THE ROLE OF GENETIC MUTATIONS IN THE DEVELOPMENT OF SYSTEMIC VASCULOPATHY IN RVCL SYNDROME – A COMPREHENSIVE REVIEW

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ABSTRACT

Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations (RVCL-S) is a rare autosomal-dominant microangiopathy caused by C-terminal mutations in the TREX1 gene. These mutations mislocalize the TREX1 protein to the nucleus, impairing DNA repair and promoting endothelial senescence and microvascular dysfunction. The disease usually begins in mid-adulthood, with progressive retinal ischemia often serving as the earliest sign, followed by multifocal leukoencephalopathy and systemic features such as liver disease, chronic kidney disease,and Raynaud's phenomenon. Due to overlapping clinical features, RVCL-S is frequently misdiagnosed as multiple sclerosis or systemic lupus erythematosus. Diagnosis relies on genetic testing and advanced imaging techniques, including wide-field fluorescein angiography and cerebrovascular reactivity mapping. Management is largely symptomatic; however, emerging therapies such as crizanlizumab, a P-selectin inhibitor and prime editing gene therapy offer potential targeted approaches for this multisystem disorder.

KEYWORDS

TREX1 gene, Microangiopathy, Retinal ischemia, Leukoencephalopathy, Endothelial senescence, Crizanlizumab.

1.INTRODUCTION

Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations (RVCL-S) is a rare, autosomal-dominant small-vessel microangiopathy that is a result of heterozygous C-terminal frameshifts or truncating mutations in TREX1 gene. The mutations disrupt the localization of TREX1 protein without necessarily eliminating exonuclease activity and result in a unique clinical disease that is a progressive retinal ischemia with adult-onset multifocal white-matter disease and multisystem injury of the microvasculature of organs such as the liver and kidney. RVCL-S is a disease that is usually acquired in mid- adulthood (most commonly the 30s-50s) though phenotypic expressivity and age of onset can differ considerably between families and individuals and limited phenotypes (such as ocular-dominant disease) have been observed in mosaic carriers. Recent discoveries that TREX1 C-terminal variants result in a microvascular systemic disease have shifted the diagnostic and research focus towards endothelial biology, neurovascular imaging and gene-targeted therapeutics. (Wilms, A. E., *et al*.,2022)

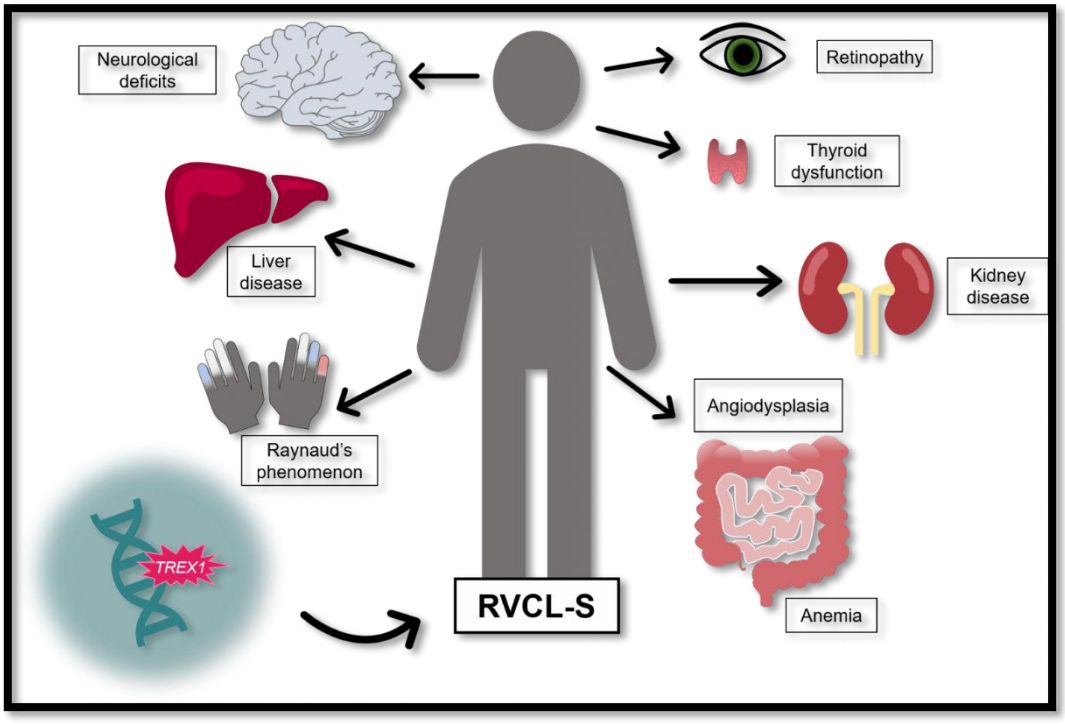

FIGURE 1.1: Systemic manifestations of RVCL-S. (Wilms, A. E., *et al*., 2022)

RVCL-S is genetically characterized by deletions (frameshift or premature stop) at the C-terminus of TREX1. Instead of mere loss of enzymatic activity, an emerging mechanistic literature suggests that mutated TREX1 mis localises (e.g. by aberrant nuclear entry), disrupts pathways of homology-directed repair of DNA damage and causes progressive DNA damage, cellular senescence and dysfunctional endothelial behaviour. The resulting cellular effects are likely to be the basis of the selective susceptibility of highly vascularized tissues and the premature microvascular ageing phenotype that is observed clinically. It has been experimentally validated in Drosophila, mice and human cells that C-terminal forms disrupt the DNA-repair mechanisms and accelerate senescence-like phenotypes which is an important mechanistic interface between the genotype and the microangiopathic phenotype. (Hoogeveen, E. S., *et al*.,2021)

