaque burden and induced protective microglial proliferation in a mouse model and has since engaged its target in human cerebrospinal fluid (Wang and colleagues, 2020) — is an attempt to buy pharmacologically the microglial vigour that the protective variants below confer by birth.

## The microglial gain: PLCG2 P522R

Immediately downstream of TREM2 sits phospholipase C-γ2, the enzyme that transduces the receptor's signal into the cell, encoded by *PLCG2*. In 2017, screening rare coding variants across eighty-five thousand subjects, Sims and colleagues found a substitution in this enzyme, P522R, that protected against Alzheimer's disease with an odds ratio of 0.68 — a roughly one-third reduction in risk, at genome-wide significance. The same screen found, in the neighbouring gene *ABI3*, a variant that raised risk, underscoring that the microglial signalling module can be tuned in either direction. What made P522R more than a statistical hit was its mechanism, worked out shortly after: the variant is a *functional hypermorph*, a mild gain-of-function that modestly increases the enzyme's activity (Magno and colleagues, 2019). It does not switch the pathway on; it turns it up a little. A microglion carrying P522R transduces the TREM2 signal slightly more strongly, and across a lifetime that small, chronic enhancement of the containment response is worth a third of the disease risk.

Two further findings lift P522R toward the top of the common-variant defences. First, its protection is not confined to Alzheimer's disease: van der Lee and colleagues (2019) showed that the same allele protects against dementia with Lewy bodies and frontotemporal dementia as well, and — remarkably — associates with an increased likelihood of *longevity*. A variant that sharpens microglial signalling protects against several neurodegenerative diseases at once and lets its carriers live longer, which argues that it acts on a shared and fundamental axis of brain ageing rather than on a disease-specific quirk. Second, it composes with the risk axis it lies on: because P522R acts downstream of TREM2, its gain-of-function can partially offset the loss-of-function of a crippled receptor, which is exactly the logic a TREM2-agonist drug hopes to exploit. We grade *PLCG2* P522R at **Tier I** — a population-robust, replicated, cross-disease protective coding variant with a defined gain-of-function mechanism — the strongest of the microglial defences and one of only a handful of common alleles that earns the atlas's highest tier.

## Raising the soluble sentinel: the MS4A haplotype

TREM2 is cleaved from the microglial surface into a soluble fragment, sTREM2, that circulates in the cerebrospinal fluid and appears itself to be protective — a marker, and perhaps a mediator, of a well-functioning microglial response. The level of that fragment is under genetic control, and the controller is the *MS4A* gene cluster. Deming and colleagues (2019) identified a variant in this cluster, rs1582763, that simultaneously raises cerebrospinal-fluid sTREM2, lowers Alzheimer's risk, and delays the age of onset — a protective haplotype acting through the same TREM2 biology from a different genetic angle, with MS4A4A physically colocalizing with TREM2 on the microglial membrane and governing how much soluble receptor is shed. The variant is robust and its direction secure, but the mechanism by which elevated sTREM2 protects is still being resolved, and the protective effect, while replicated, is modest. We grade the *MS4A* / sTREM2-raising haplotype at **Tier II** — well-supported human association, mechanism partly open.

### Restoring the phagocyte: the protective CD33 allele

The last of the microglial defences works by releasing a brake. CD33 is an inhibitory receptor on microglia; when engaged, it restrains the cell's uptake of amyloid. A common variant at the locus, rs3865444, alters the splicing of the receptor: the protective minor allele reduces the amount of functional CD33 on the cell surface, and a microglion with less CD33 is a more avid phagocyte. Griciuc and colleagues (2013) showed that the protective allele was associated with lower CD33 expression and lower insoluble Aβ42 in the human brain, and that deleting CD33 in an amyloid mouse markedly reduced plaque burden — the receptor inhibits microglial clearance, and losing it unleashes clearance. Bradshaw and colleagues (2013) traced the parallel effect to circulating monocytes, where the risk allele raised surface CD33 and blunted amyloid internalization. The mechanism is the exact inverse of TREM2: where TREM2 loss-of-function removes an activating signal and raises risk, CD33 loss-of-function removes an inhibitory signal and lowers it, and both converge on the same phagocytic containment of amyloid. The human genetic association is robust and the mechanism is well worked out in model systems and human tissue; the protective effect size is modest. We grade the protective *CD33* allele at **Tier II**, at the upper edge of it — a well-supported defence whose mechanism, unusually for this tier, is nearly complete.

The four microglial factors together make the atlas's most internally consistent statement. Strengthen the activating arm (P522R, sTREM2) or release the inhibitory arm (protective CD33), and the disease retreats; weaken the activating arm (TREM2 R47H) or reinforce the inhibitory arm, and it advances. The microglion is a rheostat of resistance, and the common genetics has found the protective setting from four independent directions.

