

JACOB'S MODEL - PAPER X

AUTISM AND THE ACID-LAL BOTTLENECK

A Bidirectional Model of Acid Availability, Lysosomal Lipid Partitioning, and the Human Autism Phenotype

Jacob Boatman and Scott Boatman

Jacob's Voice

6 October 2026

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

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

Abstract

Autism contains a reproducible but heterogeneous disturbance of lipid and acid metabolism that has generally been described as a collection of biomarkers rather than as a single biochemical problem. Human ASD studies identify abnormalities in cholesteryl-esters, free-fatty-acid and polyunsaturated-fatty-acid pools, bile acids, oxidized lipid products, eicosanoid networks, sphingolipids, microglial state, and oligodendrocyte/myelin biology. Autistic-regression cerebrospinal fluid adds a particularly strong human anchor: beta-hydroxybutyrate is decreased while ceramides, hexosylceramides, sphingosines/S1P, and sulfatides are increased and sphingomyelins are generally decreased.

Lysosomal acid lipase (LAL/LIPA) supplies a mechanistic center capable of organizing these observations. LAL hydrolyzes lysosomal cholesteryl esters and triglycerides, converting stored esterified lipid into free cholesterol and fatty acids. Loss of LAL in macrophages selectively enriches the cholesteryl-ester pool in 18:2 and 20:4 and reduces release of lipid mediators derived from these precursors. Thus LAL does not merely regulate cholesterol storage: it determines whether esterified polyunsaturated fatty acids remain stored or become available to COX, LOX, and cytochrome-P450 signaling pathways.

Acid chemistry reciprocally controls the LAL system. Proton concentration defines the catalytic environment; phospholipid composition and fatty-acyl unsaturation alter activity; phosphatidylserine can increase cholesteryl-ester hydrolysis approximately twenty-fold, increase Vmax approximately fifteen-fold, and reduce apparent Km to approximately one-twentieth of baseline; surface charge changes hydrolysis; sodium taurocholate switches from activation to inhibition as concentration and micellar state change; fatty-acid products inhibit hydrolysis; and extensively oxidized cholesteryl-linoleate products become resistant to lysosomal hydrolysis.

Paper X proposes that a biologically defined component of autism is an acid-availability disorder centered on the LAL bottleneck. In this model, abnormal LAL throughput produces a dual-availability failure: the sterol and fatty-acid components of cholesteryl ester can be present yet functionally unavailable, while acid chemistry feeds back on the same hydrolytic boundary. Direct abnormal LAL flux has not yet been demonstrated in human ASD. That is the decisive missing measurement.

Scope and Central Proposition

Paper X places three subjects at the center: AUTISM, LAL, and ACIDS. It asks whether they form a connected biochemical system. The proposed answer is explicit: LAL is a molecular partitioning gate that determines whether esterified lipid remains stored or becomes biologically available, while acid chemistry determines how that gate operates. Human autism independently occupies multiple substrate, product, signaling, and glial territories predicted by this system.

The model is bidirectional. ACIDS → LAL describes regulation by catalytic acidity, fatty-acyl identity, oxidation state, phospholipid composition, surface charge, bile-salt/interface chemistry, and product feedback. LAL → ACIDS describes liberation of esterified fatty acids that subsequently enter COX, LOX, CYP450, and related signaling pathways.

Author's Note - Origin and Governance of the Model

Jacob Boatman directed the present investigation toward acids, LAL, and autism and stated the governing model proposition as: "All acids affect all of LAL." The literature does not establish that every chemically defined acid directly binds LAL. Paper X converts the statement into a finite experimental proposition: different acid classes are predicted to affect different functional layers of the LAL system.

The evidence rules used throughout the Jacob papers remain controlling. Direct enzyme experiments, direct glial experiments, direct human autism findings, mechanistic synthesis, model predictions, negative evidence, and missing measurements are separated. Strong wording is used where experiments are direct.

1. Autism Is Already an Acid-Lipid Phenotype

Human autism is not metabolically silent. Large metabolomic and lipidomic studies identify abnormalities across cholesteryl-esters, glycerolipids, phospholipids, polyunsaturated-fatty-acid-containing species, cholesterol, oxidized lipid products, bile acids, and eicosanoid networks. The directions are not uniform across cohorts or compartments. That heterogeneity is precisely why total concentration is an inadequate description of a bottleneck whose predicted phenotype is altered partitioning and availability.