Clinically, the retinal structure is where the first and most reliable signs appear. The development of capillary non-perfusion, mid-peripheral non-perfusion configurations, abnormal distributions of microaneurysms, micro angiomas and ischemic retinopathy are examples of ophthalmic features that may resemble more prevalent pathologies (like diabetic retinopathy or ocular ischemic syndrome). Ophthalmologists are generally in a position to offer the primary diagnostic indication because retinal symptoms often occur before overt neurological deficits.(Pelzer, N., *et al*., 2021) However, in a subset of patients, the phenotypic overlap with common vascular retinopathies and inflammatory retinopathies has resulted in misdiagnosis and inappropriate management (including needless long courses of immunosuppression); harmful delays can be avoided by carefully combining early genetic testing, family history, and clinical pattern recognition. Peripheral non-perfusion, FAZ expansion and microvascular remodelling have been shown to be objective indicators of ocular illness and disease development by advanced retinal imaging modalities such wide-field fluorescein angiography and OCT-angiography. (Rhee, R. L., *et al*.,2024)

Neuroimaging in RVCL-S demonstrates a characteristic, though heterogeneous, spectrum of white-matter abnormalities. Early disease is marked by punctate T2/FLAIR hyperintensities; with progression, lesions may coalesce into larger confluent areas with persistent contrast enhancement, diffusion restriction and—over time—calcification and cystic degeneration. Some lesions exhibit rim enhancement and mass-effect features that mimic stupefactive demyelination or high-grade glioma, leading in some cases to neurosurgical biopsy. (Holley, J. A., *et al*., 2024)

In order to distinguish RVCL-S lesion progression from other diagnostic mimics and to identify that radiologic "activity" (contrast enhancement, limited diffusion) may last for months in particular lesions, longitudinal high-resolution MRI scans in mutant carriers have proven crucial. Therefore, it is essential to integrate lesion morphology, lesion chronology and clinical context in order to prevent invasive operations and misguided therapy. (Ando, S., *et al*.,2024)

These findings support the concept that diminished vascular reserve and impaired autoregulation predispose to repeated micro-ischemic insults that accumulate as chronic white-matter injury. Importantly, CVR measures show promise as an early biomarker for presymptomatic mutation carriers and as a physiologic endpoint for trials targeting vascular stabilization. (Xie, N., *et al*.,2021)

Systemic symptoms in RVCL-S reflect widespread vascular involvement, with changes in the hepatic microvasculature, proteinuria and chronic kidney disease, as well as involvement of other organs. (Muthusamy, K., *et al*.,2023) Autopsy and histological studies show small-vessel changes, including thickening and duplication of the basement membrane, loss of pericytes, degeneration of smooth muscle and hyalinization of the collagenous wall, which correlates with clinical and imaging changes. These systemic features of RVCL-S suggest that it is a multisystem microangiopathy and should be evaluated by a team of specialists. (Chen, B., *et al*.,2023)

Inflammatory vasculitis, demyelinating disorders (such as multiple sclerosis and stupefactive variants), metabolic leukodystrophies and other genetic small-vessel disorders like CADASIL (NOTCH3 mutations) and COL4A1/COL4A2-related vasculopathies are all included in the wide differential diagnosis of RVCL-S. (Sayeed, B., *et al*.,2025)

In addition, systemic autoimmune diseases, such as SLE, may share clinical and laboratory characteristics (such as leukopenia, autoantibody positivity and systemic symptoms) that complicate the diagnostic picture. Since several case reports have documented extensive immunosuppressive treatment for suspected autoimmune disease prior to definitive TREX1 testing confirming the diagnosis, raising clinical suspicion for RVCL-S in the setting of retinal vasculopathy with atypical MRI features and familial stroke or white-matter disease is important. Diagnostic algorithms that include next-generation sequencing, targeted imaging and neuro-ophthalmologic evaluation are increasing accurate rates of diagnosis. (Chaneac, L., *et al*., 2024)

Due to the disease's rarity and lack of recognition, epidemiological data for RVCL-S are still few; nonetheless, worldwide case series and pedigree analyses show that dozens of families have already been found across many continents. (Wilms, A. E., *et al*.,2022)

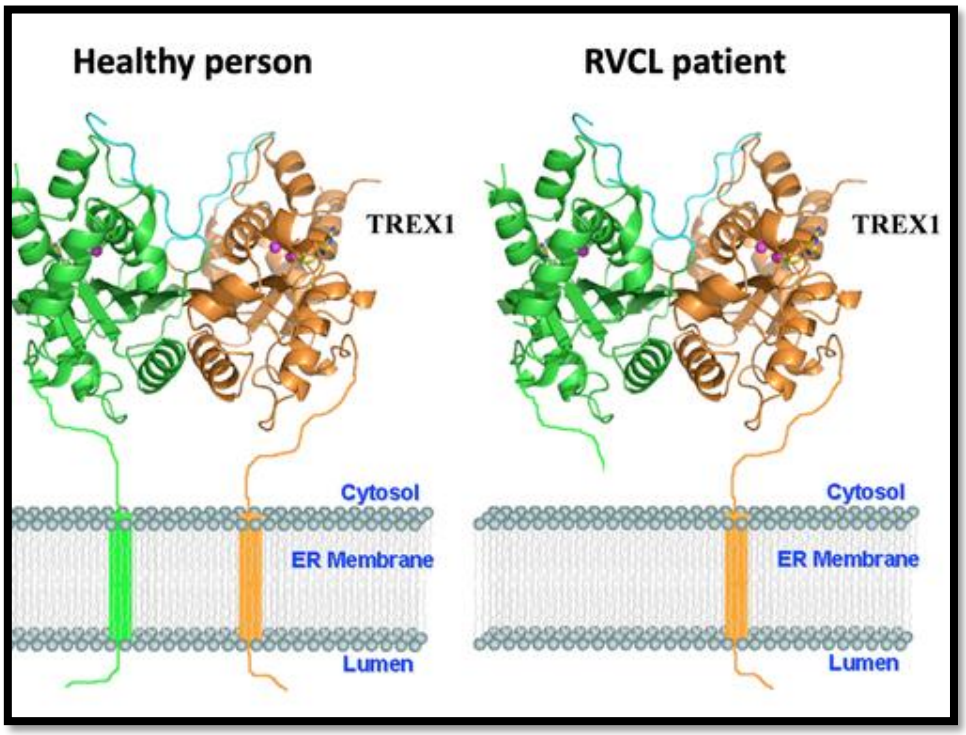

FIGURE1.2: TREX1 in healthy and RVCL-S.