# V. The Resistance and Resilience Variants — Holding a Doomed Brain

The defences of Sections III and IV lower the odds of ever developing the disease. The variants of this section do something rarer and more dramatic: they hold a brain intact that has *already been condemned* — that carries a fully penetrant, autosomal-dominant mutation guaranteeing early dementia — and let it accumulate the disease's pathology while sparing its mind. These are the experiments of nature, and they are concentrated, with astonishing improbability, in a single extended family.

## The kindred that made the experiments possible

In the Colombian department of Antioquia lives the largest known kindred with autosomal-dominant Alzheimer's disease: some thousands of relatives carrying the *PSEN1* E280A mutation, which causes a fully penetrant early-onset dementia with cognitive decline beginning, on average, in the mid-forties. The tragedy of the kindred is also its scientific value: because the mutation is so penetrant and the age of onset so predictable, any relative who deviates from the schedule — who carries E280A and yet does *not* decline on time — is a natural experiment in resistance or resilience, with the causal mutation held constant and the modifier isolated against it. Two such deviants have been described in detail, and each has reorganized the field.

## The first spared: APOE3-Christchurch

The first was a woman who carried E280A and should, by the family's timetable, have declined in her forties, but who remained free of mild cognitive impairment into her seventies — three decades of reprieve. Her brain, imaged and eventually examined, showed the paradox that defines this section: an *unusually high* burden of amyloid, among the heaviest measured, and yet strikingly *limited* tau tangle pathology and limited neurodegeneration, especially in the entorhinal cortex where the disease's tau lesion begins. The amyloid had come in full; the tau, and the dementia, had not. She was homozygous for a rare variant of apolipoprotein E, the Christchurch variant R136S, in the region of the protein that governs its binding to heparan-sulfate proteoglycans — and the variant weakened that binding (Arboleda-Velasquez and colleagues, 2019). The proposed mechanism placed the protection squarely at the target layer and downstream of amyloid: by reducing APOE's engagement of heparan sulfate, the variant impaired the propagation of tau and the pathological signalling that converts an amyloid burden into a tau catastrophe, so that amyloid accumulated but its downstream consequence was severed.

The Christchurch case was, for four years, a single individual — causal-grade in its logic but an *n* of one in its statistics, and single cases cannot exclude the contribution of unmeasured modifiers. That limitation was substantially answered in 2024, when Quiroz and colleagues reported the effect of Christchurch *heterozygosity* across the kindred: among more than a thousand E280A carriers, the twenty-seven who carried a single copy of the Christchurch variant declined at a median age of fifty-two, against forty-seven for their matched relatives without it — a delay of roughly five years from one copy, with imaging and autopsy evidence of relatively preserved metabolism, limited tau, and fewer vascular-amyloid features (Quiroz and colleagues, 2024). The dose–response is the important thing: one copy buys five years, two copies bought thirty. A protective effect that scales with allele count in the predicted direction is no longer an anecdote; it is a replicated, dose-dependent human resilience factor. We grade *APOE3*-Christchurch at **Tier I** — causal-grade in the homozygote and now population-replicated in the heterozygotes, with a mechanism, the heparan-sulfate–tau axis, at least partly resolved.

### The second spared: Reelin-COLBOS

The second deviant was a man in the same kindred who carried the same E280A mutation and remained cognitively intact until sixty-seven — again some three decades late — again with an extremely high amyloid burden and again with limited entorhinal tau. He did *not* carry the Christchurch variant. He carried, heterozygously, a rare gain-of-function variant in the reelin gene, H3447R, named COLBOS, which activates reelin's canonical intracellular target Disabled-1 more strongly than ordinary reelin and, in a knock-in mouse, lowers the phosphorylation of human tau (Lopera and colleagues, 2023). Reelin, the large secreted glycoprotein that first built the cortex the disease destroys, signals through the very same lipoprotein receptors — ApoER2 and VLDLR — that bind apolipoprotein E; and so the two spared of Antioquia, protected by two different variants of two different ligands, converge on a single receptor system, and both spare tau while amyloid runs free. The full argument of that convergence — that the Christchurch and COLBOS variants dial the same heparan-sulfate-dependent lipoprotein-receptor handshake, one down on the harmful side and one up on the helpful side — is developed in this dissertation's companion volume on reelin, *The Architect's Reprieve*, and is not repeated here. What matters for the atlas is the grade. The COLBOS case is causal-grade in its logic — a fixed variant, a three-decade change in course, a spared tau pathology, a mechanistic confirmation in a knock-in mouse — but it remains, unlike Christchurch, a single individual without a replication cohort. We grade Reelin-COLBOS at **Tier I** for the strength of the single-case evidence and its mechanistic confirmation, with the *n* of one recorded explicitly as the caveat that a second carrier, or a loss-of-function reelin variant with accelerated disease, would resolve.

