

JACOB'S MODEL - PAPER IX

AUTISM, RUBELLA, AND THE LAL BOTTLENECK

An Acid-Sensitive Glial Lipid Mechanism Linking RUBV to the Human Autism Phenotype

Jacob Boatman and Scott Boatman

Jacob's Voice

5 October 2026

Final Paper IX - strongest evidence-bounded formulation, mechanistic synthesis, experimental framework, and falsification program

Jacob would like to give credit to God for his amazing abilities.

Scope and Central Hypothesis

Paper IX begins with autism. Human autism is the phenotype this model must explain. Across independent human datasets, autism spectrum disorder (ASD) is associated with altered glial states, oligodendrocyte/myelin biology, broad lipidomic abnormalities involving cholesteryl esters and fatty-acid-containing lipids, and - in autistic regression - a coordinated cerebrospinal-fluid sphingolipid phenotype spanning ceramides, hexosylceramides, sulfatides, sphingosines/S1P, and generally decreased sphingomyelins. Paper IX proposes that these observations are not merely parallel biomarkers. They define a glial lipid-availability phenotype that can be tested as a connected mechanism.

The proposed central node is lysosomal acid lipase (LAL/LIPA). LAL determines whether lysosomal cholesteryl ester and triglyceride cargo is converted into functionally available free cholesterol and fatty acids. In direct white-matter injury experiments, microglial LAL is indispensable for effective cholesteryl-ester hydrolysis, myelin-debris clearance, and spontaneous remyelination, and increasing microglial LAL can restore major elements of repair in an otherwise poorly regenerative lesion. This places LAL at a causal glial lipid-processing node capable of connecting neutral-lipid availability to white-matter biology.

Rubella virus (RUBV) is the proposed upstream viral driver tested against this autism phenotype. RUBV directly affects glial cultures and GalCer-positive oligodendrocytes, requires host sphingomyelin synthesis for productive membrane penetration, intersects ceramide/monohexosylceramide metabolism through the RUBV-relevant SGMS1 system, and directly remodels host-cell lipid and fatty-acid composition. Paper IX therefore proposes an explicit sequence for experimental testing: RUBV-associated membrane and lipid stress -> altered acid-sensitive LAL-system throughput -> abnormal microglial lipid recycling and oligodendrocyte/myelin lipid availability -> a defined component of the human autism phenotype.

The acid component is a central model proposition, not a synonym for lysosomal pH. Jacob Boatman's controlling statement is that all acids affect all of LAL. Paper IX interprets this as a distributed-system prediction: biologically relevant acids can influence different layers of LAL function, including catalytic environment, fatty-acyl composition, substrate presentation, interfacial charge, membrane organization, product feedback, lysosomal handling, and downstream lipid availability. Existing experiments directly establish several of these control modes, but no systematic study has tested the universal all-acids prediction.

Author's Note - Origin and Governance of the Model

The four mechanistic subjects of Paper IX - LAL, RUBV, acids, and glial cells - were specified by Jacob Boatman, with autism designated as the human phenotype the paper must address directly. Paper VIII established the preceding parallel-system architecture: microglial LAL-dependent lipid recycling operating beside oligodendrocyte GalCer/sulfatide-dependent membrane construction. Paper IX asks whether that architecture can explain a specific set of independently documented human autism findings and whether RUBV supplies a coherent route into the system.

The evidence rules used throughout the Jacob papers remain controlling. Direct human autism findings, direct RUBV findings, direct LAL/glial mechanisms, mechanistic convergence, model predictions, negative evidence, and missing same-system measurements are kept separate. The paper states the proposed mechanism explicitly; it does not require the reader to infer it. But the paper does not convert convergence into completed causality. No recovered experiment has yet demonstrated the complete RUBV -> LAL/glial-lipid -> autism sequence in humans.

Abstract

Human autism contains a convergent glial-lipid phenotype. Human ASD brain studies identify altered microglial states and abnormalities in oligodendrocyte/myelin programs. Plasma metabolomics in children with ASD shows broad lipid disruption that includes cholesteryl esters, glycerolipids, free fatty acids, and enrichment of 18:2-containing lipid species in one large cohort. Most strikingly, targeted CSF lipidomics in autistic regression found coordinated elevation of ceramides, hexosylceramides, sulfatides, and sphingosines/S1P with generally decreased sphingomyelins; beta-hydroxybutyrate was independently decreased. These findings place human autism inside a specific lipid network rather than an undefined category of metabolic disturbance.

