C1q Deficiency (MONDO:0013343): A Comprehensive Disease Characteristics Report

Autonomous discovery investigation — 5 iterations, 9 confirmed findings, 32 papers reviewed

Disease: C1q Deficiency (Complement component 1q deficiency) **MONDO:** MONDO:0013343 · **OMIM:** #613652 (C1q deficiency) · **Orphanet:** ORPHA:169147 · **ICD-10:** D84.1 · **ICD-11:** 4A00.1 (complement deficiency) · **MeSH:** "Complement C1q" (D015950); "Hereditary Complement Deficiency Diseases" (D055468)

Summary

C1q deficiency is an ultra-rare autosomal-recessive inborn error of immunity and the strongest known single-gene cause of systemic lupus erythematosus (SLE). It is caused by biallelic loss-of-function mutations in any one of the three genes encoding the C1q chains — **C1QA, C1QB, or C1QC** — clustered on chromosome **1p36.12**. Because the mature C1q molecule is a hexameric assembly of six A-B-C heterotrimeric subunits, a damaging variant in a single chain prevents assembly of the entire molecule, producing complete functional C1q deficiency and abolishing initiation of the classical complement pathway. More than 90% of genetically confirmed C1q-deficient individuals develop SLE or an SLE-like disease — the highest penetrance of any known SLE susceptibility factor — typically with severe, early-childhood onset. Patients are also susceptible to invasive infection by encapsulated bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*).

The core mechanism is **impaired complement-mediated clearance of apoptotic cells and immune complexes**. C1q normally opsonizes dying cells and immune complexes for phagocytosis; in its absence, apoptotic material — a major reservoir of nuclear autoantigens — accumulates, driving autoantibody formation (ANA, anti-dsDNA), immune-complex deposition, and tissue injury (notably lupus nephritis and CNS disease). This "waste-disposal" / "clearance-deficiency" hypothesis is supported directly by gene-targeted C1q-knockout mice, which

develop glomerulonephritis with abundant apoptotic bodies and immune deposits. Downstream, **type I interferon dysregulation** amplifies the autoimmune phenotype and represents a druggable node.

Diagnosis rests on a distinctive laboratory signature — **absent total hemolytic complement activity (CH50) with normal C3 and C4** — plus demonstration of absent C1q protein and confirmatory sequencing (WES/single-gene). Management spans conventional SLE immunosuppression, type I interferon receptor blockade (anifrolumab), and — uniquely among the complement deficiencies — potentially **curative allogeneic hematopoietic stem-cell transplantation (HSCT)**, which works because C1q is synthesized predominantly by monocytes/macrophages, so replacing the hematopoietic compartment restores circulating C1q. Outcomes are variable: roughly 20% of patients die before age 20 (severe renal/CNS disease carries the worst prognosis), yet at least half reach middle age.

Section-by-Section Report

1. Disease Information

Overview. C1q deficiency is a rare autosomal-recessive complement deficiency in which functional C1q — the recognition subunit of the C1 complex that initiates the classical complement pathway — is absent. The dominant clinical consequence is a severe, early-onset SLE-like autoimmune disease, accompanied by heightened susceptibility to pyogenic (encapsulated-bacterial) infection.

Key identifiers. - **MONDO:** MONDO:0013343; **OMIM:** #613652; **Orphanet:** ORPHA:169147; **ICD-10:** D84.1; **ICD-11:** 4A00.1 - **Causal genes / loci:** C1QA (OMIM 120550), C1QB (OMIM 120570), C1QC (OMIM 120575) — chromosome 1p36.12

Synonyms / alternative names. C1q deficiency; complement component 1q deficiency; hereditary C1q deficiency; C1q monogenic lupus; C1q-deficiency SLE.

Nature of evidence. The knowledge base is derived from **aggregated disease-level resources and the published clinical/genetic literature** — principally case reports, small case series, an international survey of 45 patients across 31 families (PMID: 26119135), and a multinational HSCT cohort (PMID: 39470951) — rather than individual EHR extraction.

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2. Etiology

Primary cause — genetic. C1q deficiency is a **monogenic, autosomal-recessive disorder**. Biallelic loss-of-function mutations in any one of C1QA, C1QB, or C1QC abolish functional C1q.

