Genetic Predictors of Hypogammaglobulinemia after B-Cell–Targeted Therapy in Systemic Vasculitis and SLE: A Precision Medicine Approach

Amera Saadoun[1], Lisa Uchida[2,3], Alessandro Berghella[1], Luis Saraiva[1,4,5], David Jayne[2,3], Bernice Lo[1,5], Mohammed Yousuf Karim[5,6,7]

[1]Research Branch, Sidra Medicine, Doha, Qatar · [2]Dept. of Medicine, University of Cambridge, UK · [3]Vasculitis and Lupus Clinic, Cambridge University Hospitals NHS Foundation Trust, UK · [4]Dept. of Comparative Medicine, Yale University School of Medicine, USA · [5]College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar · [6]Pathology, Sidra Medicine, Doha, Qatar · [7]College of Medicine, Qatar University, Doha, Qatar

Background & Aims

B-cell targeted therapies (BCTT) such as rituximab may cause **hypogammaglobulinemia (HG)** requiring immunoglobulin replacement therapy (IgRT). **Systemic vasculitis (SV)** and **systemic lupus erythematosus (SLE)** patients are highly susceptible, due to underlying immune dysregulation and intensified immunosuppression. Identification of genetic predictors may help guide precision clinical management of BCTT and IgRT in future patients.

AIM

To discover novel genetic variants relevant to HG using whole-genome sequencing (WGS), supported where appropriate by detailed functional investigation.

Patients & Methods

- **Cohort:** Adult autoimmune-disease patients treated with BCTT — mainly SV and SLE – total cohort size >700 at Addenbrooke's Hospital, Cambridge
- **WGS subgroup:** 38 patients with HG receiving IgRT were sequenced at Sidra Medicine, Doha Qatar
- **Analysis platform:** WGS data for all 38 patients uploaded to ***seqr*** and screened against a curated panel of 510 genes linked to immunodeficiency and autoimmunity.
- **Rare-variant burden testing:** Gene-based burden analysis (REGENIE v4.1) of cases vs 90 "1000 Genomes–HGDP" controls, with an IUIS 2024 IEI-panel sub-analysis and carrier-level enrichment test.

Study Pipeline — From *Patient* to Genetic Insight

Whole-genome sequencing of hypogammaglobulinemic SV/SLE patients, curated against a targeted gene panel, **ACMG-classified**, and tested for **rare-variant burden & association** to identify host genetic risk factors for post-BCTT hypogammaglobulinemia.

01 · COHORT
Patients & Cohort
38 sequenced
Hypogammaglobulinemia after B-cell-targeted therapy in SV / SLE

02 · SEQUENCE
Whole-Genome Sequencing
WGS · seqr
Raw genomes uploaded & QC'd on the seqr analysis platform

03 · CURATE
Panel Screening & Filtering
510 genes → 184 entries
Variants filtered against curated immunodeficiency / autoimmunity panel

04 · CLASSIFY
ACMG / AMP Classification
ClinVar · Franklin
Five-tier calling: Pathogenic → VUS → Benign, with in-silico predictors

05 · TEST
Burden Testing & GWAS
REGENIE · 90 controls
Case–control rare-variant burden & genome-wide association

06 · TRANSLATE
Clinical Translation
Risk-informed screening before B-cell-targeted therapy begins

Every stage narrows **38 genomes** down to a short list of **candidate genetic risk markers** — turning sequencing data into a pre-therapy risk signal clinicians can act on.

Phenotype Linkage Highlights

Antibody Deficiency / CVID
TNFRSF13B
Best-established monogenic CVID gene; 2 carriers, 1 with bronchiectasis.