Developmental metabolomics strengthens this point. In pre-ASD newborns and 5-year-old children with ASD, altered lipid metabolism accounts for a major fraction of the measured metabolic impact. The same study identifies linoleic acid, cholesterol, ceramides, sphingomyelins, glycosphingolipids, eicosanoids, bile acids, phospholipids, and hydroxy-sphingomyelin species as developmentally abnormal.

2. Autistic Regression Places a Hydroxy Acid and Sphingolipid Failure in the Same CSF Phenotype

The 2025 autistic-regression CSF study provides one of the strongest direct human anchors for Paper X. Beta-hydroxybutyrate was significantly decreased and independently validated. Targeted sphingolipid analysis showed widespread dysregulation: ceramides, hexosylceramides, sphingosines including S1P, and sulfatides were generally elevated, whereas sphingomyelins were generally decreased.

This is not evidence that beta-hydroxybutyrate directly regulates LAL. It is evidence that human autistic regression simultaneously contains abnormal hydroxy-acid metabolism and a coordinated sphingolipid/myelin-related lipid phenotype.

3. LAL Is the Boundary Between Storage and Availability

LAL hydrolyzes lysosomal cholesteryl esters and triglycerides. For a cholesteryl ester, one catalytic event converts a stored molecule into two biologically available products: free cholesterol and a fatty acid. LAL therefore controls more than cholesterol storage. It controls molecular partitioning.

CE-bound 18:2 is not equivalent to free 18:2. CE-bound 20:4 is not equivalent to free arachidonic acid. Total cholesterol is not equivalent to free cholesterol available for export and signaling. Paper X therefore defines the LAL bottleneck by flux across the CE/TG → FC + FA boundary.

4. LAL Controls Acid Availability Directly

Direct macrophage experiments establish the fatty-acid side of this reaction. LAL-deficient macrophages accumulate neutral lipid, predominantly cholesteryl ester, and the cholesteryl-ester fraction becomes particularly enriched in 18:2 and 20:4.

Acute pharmacologic inhibition of LAL in otherwise wild-type macrophages reduces release of 18:2- and 20:4-derived lipid mediators across COX, LOX, and CYP450 pathways. This closes a critical mechanistic arrow: lysosomal lipid hydrolysis supplies fatty-acid precursors for downstream acid signaling.

5. Dual Availability Failure

Paper X introduces the term dual availability failure. One cholesteryl-ester molecule contains both a sterol and a fatty acid. Failure to hydrolyze that molecule can simultaneously restrict free-cholesterol availability and fatty-acid availability.

For cholesteryl linoleate, the products are FC and 18:2. For cholesteryl arachidonate, they are FC and 20:4. A single bottleneck can therefore disturb sterol disposition and PUFA signaling at the same time.

6. Acid Chemistry Controls LAL Far Beyond Bulk pH

The phrase acid lipase can invite an oversimplification: that acidity matters only because LAL works at low pH. Direct experiments reject that narrow view. LAL activity is profoundly conditioned by the chemistry and physical state of the lipid interface on which it acts.

Purified rabbit LAL responds to phospholipid acyl-chain length and unsaturation. Among unsaturated phosphatidylcholines, activity rises with increasing numbers of double bonds. In a separate cholesteryl-oleate crystal system, phosphatidylserine increases hydrolysis approximately twenty-fold, increases V_{max} approximately fifteen-fold, and reduces apparent K_m to approximately one-twentieth of baseline.

7. Surface Charge, Bile Salts, and Product Feedback Are Part of the LAL System

Classic lysosomal cholesteryl-ester hydrolase experiments show that a net negative surface charge increases hydrolysis whereas a net positive charge inhibits it. Phosphatidylcholine and phosphatidic acid stimulate activity, and a sodium-taurocholate/phosphatidylcholine mixed micelle is an exceptionally effective substrate vehicle.

Sodium taurocholate can switch direction: increasing amounts activate hydrolysis up to a defined ratio, after which activity falls rapidly as micellar behavior emerges. Oleate also inhibits cholesteryl-oleate hydrolysis. Acid output can therefore become acid input.

8. Oxidized Acid Chemistry Can Jam the Lysosomal CE Boundary

Extensively oxidized cholesteryl-linoleate products containing oxidized fatty-acid fragments are significantly resistant to hydrolysis by macrophages and by macrophage extracts at pH 4.0 compared with intact cholesteryl linoleate.

The implication is direct: the chemical state of the fatty acid attached to cholesterol can determine whether the lysosomal CE substrate is efficiently processed. Acid chemistry can be embedded inside the substrate that LAL must hydrolyze.