> *"C1q deficiency is a rare autosomal recessive genetic condition characterized by mutations in genes C1qA, C1qB, or C1qC which can cause a SLE-like disease."* — PMID: 40316395

Genetic risk factors. The causal variants themselves ARE the risk factor; this is a highly penetrant Mendelian condition rather than a complex-trait susceptibility locus. C1q deficiency confers the strongest and most severe genetic risk for SLE of any complement deficiency:

> *"The strongest susceptibility genes for the development of systemic lupus erythematosus (SLE) in humans are null mutants of classical pathway complement proteins. There is a hierarchy of disease susceptibility and severity according to the position of the missing protein in the activation pathway, with the severest disease associated with C1q deficiency."* — PMID: 10934224

Environmental risk factors / triggers. As with SLE generally, environmental triggers (UV light driving photosensitive rash; infections) likely modulate expression. **Consanguinity** is a major demographic risk factor because the disease is recessive — multiple reported pedigrees are consanguineous (PMID: 40316395 describes consanguineous siblings). Epstein–Barr virus is implicated in anti-C1q autoantibody generation in *polygenic* lupus via molecular mimicry (PMID: 41929519), though this is distinct from the genetic deficiency.

Protective factors. No established genetic or environmental protective factors specific to C1q deficiency were identified. Restoration of C1q (via HSCT) is "protective" in the therapeutic sense but not a naturally occurring modifier.

Gene–environment interactions. UV exposure precipitating photosensitive mucocutaneous flares and infectious triggers of autoimmune activity are the principal gene–environment interactions; they operate on a fixed genetic background of absent clearance capacity.

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3. Phenotypes

C1q deficiency produces a **dual immunodeficiency–autoimmunity phenotype**. Frequencies below derive chiefly from the international survey of 45 patients (PMID: 26119135):

Phenotype	Type	Frequency	HPO suggestion
SLE / SLE-like disease	Clinical syndrome	80% (36/45)	HP:0002725 (Systemic lupus erythematosus)
Infections only (no SLE)	Clinical	11% (5/45)	HP:0002719 (Recurrent infections)
Asymptomatic	—	9% (4/45)	—
Photosensitive mucocutaneous rash	Physical/sign	Very common	HP:0000992 (Photosensitivity); HP:0001025 (Urticaria)
Discoid lupus	Physical	Common	HP:0005503 (Discoid lupus rash)
Oral ulcers	Sign	Common	HP:0000155 (Oral ulcer)
Inflammatory polyarthritis	Sign	Common	HP:0001369 (Arthritis)
Recurrent encapsulated-bacterial infection	Clinical	Common	HP:0002721 (Immunodeficiency)
Lupus nephritis	Clinical	Subset (severe)	HP:0000099 (Glomerulonephritis)
CNS involvement (incl. brain parenchymal calcification)	Clinical/ imaging	Subset (severe)	HP:0002518 (Periventricular calcification)
Absent CH50 with normal C3/ C4	Lab abnormality	Universal	HP:0005339 (Abnormal complement system)

> *"Of these patients 36 (80%) suffer from SLE, of which 16 suffer from SLE and infections, 5 (11%) suffer from infections only and 4 (9%) have no symptoms."* — PMID: 26119135
>
> *"All patients exhibited mucocutaneous involvement, discoid lupus erythematosus, inflammatory polyarthritis, normal serum complements C3 and C4, coarse-speckled Antinuclear antibody positivity."* — PMID: 40556690

Characteristics. Onset is typically **neonatal–childhood** (case reports describe presentation as young as age 3; PMID: 42147803). Severity is **variable but skews severe**, with the most severe phenotype defined by **renal and/or neurological involvement**. Course is chronic with episodic lupus flares. Quality-of-life impact is substantial in severe cases (chronic immunosuppression, infection risk, renal/CNS morbidity), though formal EQ-5D/SF-36 data specific to C1q deficiency were not identified.

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4. Genetic / Molecular Information

Causal genes. C1QA, C1QB, C1QC on chromosome **1p36.12** (HGNC: C1QA, C1QB, C1QC). Each encodes one chain of the C1q molecule; all three must co-assemble into A-B-C heterotrimers, six of which form the hexameric "bouquet of flowers" structure.