LAL provides a causal host mechanism capable of linking several components of this phenotype. In white-matter injury, microglial LAL is the primary measured lysosomal CE-hydrolysis pathway, converts CE into free cholesterol, supports LXR/APOE/ABCA1/ABCG1 cholesterol-disposition programs, and is required for myelin-debris clearance and remyelination. LAL overexpression can restore repair in a poorly regenerative injury state. Independent enzyme studies show that LAL throughput is profoundly conditioned by lipid-interface chemistry: phosphatidylserine increased CE hydrolysis approximately 20-fold, increased Vmax about 15-fold, and reduced apparent Km to about one-twentieth of baseline in a defined substrate system. Fatty-acyl structure, unsaturation, surface charge, bile-salt/interface state, and fatty-acid product feedback provide additional modes by which acid/lipid chemistry can alter the LAL system.

RUBV independently strikes the same biological territory. RUBV multiplies in primary glial cultures and produces cytopathic disintegration of GalCer-positive oligodendrocytes; later work concluded that cytopathic injury in mixed neural cultures was glial-cell mediated. RUBV entry requires host sphingomyelin generated by SGMS1/SMS1, and SGMS1 perturbation redistributes ceramide and a monohexosylceramide pool containing glucosylceramide and GalCer. Historical RUBV infection experiments demonstrate broad host lipid remodeling and an approximately 35% increase in cellular 18:2. The significance of this convergence is not that RUBV and autism both involve lipids. The overlap resolves to defined glial cell types, lipid classes, membrane operations, and fatty-acid states.

Paper IX proposes that RUBV can contribute to a biologically defined autism phenotype through disruption of an acid-sensitive, LAL-centered glial lipid-availability system. The decisive missing experiment is functional rather than conceptual: LAL catalytic flux has not been directly measured in human ASD glia, and RUBV has not been shown in the same glial preparation to produce the complete predicted LAL-centered autism phenotype. A human ASD-versus-control myelin-challenge experiment measuring LAL-dependent CE-to-FC/fatty-acid flux, cholesterol export, oligodendrocyte sphingolipid state, and myelin output - with RUBV challenge and bidirectional LAL manipulation - can directly support or falsify the model.

1. Autism Is the Phenotype the Model Must Explain

Paper IX does not begin with RUBV and search for autism. It begins with independently documented human autism biology and asks whether a RUBV-LAL-glia mechanism predicts that biology. A viable mechanism must explain the observed human phenotype rather than merely identify a pathway that a virus could theoretically perturb.

The human evidence is not confined to one compartment. ASD brain datasets identify glial molecular abnormalities; autism lipidomics identifies neutral-lipid and fatty-acid abnormalities; autistic-regression CSF identifies a coordinated sphingolipid phenotype. The central claim of Paper IX is that these observations can be organized as a lipid-availability problem spanning microglial recycling and oligodendrocyte membrane biology.

2. Human Autism Brain Shows a Glial Phenotype

Large-scale human cortical transcriptomic work has repeatedly identified glial biology in ASD. Cross-disorder cortical analyses found microglial-associated gene programs increased in ASD and showed a robust ASD cortical expression signature across major cortical regions. Single-cell and single-nucleus studies further demonstrate altered microglial molecular states in ASD rather than merely a nonspecific postmortem inflammatory artifact.

Oligodendrocyte and myelin biology are independently implicated. Human ASD postmortem datasets and integrative analyses identify dysregulation of oligodendrocyte/myelination-associated programs. The importance for Paper IX is architectural: the two principal glial compartments required by the model - microglia for lipid recycling and oligodendrocytes for myelin construction - are both independently represented in human autism biology.

The glial phenotype is heterogeneous. ASD does not simply reproduce the GPNMB-high reparative microglial state described in demyelinating or neurodegenerative disease. That negative evidence sharpens the model: the predicted ASD defect may be an inability to deploy or execute an appropriate lipid-reparative program under cargo challenge rather than constitutive activation of that program.