9. LAL Is a Sterol Gate and an Acid Gate at the Same Time

The two products of CE hydrolysis enter different but interacting biological systems. FC enters lysosomal cholesterol export, sterol sensing, oxysterol/LXR signaling, membrane rebuilding, and systemic sterol metabolism. Liberated 18:2 and 20:4 enter oxygenase pathways that generate hydroxy, epoxy, dihydroxy, prostanoid, leukotriene, and related lipid mediators.

LAL therefore occupies a branch point between storage and two signaling economies. Measuring only cholesterol misses half of the reaction; measuring only total fatty acid misses whether the precursor is trapped in esterified form.

10. The 18:2 Branch

Linoleic acid can exist as CE-bound 18:2, phospholipid-bound 18:2, triglyceride-bound 18:2, free 18:2, and oxygenated 18:2 products. LAL directly controls liberation from lysosomal neutral-lipid substrates, while LAL loss selectively enriches 18:2 in the CE compartment.

Human ASD studies independently identify abnormal 18:2-containing lipid species, but direction varies by cohort and lipid class. Paper X does not treat these directions as interchangeable. It predicts that compartment-specific partitioning will outperform total 18:2 concentration as a marker of the LAL-controlled state.

11. The 20:4 Branch and the CYP450 Autism Signal

Arachidonic acid supplies an independent replication of the availability principle. LAL deficiency selectively enriches 20:4 in cholesteryl ester, and acute LAL inhibition suppresses downstream 20:4-derived mediator release. Free arachidonic acid can enter COX, LOX, and CYP450 pathways.

Human developmental data independently place CYP-derived arachidonic-acid metabolites inside the autism phenotype. In a prospective birth cohort of 200 children, cord-blood 11,12-diHETrE related to later ASD symptom severity and socialization impairment. This does not establish LAL dysfunction in those children. It places a downstream acid-output system controlled by PUFA availability directly inside prospective human autism biology.

12. Bile Acids Are Not a Side Note

Bile acids are a major cholesterol-derived acid system and a major regulator of lipid handling. Paper X does not claim that microglial LAL directly produces bile acids. The relevant intersection is more precise: LAL controls FC liberation; systemic cholesterol metabolism feeds bile-acid synthesis; and bile-salt chemistry independently alters the LAL substrate/enzyme interface.

Developmental human ASD metabolomics identifies bile-acid abnormalities at birth before ASD diagnosis and again at age five, with developmental reversal in the direction of selected conjugated bile acids. The same human dataset simultaneously identifies sphingolipid, cholesterol, eicosanoid, linoleate, phospholipid, and hydroxy-sphingomyelin abnormalities. Bile-acid dysregulation therefore occurs inside a broader autism lipid network rather than as an isolated gastrointestinal observation.

13. Autism Shows Network Failure, Not One Fixed Acid Concentration

The developmental ASD metabolome is dynamic. Some metabolites change direction between birth and age five; lipid-network connectivity is profoundly altered; normal correlations linking bile acids, cholesterol, ceramides, phospholipids, eicosanoids, and other pathways are lost or reorganized.

Paper X therefore rejects a simplistic prediction that one acid must always be high or low in autism. A flux bottleneck predicts state dependence. Age, compartment, conjugation, oxidation, carrier, substrate class, and downstream routing can move in different directions while the underlying partitioning defect persists.

14. Microglial LAL Converts the Chemistry Into a Brain Mechanism

Paper X does not rely on peripheral lipid biology to make a neural claim. Direct 2026 white-matter experiments establish microglial LAL as a central determinant of myelin-debris processing and remyelination. LAL-mediated lysosomal lipolysis is the primary measured pathway for CE hydrolysis after white-matter injury, generating FC required for cholesterol efflux and supporting 25-hydroxycholesterol/LXR signaling.

Microglia-specific LAL loss blocks effective debris clearance and spontaneous remyelination. Increasing microglial LAL is sufficient to restore major elements of repair in a poorly regenerative white-matter injury model.

LXR activation alone cannot rescue LAL deficiency, demonstrating that downstream signaling cannot substitute for physical liberation of the stored lipid.

15. Autism Occupies the Glial Endpoint of the Model

Independent human ASD brain studies identify altered microglial molecular states and abnormalities in oligodendrocyte/myelin programs. Human autistic regression shows a coordinated CSF sphingolipid phenotype involving the same membrane economy that glia must build, recycle, and repair.