Variant spectrum. C1q deficiency arises from a **diverse range of coding and non-coding loss-of-function variants**:

Variant	Gene	Type	Classification	PMID
c.622C>T	C1QA	Nonsense	Pathogenic	42147803
NM_001378156.1:c.263G>A	C1QB	Missense (novel)	Likely pathogenic	40506420
Intronic, 2 nt before exon-2 splice site	C1QB	Non-coding / splice	Pathogenic	25454803
Known A/B/C chain mutations (C1qA-Gln186, C1qB-Gly15, C1qB-Arg150, C1qC-Gly6, C1qC-Arg41)	C1QA/B/C	Nonsense/ missense	Pathogenic	18505047

A key mechanistic insight: the Dutch C1QB splice variant abolished C1qB mRNA, reduced C1qA mRNA, left C1qC mRNA normal, and caused intracellular absence of the C1qB peptide despite present C1qA/C1qC — demonstrating that **loss of a single chain prevents hexamer assembly**:

> *"Deep-sequencing revealed a homozygous mutation in the non-coding region of C1qB in the patient, whereas both parents were heterozygous. The mutation is located two nucleotides before the splice site of the second exon."* — PMID: 25454803

> *"A novel homozygous likely pathogenic missense variant in the C1QB gene, NM_001378156.1:c.263G>A, was identified."* — PMID: 40506420

Functional consequence: complete **loss of function** (null); recessive. **Allele frequencies** are extremely low (private/population-specific), consistent with an ultra-rare recessive disorder; heterozygous carriers are typically asymptomatic.

Somatic vs germline: germline. **Modifier genes / epigenetics:** no robustly established disease modifiers specific to C1q deficiency were identified, though autoantibody specificity stratifies organ involvement (see Diagnostics). **Chromosomal abnormalities:** not applicable — this is a single-gene point/small-variant disorder, not a structural/aneuploidy condition.

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5. Environmental Information

- **Environmental factors.** UV radiation precipitates the characteristic photosensitive cutaneous lupus; otherwise no specific toxin/occupational exposures are causally implicated.
- **Lifestyle factors.** None specifically established beyond general SLE triggers.
- **Infectious agents.** C1q deficiency does not have an infectious *cause*, but the deficiency increases **susceptibility to encapsulated bacteria** — *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* — because the classical pathway contributes to opsonophagocytic defense (PMID: 19418946 discusses this susceptibility in hypocomplementemia generally). EBV is relevant to anti-C1q autoantibody biology in polygenic lupus but not to the genetic deficiency itself.

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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. **Biallelic loss-of-function mutation** in C1QA, C1QB, or C1QC (germline) **leads to** absence or non-functionality of one C1q chain.
2. Missing chain **prevents assembly** of the A-B-C heterotrimer and therefore of the hexameric C1q molecule (*demonstrated* — intracellular chain studies, PMID: 25454803) **→ complete functional C1q deficiency**.

3. Absent C1q **results in** failure to initiate the **classical complement pathway** (no C1 complex formation) → **absent CH50 with preserved C3/C4** (alternative/lectin pathways intact).
4. Loss of C1q **impairs opsonization and clearance of apoptotic cells and immune complexes** (*demonstrated in vivo*; hierarchical role of classical-pathway proteins, PMID: 10934224).
5. Uncleared apoptotic cells — a **major source of nuclear autoantigens** — **accumulate** (*demonstrated*: apoptotic bodies in glomeruli of C1q-KO mice, PMID: 10072632).
6. Autoantigen exposure **drives loss of tolerance → autoantibody formation** (ANA, anti-dsDNA, and others) → **immune-complex formation and tissue deposition**.
7. **Branch A (autoimmunity):** immune complexes deposit in kidney (lupus nephritis), skin, and brain → **tissue injury** → clinical SLE. Type I interferon dysregulation **amplifies** this arm (druggable; PMID: 42597478).
8. **Branch B (immunodeficiency):** absent classical-pathway opsonization **results in** susceptibility to **encapsulated-bacterial infection**.
9. Net clinical outcome: **early-onset, often severe SLE** (>90% penetrance) ± recurrent infection; severe renal/CNS involvement **leads to** ~20% childhood mortality.

Molecular pathways / cellular processes. Classical complement activation pathway (initiation step); apoptotic-cell clearance / efferocytosis; opsonophagocytosis; immune-complex processing; type I interferon signaling (downstream amplifier).

- Suggested **GO biological-process terms:** GO:0006958 (complement activation, classical pathway); GO:0045087 (innate immune response); GO:0043277 (apoptotic cell clearance); GO:0006911 (phagocytosis, engulfment); GO:0034340 (response to type I interferon).
- Suggested **cell types (CL):** CL:0000576 (monocyte) and CL:0000235 (macrophage) — the predominant C1q-producing and phagocytic cells; CL:0000236 (B cell, autoantibody production).

Protein dysfunction. C1q is a complex glycoprotein assembled from 18 polypeptide chains (6× A-B-C), each with an N-terminal collagen-like region and a C-terminal globular gC1q head mediating ligand recognition (PMID: 28601358; PMID: 29692784). In deficiency, the molecule is simply absent (loss of function), not misfolded-and-aggregated.