The first prospective therapeutic signal in RVCL-S is the stabilization of retinal non-perfusion in treated patients, according to a Phase II open-label study of crizanlizumab, a monoclonal antibody that targets P-selectin. Nevertheless, MRI results and longer-term clinical endpoints are still being investigated and interpreted. Although these first findings are promising, before definitive treatment recommendations can be given, bigger controlled studies and the establishment of reliable clinical and imaging outcomes will be required. (Resende, L. L., *et al*.,2019)

Gene-targeted molecular therapeutics are developing quickly at the same time. Recent research has linked much milder phenotypes to both naturally occurring and artificially produced TREX1 mosaicism, indicating that partial rectification or mosaic restoration of TREX1 function may be therapeutic. (Papassin, J., *et al*.,2021)

Taking advantage of this, researchers have suggested prime-editor-based methods to replicate a favourable mosaic state and preclinical investigations employing prime-editing techniques have repaired frequent RVCL-causing variations in cell and animal models. These

findings offer a convincing proof-of-principle that treating the genetic cause of RVCL-S may be feasible in the future, despite the significant safety, delivery and regulatory challenges associated with gene editing in humans. (Miner, J. J. *et al*.,2024)

This model explains clinical facts including susceptibility to radiation-like damage patterns, the age-dependent acceleration of neurological deterioration and systemic organ involvement by connecting RVCL-S to more general biological processes linked to vascular aging and small-vessel illness. These mechanistic discoveries are guiding both biomarkers by linking genetic lesions to cellular dysfunction and tissue-level microvascular failure. Design of therapy and development. (Pin MG., *et al*., 2024)

Third, the path to gene-based correction for a dominantly inherited microangiopathy, where mosaic rescue rather than complete germline repair may be the most successful approach, will be shaped by safety and practical considerations. To speed up development, multicentre consortia, natural history registries and cooperation across the ophthalmology, neurology, genetics and vascular biology departments will be crucial. (Wang X., *et al*.,2024)

RVCL-S is a useful model of a genetically based microvascular illness where endothelial dysfunction, compromised cerebrovascular control and progressive multisystem damage are caused by a particular class of TREX1 mutations. Molecular genetics, physiological MRI and retinal imaging have all advanced. identification of the illness has uncovered treatment options, including gene editing and anti-adhesion biologics. Whether the early translational promise in RVCL-S can be translated into significant clinical benefit for patients and families affected by this debilitating small-vessel disorder will depend on ongoing efforts to standardize diagnostic criteria, develop validated biomarkers and carry out rigorous interventional studies. (Vu TV., *et al*., 2024)

2.AIM AND OBJECTIVES

AIM

To elucidate the mechanisms by which pathogenic mutations in the TREX1 gene drive systemic small-vessel vasculopathy in retinal vasculopathy with cerebral leukoencephalopathy syndrome (RVCL-S), with a particular focus on highly vascularized tissues such as the retina and brain.

OBJECTIVE

- The study aims to reduce leukocyte-mediated endothelial injury by inhibiting P-selectin, thereby decreasing cerebral and retinal ischemic lesion progression and improving clinical outcomes.
- To analyse a case of RVCL-S associated with a TREX1 mutation coexisting with systemic lupus erythematosus, highlighting the risk of misdiagnosis.
- To emphasize the importance of genetic testing and systemic immune screening to improve accurate diagnosis and guide appropriate treatment strategies in RVCL-S patients.
- To improve early diagnosis of RVCL-S by identifying key clinical, radiological, and genetic markers, particularly TREX1 mutations in patients with unexplained retinal and cerebral vascular symptoms.
- To explore underlying pathogenic mechanisms, including interferon pathways and vascular damage processes, in order to support development of targeted therapies and future clinical research trials.

3.EPIDEMEOLOGY

Tiny blood vessels throughout the body can be affected by a condition called RVCL-S. This illness stems from specific changes in the TREX1 gene found on one copy inherited from either parent. These genetic shifts chop off part of the protein near its end. Around thirty to forty-six separate family lines have shown signs globally, spanning different backgrounds. The shift known as V235Gfs6 pops up in roughly two out of every five diagnosed families. Mistaking it for diseases such as multiple sclerosis happens often. Brain tumors or eye issues tied to sugar imbalance also get confused with this disorder. (Wilms, A. E., *et al*., 2022)

Most people start noticing symptoms during their forties, on average at 42.9 years old, though some begin as early as 25 and others past 60. Vision problems tied to blood vessels in the eyes usually show up near age 40, hitting nearly every person who has the gene change. After that comes trouble with nerves and brain function - just over a quarter have these when diagnosed, but eventually nine out of ten develop them. These include weak spots in certain body areas seen in two-thirds, headaches similar to migraines in slightly more than half, thinking challenges in about half, mood or mental health shifts in less than half and sudden fits in one out of six. (Stam, A. H., *et al*., 2016)