The acid-LAL model therefore has a defined cellular endpoint. If LAL-dependent sterol and PUFA liberation is abnormal in ASD microglia, the predicted consequence is not generic inflammation. It is abnormal lipid-cargo processing, abnormal sterol disposition, abnormal acid signaling, and altered support of oligodendrocyte/myelin biology.

16. The Strong Autism Synthesis

Human autism already occupies both sides of the proposed bottleneck. Upstream and substrate territory includes cholesteryl-esters, cholesterol, PUFA-containing complex lipids, phospholipids, bile acids, and oxidized lipid chemistry. Downstream territory includes free-fatty-acid systems, eicosanoids and CYP-derived metabolites, sphingolipid networks, microglial state, and oligodendrocyte/myelin biology.

Paper X therefore proposes that these findings are components of an acid-availability disorder centered on LAL rather than a collection of unrelated metabolic abnormalities. LAL is positioned to connect them because a single catalytic event controls the availability of both the sterol and fatty-acid components of cholesteryl ester.

17. The Acid-LAL Model

ACID INPUT includes proton state, fatty-acyl identity, degree of unsaturation, oxidation, acidic phospholipids, surface charge, bile-salt concentration, and fatty-acid product feedback. These variables determine the chemical and physical conditions under which LAL encounters its substrate.

The LAL BOTTLENECK converts CE/TG into FC plus fatty acid. The outputs then diverge. STEROL OUTPUT feeds cholesterol export, oxysterol/LXR signaling, membrane rebuilding, and systemic sterol metabolism. ACID OUTPUT feeds COX, LOX, CYP450, and other fatty-acid signaling routes. Both outputs affect glial state, and several acid outputs can feed backward onto the LAL system.

The resulting topology is ACIDS -> LAL -> ACIDS. It is not a claim that every acid acts through one receptor or binding site. It is a distributed-control model in which acid chemistry regulates LAL while LAL controls which esterified acids become biologically available.

18. Predicted Availability Indexes

Paper X predicts that ratios across biochemical boundaries will discriminate the relevant ASD state better than isolated concentrations. The primary indexes are CE:FC, CE-18:2:free-18:2, CE-20:4:free-20:4, free-18:2:HODE/EpOME/DiHOME, and free-20:4:HETE/EET/diHETrE. Bile-acid species and conjugation state should be analyzed as an interacting sterol-derived acid system rather than collapsed into total bile acid.

These indexes are specified before the decisive ASD experiment. A result in which total lipid changes but the predicted partitioning ratios remain normal would argue against the central model.

19. The Decisive Human Autism Experiment

Generate matched ASD and control human iPSC-derived microglia and oligodendrocytes in a multicellular neural system. Challenge microglia with identical isotopically labeled myelin and defined CE cargo. Measure LAL catalytic activity, lysosomal pH, total CE, FC, CE-18:2, free 18:2, CE-20:4, free 20:4, oxidized CE-18:2/20:4 species, and downstream HODE, EpOME/DiHOME, HETE, EET/diHETrE, prostanoic acid, and related products.

Measure NPC2, 25-OHC/LXR, APOE, ABCA1, ABCG1, lipid droplets, cholesterol efflux, and myelin-debris clearance in the same cells. In coupled oligodendrocytes, measure maturation, cholesterol localization, sphingomyelin, ceramide, GalCer/HexCer, sulfatide, and myelin output.

Then manipulate LAL bidirectionally. Increase LAL in ASD cells without directly changing the downstream acid pathways. Reduce LAL in control cells. If the predicted sterol/acid partitioning phenotype follows LAL in both directions and the downstream glial/myelin phenotype follows with it, the mechanism gains direct causal support.

20. The Acid Matrix Experiment

Jacob's universal acid proposition should be tested, not protected. Build an acid-by-LAL matrix spanning proton concentration, free fatty acids, 18:2 and 20:4 species, hydroxy and oxidized fatty acids, acidic phospholipids, bile acids/salts, ketone-body acids, dicarboxylic acids, sulfur-containing acids, and other biologically relevant organic acids.

For each acid state measure LIPA expression, LAL protein, lysosomal localization, catalytic pH profile, CE hydrolysis, TG hydrolysis, Km, Vmax, substrate-interface behavior, FC output, fatty-acid output, oxylipin output, and downstream cholesterol disposition. The universal claim survives only to the extent the experiments support it.