Immune system involvement. The disease sits at the intersection of **immunodeficiency** (failed opsonophagocytosis) and **autoimmunity** (failed clearance → autoantibodies). C1q additionally regulates cytokine production by antigen-presenting cells and T-cell maturation, and participates in CNS synaptic pruning — functions whose loss may contribute to the breadth of phenotype (PMID: 28601358).

> *"Apoptotic cells are thought to be a major source of the autoantigens of SLE, and impairment of their removal by complement may explain the link between hereditary complement deficiency and the development of SLE."* — PMID: 10934224

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7. Anatomical Structures Affected

- **Organ level (primary):** skin (UBERON:0002097), kidney/glomerulus (UBERON:0002113 / UBERON:0000074), joints (UBERON:0001485), central nervous system / brain (UBERON:0000955).
- **Secondary / systems:** immune/hematopoietic system (UBERON:0002405), mucous membranes (oral ulcers), and systemic involvement typical of SLE (cardiovascular, serosal).
- **Tissue/cell level:** glomerular tissue (immune-complex deposition, apoptotic bodies); connective tissue/skin at the dermoepidermal junction; the key *effector* cells are **monocytes/macrophages** (CL:0000576 / CL:0000235), the main C1q source, and **B lymphocytes** producing autoantibodies.
- **Subcellular (GO Cellular Component):** extracellular space/blood plasma (GO:0005615) where C1q normally circulates; GO:0005581 (collagen trimer) describes the collagen-like stalk of the assembled molecule.
- **Localization / laterality:** manifestations (rash, nephritis, arthritis, cerebral calcification) are typically **bilateral/systemic**, consistent with a circulating-protein deficiency.

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8. Temporal Development

- **Onset:** congenital genetic lesion; **clinical onset in infancy/early childhood** is typical (cases as young as 3 years), making it a pediatric-onset monogenic lupus. Onset is usually insidious/chronic.
- **Progression:** chronic, lifelong, with **episodic (relapsing-remitting) lupus flares**. Severity ranges from mild/manageable to treatment-resistant. A severe subset with renal/CNS disease progresses to organ failure.
- **Duration / outcome spread:** highly variable. ~20% die before age 20, yet ≥50% reach middle age (PMID: 26119135).

- **Critical periods / intervention windows:** early recognition is pivotal; HSCT is most beneficial before severe renal/neurological damage accrues, since those features predict worst transplant survival (PMID: 39470951).

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9. Inheritance and Population

- **Inheritance pattern: Autosomal recessive.** Parents of affected children are obligate heterozygous carriers (PMID: 25454803).
- **Penetrance:** very high for SLE/SLE-like disease — **>90%** among genetically confirmed individuals (highest of any SLE susceptibility factor); a small minority (≈9%) remain asymptomatic, indicating penetrance is high but not absolute.
- **Expressivity:** variable (mild-to-severe; organ involvement differs between patients).
- **Consanguinity:** a major contributor; many pedigrees are consanguineous.
- **Founder effects / population distribution:** private and population-specific variants reported across Middle Eastern (Iranian, Arab), European (Dutch, Swedish), Brazilian, and other cohorts; no single global founder allele. Carrier frequency is very low but elevated in consanguineous communities.
- **Epidemiology:** ultra-rare; fewer than ~100 genetically confirmed patients described worldwide (international survey = 45 patients/31 families, PMID: 26119135; a review analyzed 69 genetically confirmed patients, PMID: 39470951). Precise population prevalence/incidence are not established.
- **Sex ratio / age distribution:** predominantly pediatric onset; sex distribution not strongly skewed in the reported series (in contrast to polygenic SLE's female predominance).

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10. Diagnostics

Screening / first-line laboratory signature (pathognomonic pattern): - CH50 (total hemolytic complement): absent / markedly reduced - C3 and C4: normal

This combination strongly points to an early-classical-pathway component deficiency and distinguishes **monogenic C1q lupus from classic polygenic SLE** (where C3/C4 are typically consumed/low).