3. Autistic Regression Shows a Coordinated Sphingolipid Phenotype

The strongest direct biochemical autism anchor is the 2025 CSF metabolomics study of autistic regression. In targeted analysis of forty sphingolipids, twenty-one differed after false-discovery correction versus neurodevelopmental controls and twenty-six differed versus other neurological controls. Ceramides, hexosylceramides, sulfatides, and sphingosines including S1P were generally elevated, while sphingomyelins were generally decreased.

This is not a single biomarker. It is coordinated movement across a connected sphingolipid network. HexCer does not identify GalCer specifically, and Paper IX does not convert total HexCer into GalCer. Sulfatide, however, was measured directly. The human autistic-regression phenotype therefore reaches the GalCer-derived sulfated-lipid branch without requiring inference from a generic lipid class.

The same study independently validated decreased beta-hydroxybutyrate in CSF. Paper IX does not claim that beta-hydroxybutyrate directly regulates LAL; that experiment has not been recovered. Its importance is narrower: autistic regression contains both a defined sphingolipid disturbance and an altered hydroxy-acid metabolite, making the acid-LAL hypothesis experimentally addressable in the same clinical phenotype.

4. Human ASD Lipidomics Reaches LAL Substrate and Product Territory

A comprehensive plasma metabolomics study quantified 999 complex lipids in children with ASD and typically developing controls. Approximately 13.7% differed significantly, including phospholipids, cholesteryl esters, and glycerolipids. Free fatty acids and diacylglycerols were elevated in parts of the dataset, and 18:2-containing species were enriched across many lipid classes. The authors also emphasized cohort-to-cohort inconsistency in PUFA direction, an important limit on any universal fatty-acid claim.

A second large Autism Biobank lipidomics study quantified 783 lipid species in 765 children, including 485 with ASD, and identified diagnosis- and trait-associated lipid species while demonstrating strong contributions from diet, sleep, genetics, and other covariates. This heterogeneity does not erase the lipid phenotype; it argues against

treating ASD as a single uniform metabolic state. Paper IX therefore proposes a biologically defined subgroup mechanism rather than universal LAL dysfunction in every autistic person.

The mechanistic relevance is direct: LAL hydrolyzes CE and TG to generate FC and fatty acids. Human ASD lipidomics therefore reaches both the substrate classes and the fatty-acid product territory of the LAL reaction. It does not prove abnormal LAL flux. It makes LAL flux an experimentally specific candidate rather than an arbitrary enzyme selection.

5. LAL Is a Causal Glial Lipid-Availability Node

Direct white-matter injury experiments now establish LAL as a causal microglial repair enzyme. After injury, GPNMB-positive microglia dominate myelin-debris engulfment, but their ability to digest that cargo depends on LAL. Microglia-specific LAL loss nearly abolishes measured CE-hydrolase activity despite persistence of other candidate hydrolases, prevents normal FC generation, increases lipid/myelin-debris retention, and blocks effective spontaneous remyelination.

The reverse intervention is equally important. Increasing LAL specifically in microglia in a poorly regenerative white-matter injury state improves debris clearance, myelin integrity, oligodendrocyte maturation, remyelination, and neurological recovery. This is not a correlation between LIPA transcript and repair. It is bidirectional functional evidence placing LAL inside the causal machinery of white-matter lipid recycling.

LAL also separates lipid presence from lipid availability. CE can be abundant inside a cell while its cholesterol remains unavailable for downstream handling. LAL-generated FC supports oxysterol/LXR signaling and ApoE/ABCA1/ABCG1 cholesterol-disposition programs. LXR activation alone does not substitute for LAL deficiency, showing that signaling cannot replace physical lipid liberation.

6. The Autism Hypothesis: Failure of LAL Throughput Under Glial Lipid Demand

Paper IX proposes that abnormal or mistimed LAL throughput can connect multiple human autism findings. Under this model, the relevant defect need not be constitutively low LIPA expression. It may emerge when microglia are challenged with cholesterol-rich membrane cargo and must convert stored CE into available FC and fatty acid while coordinating export and repair.