21. Competing Explanations

ASD lipid and acid abnormalities can arise from diet, genetics, microbiome composition, medications, sleep, gastrointestinal biology, systemic inflammation, liver metabolism, or other processes without primary LAL dysfunction. Bile-acid abnormalities can be downstream of gut-liver biology. Oxylipin abnormalities can arise from oxygenase enzymes independent of lysosomal precursor supply. Sphingolipid abnormalities can arise without a neutral-lipid bottleneck.

Paper X does not dismiss these alternatives. It forces them to compete against a functional flux test. If ASD cells show normal LAL-dependent CE-to-FC/FA flux under controlled cargo challenge, the central LAL explanation is weakened even if peripheral acid biomarkers remain abnormal.

22. Predetermined Failure Conditions

The acid-LAL autism mechanism is substantially weakened if appropriately matched ASD glia show normal LAL catalytic activity, normal CE-to-FC flux, normal CE-PUFA-to-free-PUFA flux, and normal response to standardized myelin cargo despite the predicted downstream phenotype.

The model is also weakened if bidirectional LAL manipulation fails to move the predicted acid-partitioning phenotype, or if changing the partitioning phenotype fails to alter glial/myelin output. The universal acid proposition must narrow if broad acid classes fail to alter any measured layer of LAL function.

Conversely, a reproducible ASD flux defect that is rescued by LAL restoration and phenocopied by LAL reduction in control cells would move the model from convergence toward mechanism.

23. Publication Boundaries

Paper X does not state that abnormal LAL flux has already been demonstrated in human ASD. It does not state that every acid directly binds LAL, that every autistic person shares one acid phenotype, or that every bile-acid abnormality originates at LAL.

The paper does state, strongly, what the experiments already demonstrate: acid and lipid-interface chemistry can control LAL; LAL controls the availability of esterified 18:2 and 20:4 for downstream mediator production; microglial LAL controls white-matter lipid processing and repair; and human autism independently exhibits abnormalities across the substrate, acid-output, sterol, sphingolipid, and glial territories predicted by this architecture.

24. Conclusion

Autism is the human phenotype Paper X is built to explain. Human ASD is already characterized by abnormalities across cholesteryl-esters, cholesterol, PUFA-containing lipids, bile acids, eicosanoid and CYP-derived acid systems, sphingolipids, microglia, and oligodendrocyte/myelin biology. Autistic regression adds a direct CSF phenotype combining reduced beta-hydroxybutyrate with coordinated disruption of sphingomyelin, ceramide, HexCer, sulfatide, and S1P.

LAL supplies a biochemical mechanism capable of connecting these territories. It is not merely an enzyme that removes stored cholesterol. It is a molecular partitioning gate. By splitting cholesteryl ester into free cholesterol and fatty acid, LAL simultaneously determines sterol availability and acid availability. Loss of LAL traps 18:2 and 20:4 in the cholesteryl-ester pool and suppresses downstream lipid-mediator production. In microglia, LAL-mediated CE hydrolysis determines whether cholesterol-rich myelin cargo can be processed into a reparative state.

Acids reciprocally control that gate. Proton state, phospholipid chemistry, fatty-acyl structure and unsaturation, surface charge, bile-salt state, substrate oxidation, and fatty-acid products can each change the behavior of the LAL system. The evidence therefore supports a bidirectional biochemical architecture: ACIDS → LAL → ACIDS.

Paper X advances the explicit hypothesis that a biologically defined component of autism is an acid-availability disorder centered on the LAL bottleneck. The decisive missing experiment is now narrow: measure CE-to-FC and CE-PUFA-to-free-PUFA flux in human ASD glia under standardized lipid challenge and manipulate LAL in both directions. If the predicted acid and sterol partitioning phenotype follows LAL and drives the downstream glial/myelin phenotype, the mechanism gains direct support. If it does not, the central hypothesis fails.

The central question is no longer whether acids, cholesterol, fatty acids, and glial lipid biology are individually abnormal in autism. They are. The mechanistic question is whether those abnormalities converge at the biochemical boundary that determines whether esterified lipid becomes biologically available: LAL. Paper X identifies that boundary, defines its predicted acid signature, and provides the experiment capable of deciding the model.