> *"Laboratory evaluation showed strongly positive antinuclear antibody (ANA) and anti-SSA antibodies, with normal C3 and C4 levels but markedly reduced CH50." — PMID: 42147803*

Confirmatory tests: - **C1q protein quantitation** (absent) and functional classical-pathway assays. - **Western blot** to document absent C1q chains; mononuclear-cell C1q mRNA expression studies can characterize the molecular defect (PMID: 26017655). - **Genetic testing: whole-exome sequencing** is high-yield and was diagnostic in multiple cases (PMID: 42147803); **single-gene / targeted C1QA/B/C sequencing** confirms the biallelic variant; deep/whole-genome sequencing is needed to catch **non-coding splice variants** (PMID: 25454803). Parental carrier testing confirms recessive segregation. - **Autoantibodies:** ANA (coarse-speckled), anti-dsDNA, anti-Ro/SSA, anti-RNP help characterize disease and stratify organ risk (below).

Differential diagnosis. Polygenic SLE (C3/C4 usually low; C1q present); other early-classical-pathway deficiencies (C1r/s, C4, C2 — milder hierarchy); **acquired** C1q lowering with anti-C1q antibodies (e.g., hypocomplementemic urticarial vasculitis [HUV], PMID: 40852710; acquired angioedema / C1-INH deficiency, PMID: 28687105). The critical distinction: in genetic C1q deficiency the **antigen itself is absent**, whereas anti-C1q autoantibody syndromes require **present** C1q.

Prognostic autoantibody stratification (within genetic C1q deficiency). In 69 genetically confirmed patients, autoantibody specificity mapped to organ involvement:

> *"we found that anti-Ro antibodies are associated with neurologic involvement, and anti-RNP and anti-DNA antibodies with renal [involvement]." — PMID: 39470951*

Note on anti-C1q antibodies (adjacent biology). In *polygenic* SLE, circulating **anti-C1q autoantibodies** are the best single serological marker of lupus-nephritis activity (ROC AUC 0.929; NPV 92%; PMID: 41546370) and independently predict thrombosis in membranous LN (highest tertile HR 2.71; PMID: 41895528). These markers characterize polygenic SLE/HUV, **not** Mendelian C1q deficiency, and are included here only for differential-diagnostic completeness.

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11. Outcome / Prognosis

- **Mortality: ~20% case fatality before age 20** in the largest phenotypic survey, with almost all deaths occurring before age 20 — yet outcomes are highly variable and at least half of patients survive into middle age.

> *"In total 9 (20%) of the C1q deficient individuals had died. All except for one died before the age of 20 years."* — PMID: 26119135

- **Prognostic factors:** presence of **renal and/or neurological involvement** defines the severe phenotype and predicts the worst survival after HSCT (OS 40% vs 84%; p=0.034; PMID: 39470951). Autoantibody profile (anti-Ro → neurologic; anti-RNP/anti-DNA → renal) provides a serological route to risk stratification.
- **Morbidity:** chronic immunosuppression burden, infection susceptibility, cutaneous disfigurement (discoid lupus), arthritis, renal insufficiency, and CNS sequelae.
- **Recovery potential:** autoimmune features can **resolve completely after successful HSCT** with restoration of C1q, allowing discontinuation of immunosuppression.

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12. Treatment

Conventional SLE-directed therapy. Corticosteroids, hydroxychloroquine, and immunosuppressants (mycophenolate, cyclophosphamide, azathioprine, rituximab) are used for autoimmune manifestations and nephritis, as in polygenic SLE. These control but do not cure the underlying deficiency.

Type I interferon-targeted therapy. Anifrolumab (anti-IFNAR1 monoclonal antibody) produced marked benefit in a genetically confirmed C1QA-deficient child with refractory mucocutaneous lupus:

> *"She showed significant clinical improvement and full recovery of mucocutaneous lesions, restoration of laboratory parameters and successful discontinuation of corticosteroids after the seventh monthly infusion."* — PMID: 42597478

This implicates the type I IFN pathway as a downstream, druggable amplifier distinct from C1q replacement.

Curative allogeneic HSCT. Because C1q is produced predominantly by **monocytes/macrophages**, allogeneic HSCT replaces the deficient cellular source and can **cure** the disorder:

> *"Complete donor chimerism has been maintained for 2 years after transplantation, leading to the restoration of C1q levels and the resolution of SLE symptoms. Normal C1q mRNA expression was observed in CD14 + cells."* — PMID: 33000368

The largest cohort (EBMT Inborn Errors Working Party; 18 patients, 20 HSCTs, median age 10 y) quantified outcomes:

> *"Overall survival (OS) was 71% and event-free survival was 59% at two years... In eleven patients HSCT led to resolution of autoimmune features and discontinuation of immunosuppressive treatments... Patients with a severe autoimmune phenotype, defined as neurological and/or renal involvement, had the worst OS (40% vs 84%; p = 0.034)."* — PMID: 39470951

The Karolinska experience similarly demonstrated cure in refractory cases but also transplant-related mortality (PTLD, GVHD), underscoring that HSCT should be considered **early**, before severe organ damage (PMID: 26516671; PMID: 24035158).