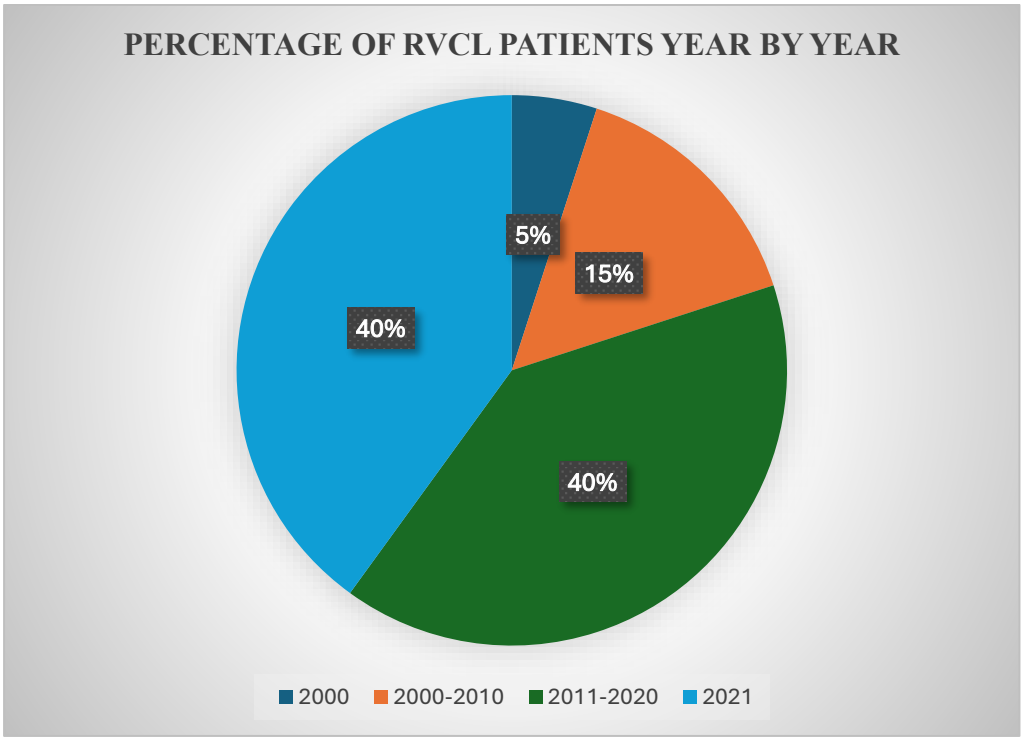

FIGURE 3.1: Percentage of RVCL patients over the years.

Folks don’t tend to live quite as long, averaging 53.1 years when they pass, give or take about ten, some making it from 32 up to 72. Most often, what ends things are problems like being worn down, lung infections, or issues following a stroke - these usually show up between five and twenty-five years after symptoms start. How fast things move differs sharply; once someone hits fifty, decline can speed up noticeably. Because of that twist, checking genes early in family lines where risk runs high makes sense - it opens space for watching closely and handling symptoms as they pop. Though nothing yet slows the core illness itself, keeping an eye on how organs respond does seem to help people do better. (de Boer, I., *et al*., 2022)

4.ETIOLOGY

A single faulty gene kicks thing off - tiny errors in DNA shift proteins where they do not belong. These displaced molecules stir disorder inside cells, messing up the genetic blueprint over time. Blood vessels throughout the body begin to weaken as damage spreads silently. Small vessel networks in organs falter, unable to maintain normal function. The brain's wiring slowly deteriorates alongside vision problems. (Richards., *et al*., 2007)

A tiny shift or stop error in one copy of the TREX1 gene brings about RVCL-S. This gene sits on chromosome 3. It makes a protein built from 314 parts, the main shredder of stray DNA inside cells. Without cleanup, immune confusion can follow. Most issues arise when trouble hits the enzyme's working core - think Aicardi-Goutières. But here, flaws show only at the tail end of the molecule. That broken tail chops off part of the structure. The cutter still works yet loses its anchor point. Gone is the greasy segment meant to plug into membranes. So, it floats free instead of staying put. (Stam., *et al*., 2016)

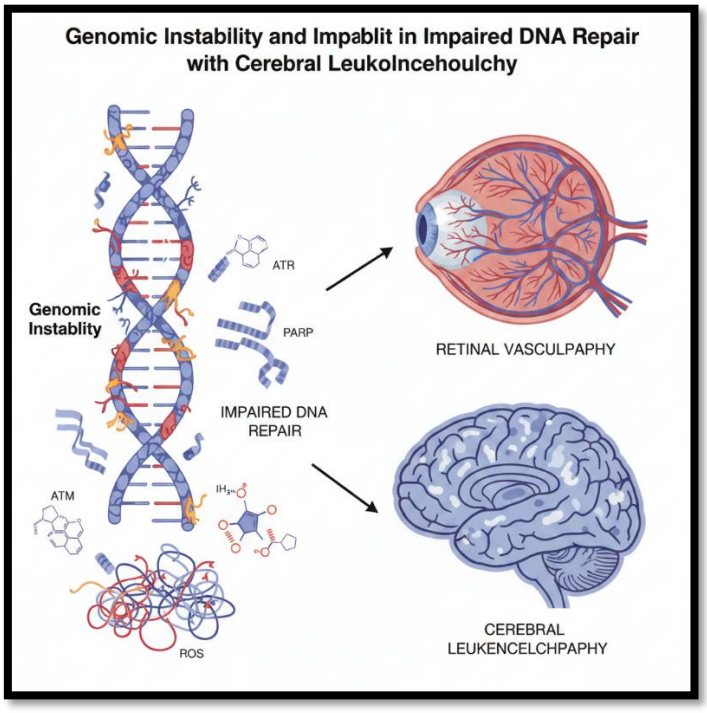

FIGURE 4.1: Genomic Instability in RVCL

When cells work properly, the TMD holds TREX1 in place near the endoplasmic reticulum, keeping it out of the nucleus. Without this tether - like in people who have RVCL-S

- the enzyme moves freely into the nucleus on its own. Because it shows up where it should not be, the exonuclease gains access to DNA it normally would never touch. Studies show that spreading across both compartments, the faulty protein poisons cells in ways other TREX1 problems do not. (Chauvin., *et al*., 2024)