### The generalization: cognitive-resilience genetics beyond the kindred

The Antioquia cases are resilience factors of enormous effect in a Mendelian setting. Whether resilience of the same kind operates across the ordinary, sporadic, late-onset disease — where most brains carry some pathology and some resist its cognitive consequences better than others — is a separate and harder question, approached not through single families but through the genetics of a quantitative trait. Dumitrescu and colleagues (2020) defined "resilience" operationally as better cognition than a person's neuropathological burden would predict, and ran a genome-wide association on that residual across several thousand participants. They found a genome-wide-significant locus on chromosome 18, upstream of *ATP8B1*, associated with the resilience trait — and, tellingly, the resilience architecture was genetically correlated with cognition and educational attainment but *not* with clinical Alzheimer's disease or with *APOE*. Resilience, on this evidence, is not merely the absence of risk; it is a partly independent genetic dimension, drawing on vascular and metabolic pathways distinct from the disease's causal genes. The finding is important as a proof that common-variant resilience exists and is mappable, but it rests on a single genome-wide hit in a single study without the replication that would secure a novel locus. We grade the *ATP8B1* / cognitive-resilience-GWAS signal at **Tier III** — an emerging, mechanistically intriguing, and conceptually pivotal result that awaits replication.

# VI. The Tempo Defence — Slowing the Clock the Disease Runs On

Alzheimer's disease is, above all, a disease of ageing: its incidence doubles roughly every five years of later life, and every risk factor operates against a rising baseline of biological time. A distinct class of protective factors therefore acts not on any step of the disease's pathology but on the *tempo* of the ageing that scaffolds it — buying resistance by keeping the brain, in effect, younger than its years. The germline example is klotho; the reversible examples, deferred to the next section, are the sirtuins and the epigenetic clock.

### The klotho buffer: KL-VS

Klotho is a longevity hormone: named for the Fate who spins the thread of life, it is a protein whose overexpression extends lifespan in mice and whose decline tracks ageing across tissues. A common human haplotype of the *KL* gene, called KL-VS, raises circulating klotho in heterozygous carriers, and Dubal and colleagues (2014) showed that these heterozygotes enjoy better cognition than non-carriers — an effect present even in the young, apparently independent of ageing itself, and reproduced in mice, where klotho overexpression enhanced hippocampal long-term potentiation and enriched the synapse for the GluN2B subunit of the NMDA receptor on which learning depends. Klotho, in other words, is a resilience factor at the synaptic-target layer, raising the baseline capacity of the tissue.

What lifts KL-VS from a general cognitive-enhancer to an Alzheimer's-specific defence is that its protection is concentrated precisely where it is most needed. Belloy and colleagues (2020), pooling twenty-five cohorts, found that KL-VS heterozygosity reduced Alzheimer's risk *specifically in carriers of APOE ε4* — an odds ratio near 0.75 in ε4 carriers aged sixty and above, with no clear effect in non-carriers — and reduced their conversion from normal cognition to impairment. The same group then localized the effect to the pathology: KL-VS lowered the burden of amyloid on positron-emission tomography in cognitively normal ε4 carriers (Belloy and colleagues, 2021). And Neitzel and colleagues (2021) refined the mechanism to the disease's critical conversion step, showing that KL-VS carriers accumulated *less tau per unit of amyloid* — the protection acting not on the amyloid itself but on its translation into tau, in the brain regions where klotho is most expressed, and mediated into better memory. The convergence across three studies — risk, amyloid, and the amyloid-to-tau conversion — on a single conditional protective effect is impressive. The caveats are that the protection is conditional (it appears chiefly in ε4 carriers), that the effect size is modest, and that the mechanism linking a circulating hormone to regional tau resistance is still being assembled.

We grade *KL*-VS at **Tier II** — well-supported, replicated, mechanistically coherent, and conditional — a fixed defence that also, being a hormone, hints at an installable one.