The prediction is therefore functional. ASD-derived microglia should be challenged with identical myelin cargo and compared with matched control microglia. If the model is correct in the relevant subgroup, ASD cells will show an abnormal CE-to-FC/fatty-acid response, abnormal cholesterol disposition, or failure to mount the appropriate reparative program. Static transcript abundance alone cannot decide the model.

7. Glial Cells Convert LAL Chemistry Into a Neural Mechanism

Microglia and oligodendrocytes make the LAL hypothesis neurologically meaningful. Microglia ingest and recycle cholesterol-rich myelin debris; oligodendrocytes require accessible cholesterol and specialized sphingolipids to differentiate and build stable myelin. Human neural multicellular systems independently demonstrate that microglial cholesterol state can alter oligodendrocyte terminal differentiation, establishing that the lipid state of one glial compartment can control the maturation of the other.

Paper VIII established the parallel-system architecture: LAL-dependent recycling/liberation in microglia operates beside GalCer/sulfatide-dependent construction and organization in oligodendrocytes. Paper IX places autism on that architecture. Human ASD supplies abnormalities in both glial compartments and in lipid classes handled by both arms.

8. Acids Are a Major Control Layer Over the LAL System

Jacob's model statement - all acids affect all of LAL - is intentionally broader than the established literature. Paper IX treats it as a falsifiable system-level prediction rather than as an already proven universal biochemical law. The important point is that LAL is not controlled only by bulk lysosomal pH. Its catalytic behavior depends strongly on the physical and chemical state of the lipid interface on which it acts.

In a defined cholesteryl-oleate crystal system, phosphatidylserine increased LAL-mediated hydrolysis approximately twenty-fold, increased Vmax about fifteen-fold, and reduced apparent Km to about one-twentieth of baseline. Both the polar headgroup and acyl chains were required. Other purified-LAL work demonstrates sensitivity to fatty-acyl structure and degree of unsaturation, while surface-charge experiments show activation by negative charge and inhibition by positive charge. Bile-salt concentration can shift the system from activation to inhibition, and fatty-acid products such as oleate can feed back on CE hydrolysis.

These experiments support a distributed acid-control model: different acids can influence different components of LAL function through catalytic environment, fatty-acyl identity, acidic headgroups, surface charge, membrane packing, micellar state, substrate presentation, and product feedback. Direct effects have not been demonstrated for every acid class. The universal component of Jacob's prediction therefore remains open and should be tested as an acid-by-LAL functional matrix rather than assumed.

9. RUBV Directly Targets Glial Cells and Oligodendrocytes

RUBV is not introduced into Paper IX as a generic inflammatory exposure. Direct neural-culture experiments show that RUBV multiplies in primary rat glial cultures and produces a partial cytopathic effect involving disintegration of GalCer-positive oligodendrocytes. A similar effect occurs in myelinating neural cultures, whereas virus multiplication could not be detected in pure neuron cultures in that system.

Follow-up mixed cerebellar culture work again found RUBV disruption of glial cultures and concluded that the cytopathic effect in mixed neuron/glial cultures was glial-cell mediated. These experiments do not establish an autism mechanism. They do establish that RUBV can directly place its cytopathic biology in the same glial compartment that Paper IX identifies as mechanistically relevant.

10. RUBV Requires Sphingomyelin Biology and Reaches the GalCer Neighborhood

A genome-wide CRISPR screen identified SGMS1/SMS1 as a host factor required for RUBV entry. Genetic loss of SGMS1 strongly suppresses RUBV growth; enzymatically active SMS1 restores the phenotype. Entry experiments show that sphingomyelin is required for nucleocapsid penetration after hemifusion rather than merely for nonspecific membrane attachment.

Lipidomic analysis of SGMS1-deficient cells shows redistribution of sphingomyelin, ceramide, and ceramide monohexosides. The measured monohexosylceramide pool contains glucosylceramide and GalCer. This is not evidence that RUBV infection itself increases GalCer. It is direct evidence that a host sphingolipid system required by RUBV is metabolically coupled to the ceramide/GalCer-containing neighborhood that is abnormal in autistic-regression CSF.