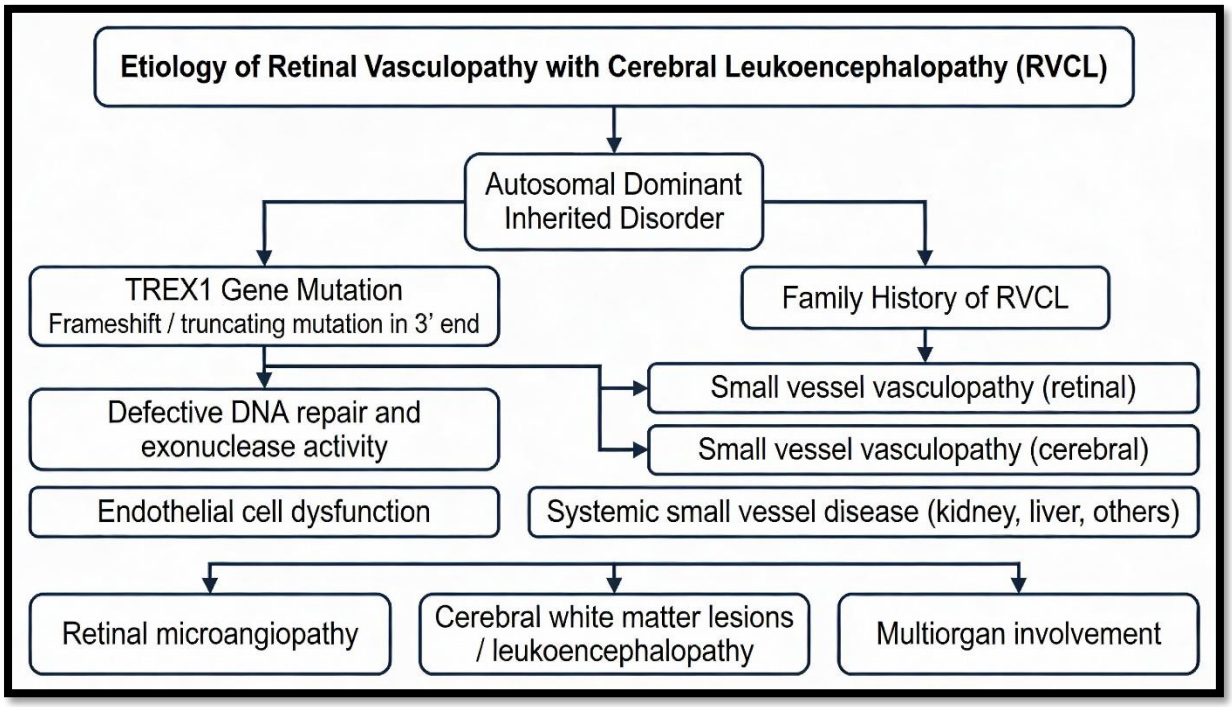

FIGURE 4.2: Etiology of RVCL

Beyond the obvious symptoms lies a deeper issue: the body's ability to fix broken DNA strands falters when homology-directed repair fails. Inside the nucleus, TREX1 shows up near these breaks, possibly chewing away at fragile 3 tails needed for accurate repairs. Without those bits, mistakes pile up fast - double-strand breaks multiply, chunks of chromosomes vanish, whole sets go missing. Cells caught in this spiral stall out early or shut down completely, much like what happens during aging driven by relentless DNA damage. (Yan., *et al*., 2021)

What happens inside the cells adds up to a type of blood vessel damage - different from plaque buildup - that hits tiny arteries and capillaries, especially in the brain, eyes and some inner organs. Seen under a microscope, one clear sign stands out: layers within the capillary walls grow thicker and split into multiple sheets, mostly found in brain and eye tissue. That shift causes vessels to stiffen, their channels shrink, then close off entirely, slowly starving

tissues of steady blood flow. Over time, leaks appear in the barrier protecting the brain, visible through lasting dye traces on MRI scans. (Ford., *et al.,* 2020)

Something odd shows up in blood work for people with RVCL-S - von Willebrand Factor runs way too high. At the same time, ADAMTS-13 hardly works at all. Because of this mismatch, tiny blood vessels face constant strain. Clots start forming more easily, especially when illness adds extra pressure. Inflammation and clotting begin feeding off each other. When the body gets hit with something like an infection, organs may suddenly stop working right. (Braune., *et al.,* 2024)

Starting in midlife, signs often show when damaged DNA builds past a breaking point. Cytokines push TREX1 activity higher if there's ongoing swelling, nudging things toward trouble. When faulty proteins pile up beyond a limit, harm speeds up - more injury, more flare-ups feed each other. How it begins depends on how it's passed down. Those born with the flawed gene always get sick and tend to die early. But people whose mutation appears in just some cells might only deal with one affected area and live fully. Not every path looks the same. (Hoogeveen*., et al*., 2021)

5.PATHOPHYSIOLOGY

Chronic microvascular ischemia brought on by endothelial damage and vessel wall hyalinization results in retinal micro-infarcts capillary obliteration and progressive leukoencephalopathy with punctate and mass-like white matter lesions that might appear on imaging as tumors (pseudotumor). As seen histologically in this case's basal ganglia lesion, persistent ischemia and disruption of the blood-brain barrier cause demyelination, tissue necrosis, macrophage infiltration and perivascular lymphocytic cuffing in the central nervous system. (Khan, M., *et al*.,2025)

Nodular regenerative hyperplasia, arterionephrosclerosis/glomerulosclerosis and occult gastrointestinal blood loss with anemia are caused by similar microangiopathic alterations in the liver, kidney and gastrointestinal tract. Diffuse microvascular dysfunction and gradual cerebral involvement result in systemic signs such Raynaud's phenomenon, hypertension, headaches and mental or cognitive problems. (Khan, M., *et al*.,2025)