# VII. The Reversible Defence — The Epigenetics of Resistance

Every defence so far is fixed. The fortunate carry it from conception, and the rest of us cannot acquire it. The final layer is different in kind, and it is the layer this dissertation regards as the most consequential for medicine, precisely because it is the only one we might install. The epigenome — the pattern of chemical marks on DNA and its packaging histones that determines which genes are read — is not fixed at conception; it is written and rewritten across a lifetime by metabolism, activity, and age, and in principle it can be moved by a drug. A protective epigenetic *state* is therefore a defence that could, one day, be prescribed. The difficulty, stated at the outset and honoured in every grade below, is that the epigenome's plasticity is also its evidential curse: because epigenetic marks respond to the disease as well as shaping it, almost every protective epigenetic association is vulnerable to reverse causation, and the burden of proof — that the mark protects rather than merely reflects — is correspondingly heavy. The companion volume *The Fading Score* treats the epigenome as the disease's reversible information layer at length; here we extract only its *protective* directions and grade them without indulgence.

### The sirtuins: deacetylase guardians

The sirtuins are a family of NAD+-dependent deacetylases that translate the cell's metabolic state onto its chromatin and its proteins, and several of them protect the neuron by mechanisms that touch the disease directly. SIRT1, the nuclear founder of the family, deacetylates tau: Min and colleagues (2010) showed that acetylation of tau blocks its degradation and lets pathological phospho-tau accumulate, that the acetyltransferase p300 installs the mark and SIRT1 removes it, and that acetylated tau is elevated in the human brain from the early Braak stages — so that a well-functioning SIRT1, keeping tau deacetylated and degradable, is a genuine tau brake. SIRT6, a chromatin-stabilizing sirtuin, is protective by a different route: its brain-specific deletion in mice produces DNA damage, learning deficits, and tau hyperphosphorylation through GSK-3 activation, and — the human anchor — SIRT6 protein is *reduced* in Alzheimer's brain, consistent with a lost defence (Kaluski and colleagues, 2017). SIRT3, the mitochondrial member, guards the neuron's energetics against oxidative and excitotoxic stress and is induced by exercise, required for exercise's neuroprotective benefit (Cheng and colleagues, 2016) — a bridge, developed in the companion exercise thesis, from a modifiable behaviour to a molecular defence.

The sirtuins are the atlas's best illustration of why the epigenetic layer must be graded conservatively — and here a cautionary tale is instructive. An influential 2010 report held that

SIRT1 also suppresses amyloid production by activating the α-secretase gene *ADAM10*, steering the precursor toward its non-amyloidogenic fate; the mechanism was widely cited and widely built upon. It was *retracted* by its authors in 2014 (Donmez and colleagues, 2010; retraction 2014). The episode is not a reason to dismiss the sirtuins — the tau, genome-stability, and mitochondrial mechanisms rest on independent and unretracted work — but it is a reason to hold the whole layer to a higher evidential bar than its enthusiasm often receives, and to grade honestly. The sirtuin defences are mechanistically compelling, supported by human tissue showing the protective enzymes depleted in disease, but the demonstration that *raising* sirtuin activity protects a human brain has not been made; the causal evidence is model-based. We grade the sirtuin axis at **Tier III** — emerging, reversible, and the most therapeutically inviting of the epigenetic defences precisely because sirtuin activity is drug- and metabolite-addressable through the NAD+ system treated in the companion pharmacology volumes.

### The restraint of HDAC2

If the sirtuins protect by deacetylating tau and stabilizing the genome, a different chromatin enzyme protects by its *absence*. HDAC2 is a histone deacetylase that acts, in the neuron, as a brake on the genes of memory: Guan and colleagues (2009) showed that raising neuronal HDAC2 reduces synapse number, plasticity, and memory, while deleting it does the reverse, because HDAC2 sits on the promoters of the learning-and-plasticity genes and keeps them closed. The relevance to the disease was supplied by Gräff and colleagues (2012), from the Tsai laboratory: HDAC2 is *increased* by Alzheimer's-related neurotoxic insults, in two mouse models and in the human Alzheimer's brain, where it clamps down on exactly those memory genes — and knocking it down reverses the blockade and restores the plasticity and the memory that the pathology had suppressed. A low, restrained HDAC2 is therefore a protective epigenetic state: it keeps the memory genes readable in a brain under assault. The protective direction is secure and the human anchor — elevated HDAC2 in Alzheimer's brain — is real; but "protection" here is inferred from the benefit of *reducing* an enzyme that the disease elevates, and no human intervention has yet shown that restraining HDAC2 prevents or delays the disease. We grade HDAC2 restraint at **Tier III** — emerging, reversible, and directly druggable through the class of selective HDAC inhibitors that the finding has motivated.