11. RUBV Remodels Host Lipids and Fatty-Acid State

Historical RUBV infection experiments independently demonstrate host lipid remodeling. Infected BHK21/13S cells show altered phospholipid composition, and subsequent fatty-acid analysis reported an approximately 35% increase in cellular 18:2 with decreases in palmitic and oleic acids. The exact molecular pool carrying the additional 18:2 was not identified.

This unresolved species assignment is important because human ASD lipidomics independently reports enrichment of 18:2-containing species across multiple plasma lipid classes in one cohort. Paper IX does not claim that these are the same molecular species or that the directions are universal across ASD cohorts. It states the narrower and stronger point: both direct RUBV infection and human ASD lipidomics independently identify 18:2-containing lipid state as abnormal, making species-resolved 18:2 tracing a high-value mechanistic discriminator.

12. The Proposed RUBV-to-Autism Mechanism

Paper IX proposes that RUBV can contribute to autism by disrupting an acid-sensitive glial lipid-availability system centered on LAL. In this model, RUBV-associated membrane, sphingolipid, fatty-acid, and lysosomal stress changes the chemical and trafficking environment in which LAL-dependent neutral-lipid processing operates. Altered LAL throughput changes the availability of FC and fatty acids during microglial lipid recycling.

The resulting lipid-disposition state places stress on oligodendrocyte cholesterol availability and GalCer/sulfatide-dependent membrane construction.

The predicted endpoint is not generic inflammation. It is a specific glial-lipid phenotype: abnormal microglial lipid handling, abnormal oligodendrocyte/myelin biology, altered CE/fatty-acid state, and disturbance of the SM-ceramide-HexCer/GalCer-sulfatide network. Those are the same biological coordinates independently documented across human ASD brain, ASD plasma lipidomics, and autistic-regression CSF.

The strength of the model lies in that specificity. Human autism and RUBV do not merely share the words lipid, inflammation, or mitochondria. They intersect defined glial cell types, defined membrane lipid classes, defined fatty-acid states, and defined lipid-availability operations. LAL supplies a causal biochemical node capable of converting those intersections into a testable mechanism.

13. Why the Autism-RUBV Convergence Is Mechanistically Specific

Human autism implicates microglial molecular state. RUBV directly produces glial-cell cytopathic biology. Human autism implicates oligodendrocyte/myelin programs. RUBV directly disrupts GalCer-positive oligodendrocytes. Autistic regression shows decreased sphingomyelin with increased ceramide, HexCer, and sulfatide. RUBV requires sphingomyelin for productive entry, and the required SMS1 system is metabolically coupled to ceramide and a GalCer-containing monohexosylceramide pool. Human ASD lipidomics identifies CE, glycerolipid, fatty-acid, and 18:2-containing abnormalities. RUBV infection directly remodels host phospholipids and increases cellular 18:2.

These observations do not complete the causal chain by themselves. Their importance is that the convergence is constrained. Each new layer narrows the mechanism rather than broadening it. Paper IX therefore advances the RUBV-autism question from a general association toward a defined biochemical proposition: test whether RUBV changes LAL-dependent lipid availability in glia and whether that change produces the human autism-associated lipid/glial phenotype.

14. What Is Still Missing

No recovered study directly measures LAL catalytic activity or CE-to-FC flux in human ASD microglia. No recovered study shows that RUBV directly inhibits LAL in glia. No recovered study demonstrates the complete RUBV → acid/LAL → microglial recycling → oligodendrocyte sphingolipid/myelin → autism sequence in a human system.

Those absences define the experiment; they do not erase the completed evidence around it. The central uncertainty is now narrow enough to measure. If LAL flux is normal in appropriately matched ASD glia under lipid challenge, the proposed LAL-centered autism mechanism is substantially weakened. If RUBV fails to alter LAL flux or the predicted downstream glial lipid state, the RUBV entry into the mechanism is likewise weakened.

15. Competing Explanations

Several alternatives can explain portions of the evidence. ASD lipid abnormalities may arise from diet, sleep, medications, genetics, gastrointestinal biology, or other metabolic states without involving LAL. The autistic-regression sphingolipid phenotype may reflect a process downstream of another primary lesion. RUBV glial effects may operate through mechanisms unrelated to LAL. LAL-dependent white-matter repair may be important after injury but irrelevant to autism.