Visual loss and photophobia result from small vessel vasculopathy with retinal capillary dilatation, non-perfusion regions, microaneurysms and progressive retinal degeneration. Chronic microangiopathy result in ischemia, white matter injury, corpus callosum and hippocampal shrinkage, subcortical punctate calcification and decreased cerebral metabolism in the brain. (Wang, X., *et al*.,2024)

Clinical manifestations of these conditions include speech difficulties, gait instability, cognitive decline and psychiatric symptoms. Through aberrant nucleic acid processing and CGAS-STING pathway activation, the same TREX1 mutation also leads to immunological dysregulation, which in this instance predisposes to systemic lupus erythematosus (SLE) characteristics including leukopenia, hypocomplementemia, autoantibodies and lupus anticoagulant positive. (Huang, J., *et al*.,2024)

While germline transmission to offspring results in severe multi-organ RVCL by age 40 and early death, somatic mosaicism (as in the maternal example) restricts the illness to the retina with a normal lifetime (age 74+). Because the wild-type TREX1 allele is intact and prevents cGAS-STING overactivation, RVCL does not exhibit systemic type I IFN increase, in contrast to AGS (catalytic loss producing IFNopathy). By correcting common variations (like V235fs) in cells and animals, prime editing gene therapy restores localization and suggests

the formation of mosaicism as a potential future treatment to reduce vasculopathy. (Holley, J. A., *et al*.,2025)

Capillary dropout, ischemia, neovascularization, vitreous hemorrhage, neovascular glaucoma and vision loss result from endothelial failure, which also causes microvascular blockage, ischemia and retinal nonperfusion that moves centrifugally from peripheral to central retina. P-selectin-mediated leukocyte adhesion to active endothelium aggravates vaso-occlusion, causing ischemic lesions in several organs, such as mini-strokes, nephropathy, cognitive decline and early mortality around age 50. The quantified nonperfusion index in the retina increases quickly at first (7.22% year 1) but plateaus with P-selectin inhibition by crizanlizumab (–0.69% year 2), indicating that treatment slows the course of ischemia while maintaining retinal thickness and visual acuity. (Rao, P. K., *et al*.,2024)

Genomic DNA is broken down by aberrant nuclear TREX1, which causes endothelial dysfunction, premature cellular senescence, persistent DNA damage and "inflammaging" mostly in vascular cells. This mimics MS, vasculitis, or SLE and presents as small vessel vasculopathy with retinal microangiopathy (onset ~age 40), brain white matter lesions/necrosis, liver damage, renal failure and osteonecrosis. While germline transmission to offspring results in severe multi-organ RVCL by age 40 and early death, somatic mosaicism (as in the maternal example) restricts the illness to the retina with a normal lifetime (age 74+). (Chauvin, S. D., *et al*.,2025)

Microvascular blockage, ischemia and retinal nonperfusion resulting from endothelial dysfunction cause capillary dropout, ischemia, neovascularization, vitreous haemorrhage, neovascular glaucoma and vision loss as they move centrifugally from peripheral to central retina. P-selectin-mediated leukocyte adhesion to active endothelium worsens vaso-occlusion, causing ischemic lesions in several organs, such as mini-strokes, nephropathy, cognitive decline and early mortality around age 50. (Spiegelman, D., *et al*.,2024)

The von Willebrand factor (vWF)–ADAMTS-13 axis is out of balance in these patients: ADAMTS-13 activity is comparatively low and gradually decreases, while vWF antigen and activity are noticeably higher. This mismatch encourages the build-up of ultra-large vWF multimers on endothelial surfaces, which in turn promotes platelet adhesion, the formation of microthrombi and thromboinflammation in small vessels in the brain and kidney (small vessel thromboinflammation in brain autopsy and thrombotic microangiopathy in kidney biopsy). Diffuse endotheliopathy with vWF deposition is supported by immunohistochemistry, which

reveals significant vWF staining in brain and renal micro vessels in RVCL-S compared to very modest staining in controls. (Braune, M., *et al*.,2024)

A compensatory attempt to upregulate ADAMTS-13 expression in response to persistent microvascular stress is suggested by cerebral methylome analysis, which shows hypomethylation of a CpG shore in the ADAMTS-13 gene. Overall, in RVCL-S, the ensuing chronic microvascular ischemia leads to progressive white matter lesions, blindness, renal illness. (Pfrepper, C., *et al*.,2024)

These shortened TREX1 proteins build up in the cytoplasm and nucleus, resulting in endothelial dysfunction due to oxidative stress or DNA damage during replication, which impairs vascular homeostasis in the brain, kidneys, liver and retina. Retinal capillary non-perfusion, white matter lesions, nephropathy and systemic symptoms including Raynaud's, anemia and hypertension are all signs of progressive small-vessel ischemia, which is frequently misinterpreted as MS, SLE, or stroke. (Versluis, D., *et al*.,2023)

Mutant TREX1 dysregulation of the OST complex lowers protein glycosylation, revealing peptides that cause inflammation and autoimmune (higher ESR, CRP, IL-6, autoantibodies), whereas TREX1+ microglia help remove debris from ischemic regions. In contrast to AGS/SLE (exonuclease-inactivating mutations producing IFNopathy), RVCL-S emphasizes vasculopathy over interferonopathy by maintaining DNase activity without systemic IFN increase. Endothelial/inflammatory biomarkers (vWF, ICAM-1, VEGF) are suggested for diagnosis and anti-endothelial/P-selectin medicines are prospective objectives. There is currently no curative therapy; symptomatic care focuses on consequences. (Versluis, D., *et al*.,2023)