Supportive / preventive. Prophylactic/therapeutic antibiotics and vaccination against encapsulated bacteria (pneumococcus, meningococcus, *H. influenzae* type b) address the infection-susceptibility arm.

Investigational / theoretical. Recombinant human C1q has been produced and is functional in vitro (PMID: 33621564), raising the prospect of **C1q protein-replacement therapy**, though no clinical replacement product is established. Gene therapy is conceptually attractive but not clinically available.

Suggested NCIT intervention terms: anifrolumab; allogeneic hematopoietic stem cell transplantation; corticosteroid therapy; rituximab; hydroxychloroquine; mycophenolate mofetil; cyclophosphamide.

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13. Prevention

- **Primary prevention:** none for the genetic lesion itself. **Genetic counseling** for consanguineous and carrier families; **carrier screening** and **prenatal/preimplantation genetic testing** are options once a familial variant is known.
- **Secondary prevention:** early recognition via the CH50-absent/normal-C3-C4 signature in any child with early-onset lupus and/or recurrent infection, enabling timely genetic confirmation and consideration of HSCT before severe organ damage.
- **Tertiary prevention:** vaccination against encapsulated bacteria; infection prophylaxis; vigilant monitoring/treatment of nephritis and CNS disease to prevent irreversible organ damage.
- **Counseling:** recessive recurrence risk (25% per pregnancy for carrier couples); cascade testing of relatives.

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14. Other Species / Natural Disease

- **Model-relevant taxonomy:** *Mus musculus* (NCBI Taxon:10090) is the principal experimental species. C1q genes are conserved across vertebrates, and the gC1q domain has an ancient evolutionary history conserved from bacteria to mammals (PMID: 24400480).
- **Orthologous genes:** murine *C1qa*, *C1qb*, *C1qc*.
- **Natural disease in other species:** no well-characterized spontaneous companion-animal/wildlife C1q-deficiency disease was identified in this investigation; the evidence base is dominated by engineered mouse models rather than naturally occurring animal disease. (OMIA/veterinary entries were not confirmed here.)
- **Zoonotic potential:** not applicable (non-infectious genetic disorder).

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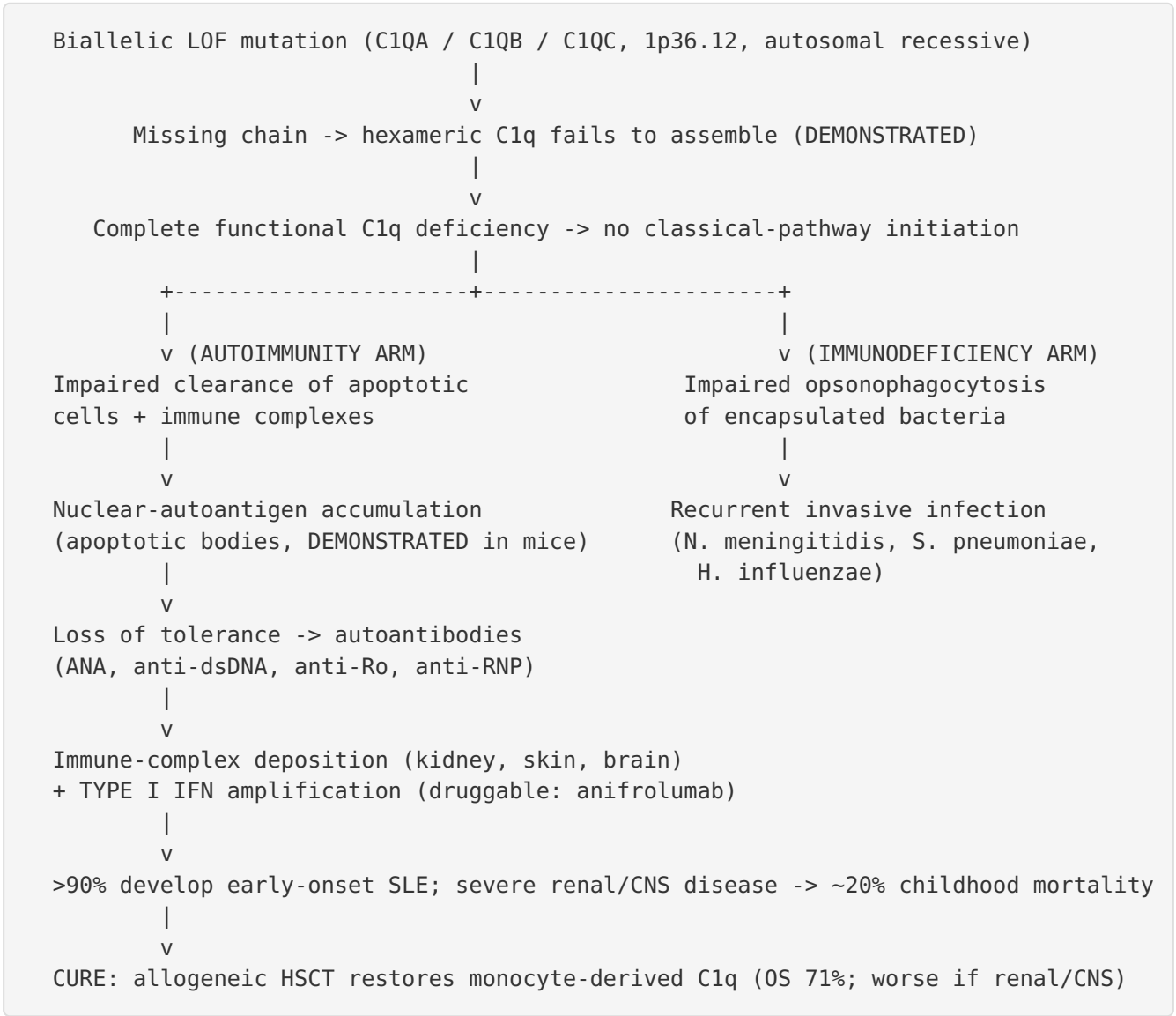
15. Model Organisms