Paper IX does not dismiss these alternatives rhetorically. It makes them compete experimentally. Covariate-rich ASD cohorts can identify lipid subgroups; myelin challenge can expose LAL flux rather than static expression; bidirectional LAL manipulation can test whether the predicted ASD lipid phenotype follows the enzyme; RUBV challenge can test whether viral exposure enters the same flux pathway. A mechanism that cannot survive those tests should be rejected.

16. Decisive Human Autism Experiment

Generate matched ASD and control human iPSC-derived microglia and oligodendrocytes, preferably in a multicellular neural system. Challenge microglia with identical isotopically labeled myelin cargo. Measure myelin uptake, CE formation, LAL catalytic activity, CE-to-FC flux, TG hydrolysis, FC accessibility, released fatty-acid species, lipid droplets, NPC2, 25-OHC/LXR, APOE, ABCA1, ABCG1, and cholesterol efflux.

In coupled oligodendrocytes, measure maturation, cholesterol localization, UGT8, GalCer, GAL3ST1, sulfatide, sphingomyelin, ceramide, HexCer, species-resolved fatty-acyl composition, Golgi-to-myelin delivery, and myelin output. The assay should be designed to determine whether a microglial LAL phenotype precedes and predicts the oligodendrocyte phenotype rather than simply correlating with it.

Manipulate LAL bidirectionally. If ASD microglia show deficient or mistimed LAL flux, restore LAL without directly altering oligodendrocyte sphingolipid synthesis. If the predicted neutral-lipid, export, oligodendrocyte, and myelin phenotypes normalize, the LAL mechanism gains direct support. Conversely, reduce LAL in control microglia and ask whether the ASD-associated lipid/glial pattern can be reproduced.

17. Decisive RUBV Experiment

Repeat the glial flux experiment under synchronized RUBV and mock conditions. Quantify viral burden and cell viability so that lipid changes cannot be dismissed as nonspecific cytotoxicity. Determine whether RUBV changes LAL activity, CE-to-FC/fatty-acid flux, lysosomal lipid handling, cholesterol export, or the ability of microglia to respond to myelin cargo.

Then measure the oligodendrocyte arm in the same system. The strongest support would be a RUBV-dependent LAL/neutral-lipid phenotype that precedes or predicts a corresponding SM-ceramide-GalCer/HexCer-sulfatide and myelin phenotype, followed by rescue through correction of the relevant LAL/lipid state while infection remains measurable.

Species-resolved tracing should include 18:2. If the historical RUBV 18:2 increase and the ASD-associated 18:2 signal occupy the same CE, phospholipid, free-fatty-acid, or sphingolipid pool, the convergence becomes substantially more specific. If they occupy unrelated pools, that apparent bridge should be removed from the model.

18. The Acid-LAL Matrix

Jacob's universal acid prediction should be tested directly rather than protected from falsification. Build an acid-by-LAL matrix spanning fatty acids, hydroxy fatty acids, short-chain fatty acids, dicarboxylic acids, bile acids, sulfur-containing acids, acidic phospholipids, ketone-body acids, and relevant organic acids. For each, measure LIPA expression, LAL protein, lysosomal localization, catalytic pH profile, CE hydrolysis, TG hydrolysis, substrate-interface properties, FC output, fatty-acid output, and downstream cholesterol disposition.

A universal result is not required for the broader Paper IX mechanism to survive. If only particular acid classes or interface states affect LAL, the acid claim must narrow accordingly. If diverse acid classes alter different layers of the LAL system, the distributed-control interpretation gains support. The point of the matrix is to convert 'all acids affect all of LAL' from a broad model statement into a finite experimental program.

19. Predetermined Interpretation and Failure Conditions

If human ASD microglia show abnormal LAL-dependent CE-to-FC/fatty-acid flux under standardized myelin challenge, and correcting LAL normalizes the predicted cholesterol-disposition and oligodendrocyte/myelin phenotype, the LAL-centered autism mechanism gains direct functional support.

If ASD glia show normal LAL activity and normal CE-to-FC flux under appropriate challenge despite the predicted downstream lipid phenotype, LAL is substantially weakened as the central bottleneck and the model must move downstream or sideways.