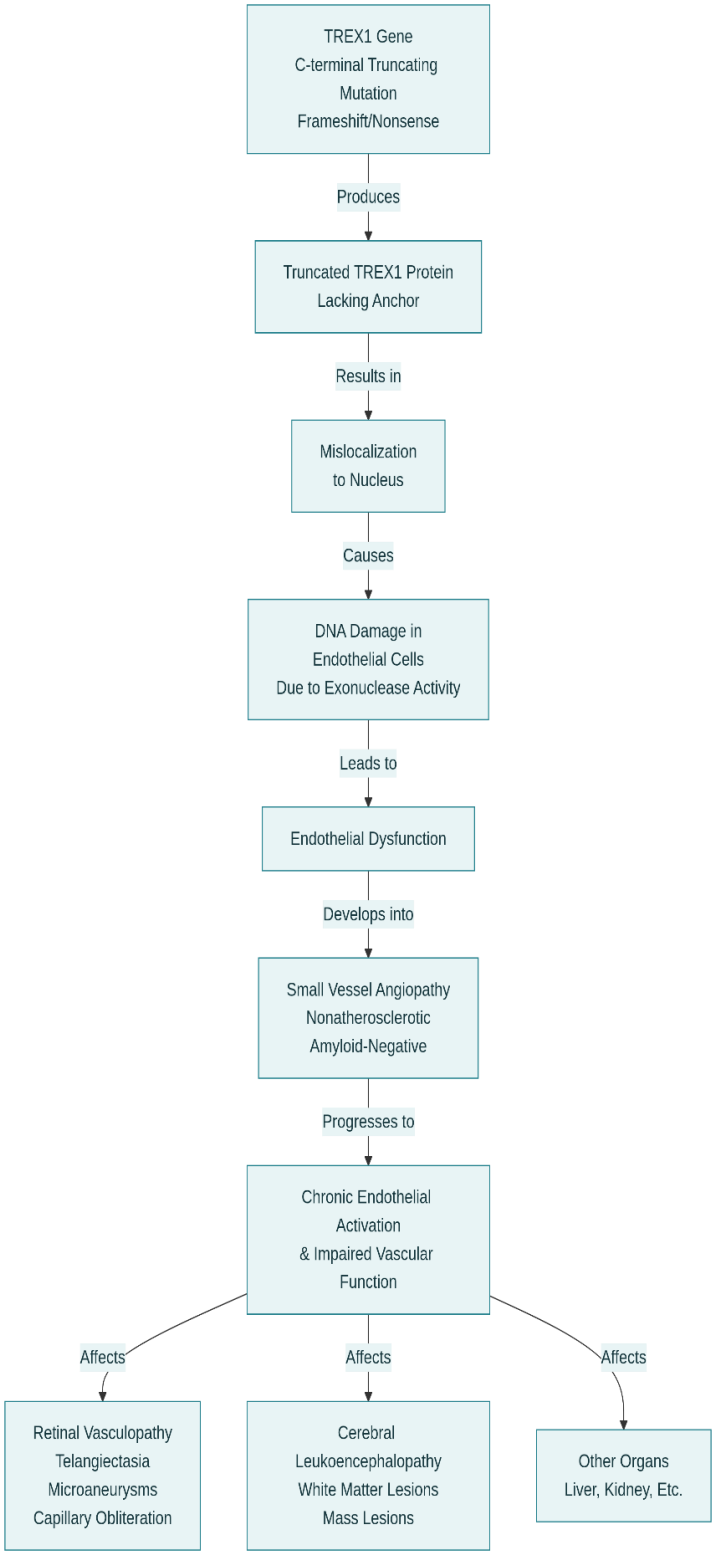

FIGURE 5.1: Pathogenesis of TREX1-Related Vasculopathy

With autosomal dominant inheritance across several generations, progressive TMA results in nephrotic-range proteinuria (3–6 g/d), chronic kidney disease (eGFR drop to 14 ml/min/1.73 m^2 by age 34) and end-stage kidney disease needing dialysis or transplant. Although mild brain white matter lesions and osteonecrosis imply systemic microvascular illness, kidney involvement predominates without microangiopathic haemolytic anaemia, thrombocytopenia, or substantial retinal/CNS symptoms at presentation, in contrast to typical RVCL-S. Complementopathy/TA-TMA is ruled out by normal complement (C3/C4/factor H), ADAMTS13 activity and autoantibodies, indicating that TREX1 is the main genetic cause of this unusual renal-limited phenotype. A TREX1 hotspot for severe nephropathy, D278fs highlights phenotypic variability in which extrarenal characteristics occur later and kidney presents first. (Song, Z. R., *et al*.,2023)

6.GENETIC DISEASE MODELLING

Not many conditions offer such a clear window into brain blood vessel trouble like RVCL-S does. Starting early, long before symptoms show, changes quietly build due to one specific gene error - a shortened form of TREX1 inherited from one parent. This single flaw makes it easier to track how tiny vessels break down over time compared to messy, random cases seen in typical patients. What unfolds in these individuals often mirrors what happens in common strokes or age-related cognitive decline. Learning from this rare setup reveals hidden steps in damage others usually miss. Patterns spotted here could reshape how scientists understand widespread diseases hiding behind similar chaos. (Wilms, A. E., *et al*.,2022)

When cells act out of balance, one clue hides in how vWF and ADAMTS-13 behave - like a tug-of-war pulled too far. Studies mixing patient records, tissue stains and chemical tags on DNA caught odd patterns, including looser control near the ADAMTS-13 gene, hinting the body might be pushing back under strain. Watching these shifts helps spot warning signs in blood long before harm becomes irreversible. What unfolds here shapes how doctors see early danger in small vessels. (Braune, M., *et al*.,2024)

Genetic research now looks at how body cells change differently within one person, using tools like precise gene editing to find new ways forward. Instead of relying on standard methods, researchers turn to mice engineered with human versions of the TREX1 gene, testing whether harmless viruses can carry fixes directly into damaged DNA. Surprisingly, even when just some cells receive the correction, health outcomes improve across organs. Results show animals live much longer than expected, avoiding early death once thought unavoidable. This patchwork repair - called synthetic mosaicism - might do enough to shift disease course without fixing every single cell. What matters most isn’t total perfection, but meaningful function restored. (Chauvin, S. D., *et al*.,2025)