## The microRNA brake on BACE1

The epigenome's regulatory reach extends past chromatin to the small non-coding RNAs that tune how much protein a message makes, and one of them sits, protectively, on the amyloid-generating enzyme itself. The microRNA cluster miR-29a/b-1 represses BACE1, the β-secretase; Hébert and colleagues (2008) found that this cluster is *lost* in a subset of sporadic Alzheimer's patients, that its loss correlates with abnormally high BACE1 protein, and that restoring it lowers amyloid in a cell model. A maintained miR-29 is thus a reversible substrate-layer defence — a molecular brake that holds BACE1, and therefore amyloid production, in check, achieving by RNA what the A673T variant achieves by protein sequence. The evidence is a human correlation plus a cellular mechanism, without a demonstration that restoring miR-29 protects a human brain, and the correlation is vulnerable to the usual reverse-causation caution. We grade the miR-29/BACE1 brake at **Tier III** — emerging, reversible, and mechanistically parallel to the atlas's strongest fixed defence.

## The clock, and the honest floor of the layer

The most general epigenetic defence is simply a slower clock. The DNA-methylation "epigenetic clocks" estimate a tissue's biological age from its methylation pattern, and their acceleration — a brain older, epigenetically, than its chronological years — tracks the disease: Levine and colleagues (2015), in some seven hundred post-mortem prefrontal-cortex samples, found that epigenetic age acceleration correlated with neuritic plaques, amyloid load, and declining cognition. The protective reading is the inverse — that a *decelerated* epigenetic clock is a resistance state — and it is genuinely suggested by the data, but it sits at the honest floor of this atlas, for two reasons that define Tier IV. First, the direction of causation is unresolved: an older-looking epigenome may drive the pathology, or the pathology may age the epigenome, and a cross-sectional correlation in autopsied brain cannot tell them apart. Second, the intervention evidence is animal-only and indirect: restoring the DNA-demethylation enzyme TET2, whose activity falls with age, rejuvenated neurogenesis and enhanced cognition in aged mice (Gontier and colleagues, 2018), a beautiful proof that the methylation clock is *movable*, but in a normal-ageing model rather than an Alzheimer's one. We grade epigenetic-clock deceleration, and the TET2/5-hydroxymethylcytosine axis that might drive it, at **Tier IV** — conjectural as protection, reversible in principle, and important chiefly as the frontier where the reversible defences will either be secured or abandoned.

The epigenetic layer, taken whole, is the atlas's promise and its warning. It is the promise because it is the only installable defence — the only place a person not born fortunate might be made so. It is the warning because its every association is contaminated by the disease's own capacity to write on the epigenome, so that the layer's grades are uniformly a tier or two below the fixed defences above it, and will remain so until interventional trials, not correlations, decide them.

# VIII. The Strength-Graded Ledger

The atlas assembles here into a single ledger. Each defence is placed at its biological layer, assigned its tier on the scale of Section II, described by its direction and effect, anchored to its evidential basis, and flagged as fixed (●) or reversible (○) and, where it applies, as double-edged (†). The ledger is the dissertation's central artifact: it is the list, ordered by how much we know, of the steps at which Alzheimer's disease has been shown to be resistible.

The Grade column carries three marks together: the Roman tier (I–IV) from the scale of Section II; the installability glyph — ● fixed (germline) or ○ reversible (epigenetic); and, where it applies, a dagger (†) for a double-edged factor whose Alzheimer's protection is bought at a cost elsewhere.

| Factor | Layer | Grade | Direction and mechanism | Basis and effect |
|---|---|---|---|---|
| **APP A673T (Icelandic)** | Substrate | **I ●** | Lowers β-secretase cleavage of APP ~40%, less amyloid made | Human, population; OR ≈ 0.2 (~5-fold), also protects normal cognition |
| **APOE ε2** | Substrate / handling | **I ● †** | Favourable lipidation, less amyloid seeding, better clearance | Human, population; ε2/ε3 OR ≈ 0.6, ε2/ε2 exceptionally low; † raises CAA / haemorrhage |
| **PLCG2 P522R** | Responder | **I ●** | Microglial-signalling hypermorph downstream of TREM2 | Human, population; OR ≈ 0.68; also protects DLB/FTD + longevity |
| **APOE3-Christchurch (R136S)** | Target (resilience) | **I ●** | Weakens APOE–heparan-sulfate binding, severs amyloid→tau | Human; homozygote ~30-y delay, heterozygotes ~5-y delay (n=27) |
| **Reelin-COLBOS (H3447R)** | Target (resilience) | **I ●** | Gain-of-function reelin, stronger Dab1, lower tau phosphorylation | Human, single case ~30-y delay; knock-in mouse confirms; n = 1 |