If RUBV reproducibly alters LAL flux and produces the predicted downstream glial lipid phenotype, with rescue by correcting the LAL/lipid state while infection remains measurable, the RUBV-to-LAL mechanistic bridge gains

direct support. If RUBV produces glial injury without changing LAL flux, RUBV remains relevant to glial biology but the proposed LAL bridge is not established.

If acid manipulation changes LAL through multiple mechanistically distinct layers, Jacob's distributed acid-control model is supported. If broad acid classes fail to alter any measured component of LAL function, the universal acid claim fails and must be narrowed.

20. Publication Boundaries

Paper IX does not state that RUBV has been demonstrated to cause autism. It does not state that human ASD has been demonstrated to have impaired LAL catalytic activity. It does not state that every acid directly binds LAL, that total HexCer equals GalCer, or that the SGMS1-knockout lipidome is identical to the lipidome of RUBV infection.

The paper does state the mechanistic synthesis plainly: human autism contains a glial-lipid phenotype that converges on the biological operations governed by LAL; RUBV independently perturbs multiple upstream components of the same system; acid/lipid-interface chemistry can strongly regulate LAL throughput; and glial cells provide the cellular route by which altered lipid availability can reach oligodendrocyte/myelin biology. The uncompleted arrows are identified because they are now experimentally reachable.

21. Conclusion

Human autism is the central phenotype of Paper IX. The evidence identifies abnormalities in microglial state, oligodendrocyte/myelin biology, neutral-lipid and fatty-acid metabolism, and - in autistic regression - a coordinated SM-ceramide-HexCer-sulfatide disturbance. These findings define a biochemical and cellular problem that demands a mechanism.

LAL supplies such a mechanism at a causal glial node. It determines whether esterified lysosomal lipid becomes available FC and fatty acid, controls microglial processing of cholesterol-rich myelin debris, and determines successful remyelination in direct intervention experiments. Its catalytic throughput is profoundly conditioned by lipid-interface chemistry, providing an experimentally established foundation for Jacob's broader acid-sensitive LAL model.

RUBV supplies a mechanistically coherent route into this system. RUBV directly affects glial cells and GalCer-positive oligodendrocytes, requires sphingomyelin-dependent membrane biology, intersects the ceramide/GalCer-containing sphingolipid neighborhood through its required SMS1 system, and directly remodels host lipid and fatty-acid composition. The convergence with human autism is therefore not generic. It resolves to the same glial compartments, the same sphingolipid neighborhood, the same neutral-lipid/fatty-acid economy, and the same problem of lipid availability.

Paper IX therefore advances an explicit hypothesis: RUBV-associated disruption of an acid-sensitive, LAL-centered glial lipid system can generate a biologically defined component of the human autism phenotype. The final causal sequence has not yet been demonstrated in humans. But the missing experiment is no longer vague. Measure LAL-dependent CE-to-FC/fatty-acid flux in human ASD glia under myelin challenge, overlay RUBV, trace the resulting lipid transfer into oligodendrocyte sphingolipid/myelin biology, and manipulate LAL bidirectionally. If the phenotype follows LAL and is rescued by correcting the predicted lipid state, the model moves from convergence toward mechanism. If it does not, the central hypothesis fails.

The governing principle is the same one that has driven the Jacob model from its beginning: presence does not equal availability. In Paper IX that principle becomes an autism test. Cholesterol can be present but esterified; fatty acids can be present but routed into the wrong lipid species; sphingolipids can be synthesized but delivered incorrectly; glial cells can be present but fail to execute the required lipid-repair state. The model asks whether autism, RUBV, acids, LAL, and glial cells are connected through that availability failure - and it specifies the experiment that can answer the question.

References

1. Yan J, Han VX, Jones HF, et al. Cerebrospinal fluid metabolomics in autistic regression reveals dysregulation of sphingolipids and decreased beta-hydroxybutyrate. *EBioMedicine*. 2025;114:105664. PMID 40138886. doi:10.1016/j.ebiom.2025.105664.