7.MOLECULAR MECHANISM OF DISEASE

Something strange happens inside cells when certain broken parts of a gene show up. These changes occur in one copy of the TREX1 gene, affecting how its protein gets positioned within the cell. That gene normally makes a common enzyme that breaks down DNA bits floating around. Usually, the tail-end section keeps the protein stuck to a cellular structure called the endoplasmic reticulum. Without that anchor, due to shortened versions caused by mutations, the protein drifts into places it should not go. It ends up settling in the nucleus even though it remains fully capable of cutting DNA. Scientists think this wrong placement triggers blood vessel damage unlike typical hardening seen in aging. Tiny vessels respond by growing thicker walls and narrowing their inner paths. The whole process stems from misplaced activity rather than plaque buildup. (Wilms, A. E., *et al*.,2022)

Something shifts deep inside the system when vWF and ADAMTS-13 fall out of sync, pushing the body toward serious blood vessel damage. High amounts of vWF-Ag float in the bloodstream while ADAMTS-13 struggles to keep up, setting off clots tied closely to immune activity. Tiny blood vessels become sites where clotting and inflammation overlap. When scientists looked at DNA markers, they spotted less methylation near the ADAMTS-13 gene in brain samples. That loss of chemical tags might be the body trying harder to make more enzyme yet still failing under ongoing strain. (Braune, M., *et al*.,2024)

When TREX1 ends up in the wrong part of the cell, trouble follows - DNA across the genome gets broken. This damage pushes cells into early aging, sometimes called "inflammaging." Mutations behind RVCL-S dominate their genetic space without wiping out the enzyme’s cutting ability; instead, they let it run loose in the nucleus. Once inside, the working enzyme begins shredding the body's own DNA. That path isn’t shared by every TREX1-linked illness. Take Aicardi-Goutières syndrome: there, both gene copies fail completely, silencing the enzyme entirely, triggering strong interferon alarms throughout the body. But people with RVCL-S still have one good copy their cells manage enough cleanup to dodge that full-body alarm signal. (Chauvin, S. D., *et al*.,2025)

8.CONCLUSIONS

RVCL-S shows how lab findings can move into real medical progress, especially when tracking symptoms over time - starting with vision issues then expanding to multiple failing organs. Because it stems from just one gene, TREX1, scientists study it closely to understand more common small blood vessel disorders. These conditions often show similar signs: strained inner linings of vessels, swelling in tissues, blocked arteries.

At new treatments reveals CRISPR/Cas9 prime editing fixing TREX1 flaws in cells and mice. Instead of combining approaches, one study used Crizanlizumab alone; its phase II trial found slower worsening of retinal blood flow issues thanks to P-selectin blockage, pointing to small vessel perks without major side effects. Odd brain scans sometimes resemble tumors that act like gliomas - yet careful checks often trace them back to eye tests, inherited patterns and DNA proof.

Blood vessel problems cause repeated strokes and growing damaged areas, when middle-aged people lose the brain’s ability to manage blood flow properly. Because of faulty vessels struggling to adapt, harm spreads through nerve cells. When TREX1 stops working right, signals called type I interferons go unchecked, making damage worse in the lining of blood vessels. This sparks long-term swelling that reaches into the brain, eyes, even organs such as liver and kidneys. Scans from imaging tools, eye tests and DNA clues help track disease more clearly. Strange as it seems, TREX1 also acts in ways tied to viruses during infections, showing how one gene can do many different things.

The RVCL-S speeds up finding markers and treatments for many vascular dementias, using inherited patterns to follow changes closely. Because it damages blood vessels step by step - first sight, then brain and body functions - it shapes how care is planned and explained. Later on, gene fixes targeting mixed cell types may add years, turning a small condition into a guide for widespread diseases.

RVCL-S studies point to key next steps - tracking how illness unfolds over time shapes what comes after. Interferon-linked markers open paths, especially when paired with medicines that protect blood vessels, such as Crizanlizumab, which might shift outcomes. Spotting cases early through TREX1 checks avoids detours later down the line. Understanding how blood cells and immune signals interact brings light into rare but similar conditions. Progress here could mean fewer setbacks, even changes at the genetic level, if attention stays steady.

9.FUTURE ASPECTS OF RVCL-S

Fixing the root cause means targeting the faulty TREX1 gene directly. Scientists are exploring tools like CRISPR-Cas9 or base editing - not just to cut but to precisely correct errors - in blood-forming stem cells or early vessel-lining cells, which might stop widespread damage to blood vessels. Because TREX1 normally clears excess DNA inside cells, when it fails, leftover genetic material piles up. That pileup wakes up the cGAS-STING system, turning on strong immune reactions. Coming studies may test drugs that quiet this pathway, reducing the constant interferon signals linked to inflamed vessels.

Since RVCL stems from harmful effects of a shortened protein acting abnormally, finding drugs that remove this faulty version or replace its missing enzyme function inside the cell's core becomes crucial. Through tiny engineered systems mimicking human organs, scientists build miniature blood vessels impacted by RVCL right in the lab. These setups let them watch directly as gene errors weaken the brain’s protective barrier and cause vessel walls to grow fragile.

Not everyone with RVCL shows symptoms at the same pace - even identical mutations can lead to different outcomes. What sparks the condition in midlife might come down to hidden factors like chemical tags on DNA or outside stressors piling up over time. Signs in the bloodstream, maybe fragments of damaged nerves or tiny RNA patterns, may one day reveal early vessel leaks. These clues could spotlight trouble long before scans catch lasting harm in the brain.

Later studies might use fast protein scanning to spot the very first proteins breaking down in blood vessel walls. That knowledge may help design treatments aimed at strengthening those vessels. Machines that learn are now studying tiny changes in eye blood vessels and brain tissue spots. Spotting these early signs could improve how soon patients get diagnosed. Better detection also means measuring therapy results more accurately in medical tests.

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