- **Principal model:** the **gene-targeted C1q-knockout mouse** (C1qa-deficient), which recapitulates the central human mechanism:

> *"C1q-deficient mice, generated by gene targeting, showed an increased mortality and 25% of the mice had histological evidence of glomerulonephritis characterised by multiple apoptotic cell bodies and immune deposits... These observations are compatible with the hypothesis that C1q deficiency causes autoimmunity by an impaired clearance of apoptotic cells."* — PMID: 10072632

- **Phenotype recapitulation:** strong — high-titer antinuclear antibodies in ~50% of animals, immune-complex glomerulonephritis in ~25%, and accumulation of apoptotic bodies in diseased glomeruli, directly modeling the human "clearance-deficiency → autoimmunity" axis (PMID: 9777411).
- **Limitations:** murine lupus is background-dependent and does not fully reproduce the human severity spectrum, CNS calcification, or infection phenotype; penetrance is lower than in humans.
- **In vitro systems:** recombinant human C1q production in HEK293-F cells enables structure–function and potential replacement-therapy studies (PMID: 33621564); patient CD14+ monocyte cultures document the cellular C1q-production defect and its correction post-HSCT (PMID: 33000368; PMID: 26017655).

Mechanistic Model / Interpretation



Laboratory signature table (diagnostic discriminator):

Marker	Genetic C1q deficiency	Classic polygenic SLE
CH50	Absent / markedly low	Variable (often low in flare)
C3	**Normal**	Often low (consumed)
C4	**Normal**	Often low (consumed)
C1q antigen	**Absent**	Present (may be lowered by anti-C1q Ab)
Anti-C1q antibodies	N/A (no antigen)	Present; marks LN activity

The unifying concept is that C1q sits at the **apex of a clearance hierarchy**: the earlier in the classical pathway the deficiency, the more severe the lupus. C1q deficiency, being the most upstream, produces the most penetrant and severe disease (PMID: 10934224). Crucially, because the deficient protein is **hematopoietically produced (monocyte/macrophage)**, the disorder is uniquely curable by HSCT — a rare instance of a monogenic autoimmune disease with a definitive cellular cure.