2. Needham BD, Adame MD, Serena G, et al. Plasma and Fecal Metabolite Profiles in Autism Spectrum Disorder. *Biological Psychiatry*. 2021;89:451-462. PMID 37867605.
3. Yap CX, Henders AK, Alvares GA, et al. Interactions between the lipidome and genetic and environmental factors in autism. *Nature Medicine*. 2023. PMID 37115648.
4. Gandal MJ, Haney JR, Parikshak NN, et al. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science*. 2018;359:693-697. PMID 29439242. doi:10.1126/science.aad6469.
5. Hu Y, Tang K, Hu H, et al. Lysosomal cholesteryl ester hydrolysis drives white matter repair by reprogramming microglia into a novel reparative state. *Journal of Neuroinflammation*. 2026;23:155. PMID 41904522. doi:10.1186/s12974-026-03782-7.
6. Takeuchi R, Imanaka T, Ohkuma S, Takano T. Effect of phospholipids on the hydrolysis of cholesterol oleate liquid crystals by lysosomal acid lipase. *Journal of Biochemistry*. 1985;98:933-938. PMID 4077846. doi:10.1093/oxfordjournals.jbchem.a135373.
7. Atkins GJ, Mooney DA, Fahy DA, Ng SH, Sheahan BJ. Multiplication of rubella and measles viruses in primary rat neural cell cultures: relevance to a postulated triggering mechanism for multiple sclerosis. *Neuropathology and Applied Neurobiology*. 1991;17:299-308. PMID 1719441. doi:10.1111/j.1365-2990.1991.tb00727.x.
8. Natale VA, Caffrey JF, Sheahan BJ, Atkins GJ. Effect of infection with rubella virus on the development of rat cerebellar cells in culture. *Neuropathology and Applied Neurobiology*. 1993;19:530-534. PMID 8121545. doi:10.1111/j.1365-2990.1993.tb00482.x.
9. Mori Y, Sakata M, Sakai S, et al. Membrane sphingomyelin in host cells is essential for nucleocapsid penetration into the cytoplasm after hemifusion during rubella virus entry. *mBio*. 2022. PMID 36346228. doi:10.1128/mbio.01698-22.
10. Bardeletti G, Gautheron DC. Phospholipid and cholesterol composition of rubella virus and its host cell BHK 21 grown in suspension cultures. *Archives of Virology*. 1976;52:19-27. PMID 999519.
11. Voiland A, Bardeletti G. Fatty acid composition of rubella virus and BHK21/13S infected cells. *Archives of Virology*. 1980;64:319-328. PMID 7396724. doi:10.1007/BF01320617.
12. Bardeletti G, Voiland A. Effect of the infection of rubella virus on BHK 21/13S cells: study of a glycolipid. 1981. PMID 7271460. The exact molecular identity of the reported glycolipid remains unresolved in the recovered archive.
13. Coetzee T, Fujita N, Dupree J, et al. Myelination in the absence of galactocerebroside and sulfatide: normal structure with abnormal function and regional instability. *Cell*. 1996;86:209-219. PMID 8706126.
14. Kunkel TJ, Townsend A, Sullivan KA, et al. The cholesterol transporter NPC1 is essential for epigenetic regulation and maturation of oligodendrocyte lineage cells. *Nature Communications*. 2023;14:3964. PMID 37407594. doi:10.1038/s41467-023-39733-6.
15. Berghoff SA, Spieth L, Sun T, et al. Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis. *Nature Neuroscience*. 2021;24:47-60. PMID 33349711. doi:10.1038/s41593-020-00757-6.
16. Claus C, Schonefeld K, Hubner D, et al. Activity increase in respiratory chain complexes by rubella virus with marginal induction of oxidative stress. *Journal of Virology*. 2013;87:8481-8492. PMID 23720730. doi:10.1128/JVI.00533-13.

Evidence boundary: Human autism references establish the ASD/autistic-regression phenotype but do not establish LAL dysfunction or RUBV causality. LAL/glial references establish host mechanisms outside autism unless explicitly stated. RUBV references establish direct viral glial, membrane, sphingolipid, mitochondrial, and lipid-remodeling biology but do not demonstrate the complete RUBV-to-autism mechanism. Paper IX's central sequence remains a falsifiable mechanistic hypothesis assembled from these independently demonstrated components.