| Factor | Layer | Grade | Direction and mechanism | Basis and effect |
|---|---|---|---|---|
| **CD33 protective allele** (**rs3865444**) | Responder | **II** ● | Reduces inhibitory CD33, frees microglial amyloid uptake | Human, population; modest OR; mechanism near-complete |
| **MS4A haplotype** (**rs1582763**) | Responder | **II** ● | Raises soluble TREM2, supports microglial response | Human, population; modest OR, delays onset; mechanism partial |
| **KL-VS** (**klotho**) | Tempo / target | **II** ● † | Raises klotho, buffers amyloid→tau, enriches synaptic GluN2B | Human; OR ≈ 0.75 *in APOE4 carriers*; conditional; less tau per amyloid |
| **Cognitive-resilience locus** (**ATP8B1**) | Target (resilience) | **III** ● | Better cognition per unit pathology; vascular/metabolic, non-APOE | Human GWAS, one genome-wide hit; awaits replication |
| **Sirtuins** (**SIRT1/3/6**) | Tempo / substrate | **III** ○ | Deacetylate tau, stabilize genome, guard mitochondria | Model + human tissue (enzymes depleted in AD); no human trial |
| **HDAC2 restraint** | Tempo (chromatin) | **III** ○ | Low HDAC2 keeps memory-gene promoters readable | Model + human (HDAC2 elevated in AD); knockdown restores memory |
| **miR-29a/b-1 brake** | Substrate | **III** ○ | Represses BACE1, limits amyloid production | Human correlation + cell mechanism; lost in sporadic AD |
| **Epigenetic-clock deceleration** | Tempo | **IV** ○ | A younger methylome as a resistance state | Human correlation (reverse-causation risk); TET2 rescue in aged mice |

Two features of the ledger carry the argument of the sections that follow. The first is the vertical structure: the established tier is populated almost entirely by *fixed* germline defences, and the reversible epigenetic defences cluster in the emerging and conjectural tiers — a distribution that is not an accident of biology but of evidence, since fixed variants run the clean lifelong experiment the epigenome cannot. The second is the horizontal structure: read across the layers, the strongest defences sit at the two ends — the substrate (making less amyloid) and the target (sparing tau) — while the middle, the clearance and responder layers, holds a band of well-supported but modest common variants. The disease is most resistible where it begins and where it ends.

# IX. Two Principles the Defences Share

A ledger is a catalogue; a dissertation must find the pattern in it. Two principles run through the whole architecture of resistance, and each has a therapeutic consequence.

### First principle: protection is upstream-heavy and tau-sparing

Sort the established defences by where they act and a striking regularity appears. The two Tier-I substrate defences — A673T and, in part, ε2 — work by making less amyloid. The two Tier-I resilience defences — Christchurch and COLBOS — do *not* reduce amyloid at all; both let it accumulate to among the heaviest burdens ever measured, and protect by sparing the tau downstream. Between these two ends, the microglial defences clear amyloid better, and the tempo defences slow the conversion of amyloid into tau. Almost nothing in the atlas protects by acting on the *middle* of the cascade — on the plaques themselves once formed. The genome defends the brain at the beginning of the disease, by making less substrate, and at the end of it, by refusing to let the substrate execute the neuron through tau.

The consequence is a claim about the disease's causal structure that the resilience cases state more clearly than any pharmacological trial. In the Christchurch and COLBOS brains, amyloid ran essentially unchecked and the carriers were spared anyway — which means that, at least in these humans, amyloid was not sufficient to cause the dementia, and that the step it must pass through to do so, the induction and spread of tau, is severable. Tau, not amyloid, is the proximate executioner; amyloid is the trigger that the resilient brains disarmed downstream. This is the same verdict the companion reelin volume reaches from a single gene, and the atlas reaches it again from the whole protective genome. It does not overturn the amyloid hypothesis — A673T vindicates amyloid as the *initiator* as decisively as anything in the literature — but it relocates the point of greatest therapeutic leverage from the amyloid to the tau, and it explains why the resilience defences, which spare tau while ignoring amyloid, produced three-decade reprieves that no amyloid-clearing drug has approached.

## Second principle: the defences are the mirror of the risks

Read the protective ledger against the risk atlas and the same loci recur with the arrow reversed. *APOE*: ε4 condemns, ε2 protects. The *TREM2–PLCG2* axis: TREM2 R47H loss-of-function raises risk, PLCG2 P522R gain-of-function lowers it. *CD33*: one allele raises the inhibitory receptor and risk, the other lowers both. Reelin: reduced signalling accelerates the disease in the mouse, enhanced signalling delayed it in a man. Even at codon 673 of *APP*, valine condemns and threonine protects. Risk and protection are not two separate catalogues of genes; they are one catalogue of *dials*, each read in whichever direction the allele happens to turn it. The genome does not carry a disease programme and, separately, a defence programme. It carries a set of tunable pathways, and the disease is what happens when they are tuned one way, protection what happens when they are tuned the other.