Evidence Base

PMID	Role	Key contribution
10934224	Supports F001, F002, F009	Establishes C1q as apex of the classical-pathway severity hierarchy; links apoptotic clearance to SLE
10072632	Supports F002, F009	C1q-KO mouse: glomerulonephritis + apoptotic bodies → mechanistic proof
9777411	Supports mechanism	Reviews immune-complex/apoptosis hypothesis; murine ANA data
26119135	Supports F004, F009	Largest phenotype survey (45 pts): 80% SLE, 20% mortality
40556690	Supports F004	Case series: mucocutaneous/arthritis phenotype, normal C3/C4
42147803	Supports F006, diagnostics	C1QA nonsense variant; CH50-low/normal-C3-C4 diagnostic pattern; WES utility
40316395	Supports F001	Confirms AR inheritance & three causal genes; consanguineous siblings
25454803	Supports F006	Non-coding splice variant; chain-assembly dependence; AR segregation
40506420	Supports F006	Novel C1QB missense (c.263G>A), expands spectrum
26017655	Supports genetics/ diagnostics	C1q mRNA expression studies in juvenile SLE
39470951	Supports F003, F008	EBMT HSCT cohort: OS 71%; severe-phenotype OS 40% vs 84%; autoantibody-organ mapping
33000368	Supports F003	HSCT restores CD14+ C1q production, resolves SLE
26516671	Supports F003	Karolinska HSCT cures; documents transplant risks
24035158	Supports F003	Early report of HSCT cure
42597478	Supports F005	Anifrolumab efficacy → type I IFN as downstream target
33621564	Supports treatment outlook	Functional recombinant human C1q → replacement-therapy prospect

PMID	Role	Key contribution
28601358 / 29692784 / 24400480	Background	C1q structure (18 chains, gC1q head), multifunctionality, evolutionary conservation
19418946	Supports infection arm	Hypocomplementemia → encapsulated-bacterial infection risk
41546370 / 41895528	Supports F007 (adjacent)	Anti-C1q antibodies mark LN activity / predict thrombosis (polygenic SLE)
41929519	Differential/ adjacent	EBV mimicry induces pathogenic anti-C1q in lupus-prone mice
40852710 / 28687105	Differential dx	HUV and acquired C1-INH deficiency (distinguish from genetic C1q loss)

Limitations and Knowledge Gaps

1. **Small-N evidence base.** The disorder is ultra-rare; the largest datasets are a 45-patient survey and an 18-patient HSCT cohort. Prevalence/incidence are not formally established, and frequency estimates carry wide uncertainty.
2. **Anti-C1q antibody confound.** Much of the richest "C1q" literature concerns *acquired* anti-C1q autoantibodies in polygenic SLE/HUV — biologically distinct from genetic deficiency (antigen absent vs present). Care is needed to avoid conflating the two; this report flags the distinction explicitly (Finding F007).
3. **Modifier genetics and epigenetics** underlying the variable expressivity/penetrance (~9% asymptomatic) are essentially unknown.
4. **Quality-of-life and natural-history data** specific to C1q deficiency are sparse; no validated EQ-5D/SF-36 datasets were identified.
5. **No naturally occurring animal disease** was confirmed; comparative pathology rests on engineered mouse models with incomplete phenotype recapitulation.
6. **Replacement therapy** remains preclinical; recombinant C1q is functional in vitro but untested clinically.

7. **Causal statements** for the apoptotic-clearance mechanism are strongest in mice; the human causal chain from clearance failure to specific organ involvement is inferred from concordant (not interventional) human data.

Proposed Follow-up Experiments / Actions

1. **International registry & natural-history study** to firm up prevalence, penetrance, organ-involvement frequencies, and long-term survival with standardized phenotyping (and QoL instruments).
2. **Prospective HSCT-timing trial/registry** testing the hypothesis that transplanting *before* renal/CNS involvement improves OS beyond the current 71% — directly actionable given the 40% vs 84% split.
3. **Biomarker-guided risk stratification:** validate the autoantibody→organ map (anti-Ro→CNS; anti-RNP/anti-dsDNA→renal) prospectively to guide early intervention/transplant decisions.
4. **Recombinant C1q replacement therapy:** advance functional recombinant C1q (PMID: 33621564) toward pharmacokinetic/efficacy studies in C1q-KO mice, then first-in-human trials — a non-transplant option for patients ineligible for HSCT.
5. **Type I IFN pathway characterization:** systematically measure IFN signatures across the C1q-deficient cohort to define which patients benefit from anifrolumab, building on the index case (PMID: 42597478).
6. **Gene-therapy feasibility:** evaluate monocyte/HSC-directed gene addition or editing of C1QA/B/C as a less toxic alternative to allogeneic HSCT.
7. **Deep/whole-genome sequencing adoption** in diagnostic workflows to capture non-coding splice variants that panels/WES may miss (PMID: 25454803).

Evidence source legend: human clinical (case reports/series, cohorts, surveys), model organism (C1q-KO mouse), in vitro (recombinant C1q, patient monocyte cultures). This report synthesizes 9 confirmed findings across 32 reviewed papers.