References

1. Triglyceride and cholesteryl-ester hydrolysis by lysosomal acid lipase: Imanaka T, Amanuma-Muto K, Ohkuma S, Takano T. Effects of phospholipids on lysosomal acid lipase purified from rabbit liver. *J Biochem.* 1983;93:1517-1521. PMID 6885736. doi:10.1093/oxfordjournals.jbchem.a134289.
2. Takeuchi R, Imanaka T, Ohkuma S, Takano T. Effect of phospholipids on the hydrolysis of cholesterol oleate liquid crystals by lysosomal acid lipase. *J Biochem.* 1985;98:933-938. PMID 4077846. doi:10.1093/oxfordjournals.jbchem.a135373.
3. Substrate specificity of lysosomal cholesteryl ester hydrolase isolated from rat liver. 1986. PMID 3762320. Direct evidence for taurocholate-dependent activation/inhibition, phospholipid dependence, surface-charge effects, and oleate product inhibition.
4. Effect of substrate properties on the activity of lysosomal cholesteryl ester hydrolase. 1978. PMID 35235. Direct evidence for phosphatidylcholine/phosphatidic-acid stimulation and taurocholate-PC mixed-micelle substrate presentation.
5. Imanaka T, et al. Characterization of lysosomal acid lipase purified from rabbit liver. 1984. PMID 6520114. Direct evidence for CE/TG hydrolysis and fatty-acyl chain-length substrate dependence.
6. Schlager S, et al. Lysosomal lipid hydrolysis provides substrates for lipid mediator synthesis in murine macrophages. *Oncotarget.* 2017;8. PMID 28402950. PMCID PMC5522325.
7. Hoppe G, Ravandi A, Herrera D, Kuksis A, Hoff HF. Oxidation products of cholesteryl linoleate are resistant to hydrolysis in macrophages, form complexes with proteins, and are present in human atherosclerotic lesions. *J Lipid Res.* 1997;38:1347-1360. PMID 9254061. doi:10.1016/S0022-2275(20)37418-6.
8. Hu Y, Tang K, Hu H, et al. Lysosomal cholesteryl ester hydrolysis drives white matter repair by reprogramming microglia into a novel reparative state. *J Neuroinflammation.* 2026;23:155. PMID 41904522. PMCID PMC13169559. doi:10.1186/s12974-026-03782-7.
9. Needham BD, Adame MD, Serena G, et al. Plasma and Fecal Metabolite Profiles in Autism Spectrum Disorder. *Biol Psychiatry.* 2021;89:451-462. PMCID PMC7867605. doi:10.1016/j.biopsych.2020.09.025.
10. Yap CX, Henders AK, Alvares GA, et al. Interactions between the lipidome and genetic and environmental factors in autism. *Nat Med.* 2023. PMCID PMC10115648. doi:10.1038/s41591-023-02271-1.
11. Lingampelly SS, Naviaux JC, Heuer LS, et al. Metabolic network analysis of pre-ASD newborns and 5-year-old children with autism spectrum disorder. *Commun Biol.* 2024;7:536. doi:10.1038/s42003-024-06102-y.
12. 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.
13. Hirai T, Umeda N, Harada T, et al. Arachidonic acid-derived dihydroxy fatty acids in neonatal cord blood relate symptoms of autism spectrum disorders and social adaptive functioning: Hamamatsu Birth Cohort for Mothers and Children. *Psychiatry Clin Neurosci.* 2024;78:546-557. PMCID PMC11488600. doi:10.1111/pcn.13710.

JACOB'S VOICE | PAPER X | AUTISM AND THE ACID-LAL BOTTLENECK

14. Lusa S, Tanhuanpaa K, Ezra T, Somerharju P. Direct observation of lipoprotein cholesterol ester degradation in lysosomes. *Biochem J.* 1998;332:451-457. PMID 9601074.
15. Anderson J, Walker G, Pu J. BORC-ARL8-HOPS ensemble is required for lysosomal cholesterol egress through NPC2. *Mol Biol Cell.* 2022;33:ar81. PMID 35653304.
16. Abdul-Hammed M, Breiden B, Adebayo MA, Babalola JO, Schwarzmann G, Sandhoff K. Role of endosomal membrane lipids and NPC2 in cholesterol transfer and membrane fusion. *J Lipid Res.* 2010;51:1747-1760. PMID 20179319.
17. Oninla VO, Breiden B, Babalola JO, Sandhoff K. Acid sphingomyelinase activity is regulated by membrane lipids and facilitates cholesterol transfer by NPC2. *J Lipid Res.* 2014;55:2606-2619. PMID 25339683.

Evidence boundary: Human autism references establish ASD/autistic-regression acid, lipid, developmental, and glial phenotypes but do not establish LAL dysfunction. LAL references establish direct enzyme, macrophage, and microglial mechanisms outside autism unless explicitly stated. Paper X's central acid-LAL-autism sequence remains a falsifiable mechanistic hypothesis assembled from these independently demonstrated components.