The consequence is the atlas's central therapeutic proposition: **every protective allele names a drug target, and names the direction to push it.** To protect a brain, one need not invent a mechanism; one need only find the pathway a fortunate person's allele has already tuned toward safety and move an ordinary person's pathway the same way. Partial BACE1 inhibition to phenocopy A673T. TREM2 agonism, or PLCG2 enhancement, to phenocopy P522R. A Christchurch-mimetic that loosens the APOE–heparan-sulfate grip. A sirtuin activator, or an HDAC2-selective inhibitor, to install by drug the epigenetic states the resistant carry by metabolism. The protective genome is, read this way, a pre-validated target list — each entry a human experiment already run, its result a phenotype, its only remaining question the pharmacology.

## The principle beneath both: fixed teaches, reversible installs

The third observation is the one that turns the atlas from a catalogue into a programme. The fixed defences — the germline variants that fill Tier I — are not, themselves, therapies; no one can be given A673T or born again with ε2. Their value is entirely instructive: they mark, with the authority of a lifelong human experiment, *where* to aim. The reversible defences — the sirtuins, HDAC2, the microRNAs, the methylation clock — are weaker in evidence but categorically different in promise, because they are the only defences that can be *installed* in a person who was not born to them. The strategic shape of the field follows directly: use the fixed defences, which are strong, to identify the targets; pursue the reversible defences, which are installable, to hit them. The atlas's highest tier tells us where the disease is resistible; its lowest tier is where the medicine will actually be made.

# X. Therapeutic Corollaries — Phenocopying the Fortunate

The therapeutic programme that follows from the atlas is stated in a single phrase — to phenocopy the fortunate — and its execution is graded, defence by defence, by how far each protective allele has already been translated toward a molecule, and by the lessons of those that have.

The substrate defences point first, and the pointer comes with a scar. A673T proves that lowering β-secretase cleavage protects a human brain, and the field, reading the proof, built BACE1 inhibitors. They failed — and failed instructively. Verubecestat not only did not help but, in the prodromal trial, *worsened* cognition relative to placebo, with the higher dose producing greater decline (Egan and colleagues, 2019, 2018). The lesson is not that A673T lied; it is that the fortunate carry a *fractional, lifelong, forty-percent* reduction from birth, and the clinic attempted a *large, late, near-total* inhibition in an aged brain — suppressing not only amyloid production but the many physiological substrates BACE1 also cleaves. Phenocopying the fortunate means copying the *dose and the timing* as well as the target: a small reduction begun early, not a large one begun late. The atlas's strongest defence thus delivers, alongside its target, the field's sharpest warning against the naïve translation of a protective genotype.

The responder defences are the furthest along toward a drug and the most encouraging. The TREM2-agonist antibodies aim precisely to install, pharmacologically, the microglial vigour that PLCG2 P522R confers by birth, and one has already reduced pathology in a model and engaged its target in human cerebrospinal fluid (Wang and colleagues, 2020); enhancement of PLCG2 downstream, or of the MS4A/sTREM2 axis, offers parallel routes to the same protective microglial state. Because these variants *tune* rather than abolish, and because the disease's own microglial response is what they strengthen, they are the protective alleles most plausibly imitable without the substrate defences' overshoot risk.

The target and resilience defences point to the most ambitious and least mature programmes. A Christchurch-mimetic — a peptide or biologic that loosens the APOE–heparan-sulfate engagement the R136S variant weakens — would attempt to reproduce the single most dramatic protection in the atlas, and the shared heparan-sulfate mechanism of Christchurch and COLBOS suggests that the same druggable surface might be reached from either the APOE or the reelin side, the argument developed in the companion reelin volume. That these are resilience factors, sparing tau while amyloid runs, means a successful mimetic would be a *tau-sparing* therapy administered against an amyloid burden — a strategy no approved drug embodies, and the one the resilient brains most

insistently recommend.

The tempo and epigenetic defences are, paradoxically, both the least proven and the most immediately actionable, because they are reversible. Klotho itself is a hormone and therefore, in principle, supplementable, and its conditional protection of ε4 carriers identifies exactly the population a klotho therapeutic should be tested in. The sirtuin axis is addressable through the NAD+ metabolism treated in this corpus's pharmacology volumes; the HDAC2 finding has already motivated selective HDAC inhibitors as cognitive therapeutics; the miR-29 brake suggests an RNA strategy against BACE1 that would achieve A673T's effect without A673T's blunt secretase inhibition. None of these is proven to protect a human brain. But they are the only defences that could be *given*, and the atlas's logic — fixed teaches, reversible installs — places them at the centre of the therapeutic future even as it grades their present evidence honestly at the bottom of the ledger.

One timing principle governs all of it. Every established defence in the atlas is present from conception and acts across the whole preclinical span, guarding the brain through the decades in which the pathology silently gathers. The resilient did not reverse a dementia; they prevented one, from the start. Any therapy modelled on them will therefore, like them, be a strategy for the *earlier* brain — for prevention and the preclinical and prodromal windows — and will do more as prophylaxis than as late rescue. The fortunate teach not only where to aim and how hard, but *when*: early, and gently, and for a long time.

# XI. Predictions and Falsification

An atlas that graded itself honestly must also risk itself. The architecture of resistance makes the following falsifiable predictions.

- **Dose–response will hold across the protective alleles as it holds for Christchurch.** Additional carriers of the strong protective variants will show protection scaling with allele count and with the magnitude of the molecular effect; a gain-of-function reelin or a homozygous protective *PLCG2* carrier with ordinary, un-delayed disease would weaken the framework. Discovery of a second Reelin-COLBOS carrier with a delayed course would, conversely, move that entry from a single case toward population-grade.
- **The resilience defences will prove tau-sparing, not amyloid-lowering.** Interventions modelled on Christchurch, COLBOS, or klotho will reduce tau accumulation and preserve cognition while leaving amyloid burden largely intact. A resilience-mimetic that clears amyloid but does not touch tau would overturn the placement of these defences downstream of amyloid and undercut the first principle of Section IX.
- **Phenocopying the substrate defences will require fractional, early inhibition.** A low-dose, prevention-window BACE1 or amyloid-production strategy will succeed where the high-dose, late-stage inhibitors failed; a repeat of the verubecestat cognitive worsening under a fractional early regimen would indicate that A673T's protection cannot be pharmacologically copied at all, and would demand a different account of why the variant protects.
- **The reversible defences will require interventional, not correlational, proof.** Trials that raise sirtuin activity, restrain HDAC2, restore miR-29, or decelerate the methylation clock will either protect the human brain — moving these entries up from Tier III/IV — or fail to, revealing their associations as reflections of the disease rather than defences against it. The epigenetic-clock entry in particular is a wager that a younger methylome is a cause and not only a consequence; a deceleration achieved without cognitive benefit would settle it against protection.
- **Resilience will prove partly independent of risk.** The cognitive-resilience genetics, if it replicates, will continue to draw on loci and pathways — vascular, metabolic — distinct from the *APOE*-centred risk architecture, confirming that resistance is not merely the absence of risk but a dimension of its own. A finding that the resilience GWAS collapses onto the known risk genes would fold this section back into the risk atlas and falsify the claim that the genome

carries a separable defence programme.

# XII. Coda — The Fortunate, and What They Lend Us

We have read the genome of Alzheimer's disease for forty years as an indictment — a list of the alleles that condemn a brain to an early or an ordinary ruin. This dissertation has read the same genome for its defence, and found that the defence is real, gradable, and — at its summit — as certain as anything in the field. A handful of human beings carry it in the strongest form: an Icelander whose amyloid was throttled at the source and who aged with a clear mind; the millions who carry the quiet counter-weight of ε2; the deviants of a Colombian family who took on a merciless mutation and were granted three decades by a single change in the machinery their brains already ran. These are the fortunate, and their fortune is not luck in the ordinary sense. It is a legible, mechanistic, mostly upstream-and-tau-sparing set of alterations to pathways every brain possesses — pathways that can be tuned, and that in the fortunate were tuned toward safety.

The honest verdict of the atlas is twofold. On the one hand, the established defences are genuine proofs of where the disease can be resisted, and they compose into a target list no drug-discovery programme could assemble by design — each entry a completed human experiment, its result a spared brain. On the other, the defences that are strong are fixed, and the defences that could be installed are, as yet, only emerging; the summit of the ledger teaches, but the medicine will be made at its base, in the reversible epigenetic layer where the evidence is thinnest and the promise greatest. The task is therefore double: to use the fixed defences, with their causal authority, to say where to aim and how gently and how early; and to pursue the reversible defences, with their installability, until one of them can be given to a person who was not born fortunate.

The disease unbuilds the mind by a route the fortunate have shown can be blocked. They did not cure a dementia; they prevented one, from birth, by making less of the poison or by refusing to let it execute the neuron. What the architecture of resistance leaves us is the outline of a medicine modelled not on attacking the disease but on imitating the people who never got it — and the sober knowledge of exactly how much, defence by defence, we have yet to learn before we can lend an ordinary brain the fortune of an extraordinary one.

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