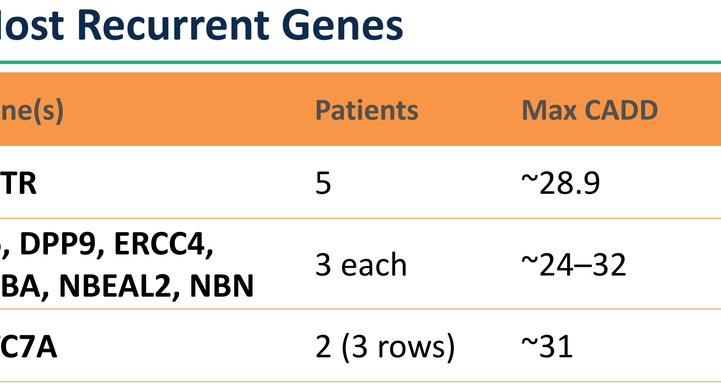
Infection / Immunodeficiency Terms
LRBA *DOCK8* *CR2* *C6* *C8B* *C8G*

DNA-Repair / Cancer-Predisposition
ERCC4 *NBN* *SMARCAL1* *BLM* *ATM*

Cohort & Variant Landscape

Across the 38-patient cohort, **138 unique genes** carried a recorded variant, reviewed as **184** variant–gene entries.

ACMG classification of the 184 entries



Genome-Wide Association Analysis (GWAS)

Case–control GWAS (PLINK2, Firth) — 38 cases vs 90 ancestry-matched 1000 Genomes–GBR controls; 106,337 QC-passed variants, λ = 1.128; no PCA substructure.

TOP SIGNAL — GENOME-WIDE SIGNIFICANT
chr21:· locus mapping to ICOSLG $p = 2.40\times10^{-8}$
94.7% of cases vs 13.3% of controls carry the risk allele. ICOSLG, a gene critical for Tfh-B-cell interactions and effective antibody responses.
⚠ Flagged by gnomAD as a low-coverage site — requires independent confirmation before biological interpretation.

Six additional loci reached suggestive significance ($p<1\times10^{-5}$); one cluster was excluded from primary reporting (see Limitations).

Most Recurrent Genes

Gene(s)	Patients	Max CADD
CFTR	5	~28.9
C6, DPP9, ERCC4, LRBA, NBEAL2, NBN	3 each	~24–32
TTC7A	2 (3 rows)	~31
ATM, BLM	2 each	—

Rare-Variant Burden Analysis

Gene-based rare-variant burden testing (**REGENIE v4.1**) compared the 38 cases against 90 population controls (1000 Genomes + HGDP) across the IUIS 2024 IEI gene panel (223 genes with qualifying variants), using loss-of-function and damaging-missense variant masks.

- **Genome-wide burden test:** no significant associations — expected given the small cohort (genomic inflation λ ≈ 0).
- **IEI panel (103 genes tested):** none survived Bonferroni correction ($p < 4.9\times10^{-4}$); lowest p ≈ 0.025.

PRIMARY RESULT — CARRIER ENRICHMENT

Cases were **~2.3× more likely** to carry ≥1 rare damaging IEI variant than controls.



OR = 2.32 (95% CI 1.00–5.45), Fisher p = 0.046 (uncorrected)

Top individual genes (case-only carriers): *BRCA2, DPP9, TMC6, RANBP2* (3 cases, 0 controls; p=0.025); *VPS13B* (4 cases, 1 control; OR=10.3, p=0.027).

Limitations & Future Work

- The burden analysis (n=38 cases) and pilot GWAS are both severely underpowered — a realistic signal typically needs ~500–1,000 cases; all results are **hypothesis-generating, not confirmatory**.
- Controls were population-based, not individually matched, and the GWAS shows modest residual inflation (λ=1.128). However, some extreme OR values suggest **near-perfect separation, possibly related to batch effects arising from the two different sequencing methods** — these findings are preliminary, not for clinical use.
- **Next steps:** replicate the chr21 GWAS signal in an independent, coverage-verified cohort; extend burden testing cohort-wide; and pursue functional validation of the 51.6% VUS burden.

Pathway-Based Gene Classification

Antibody-related · 5 genes
RAG2 *(P) · RAG1, TNFRSF13B (LP) · LRBA, PIK3R1 (VUS)*

Autoinflammatory · 5 genes
IFIH1, LPIN2, PSTPIP1, TNFAIP3, TREX1 (all VUS)

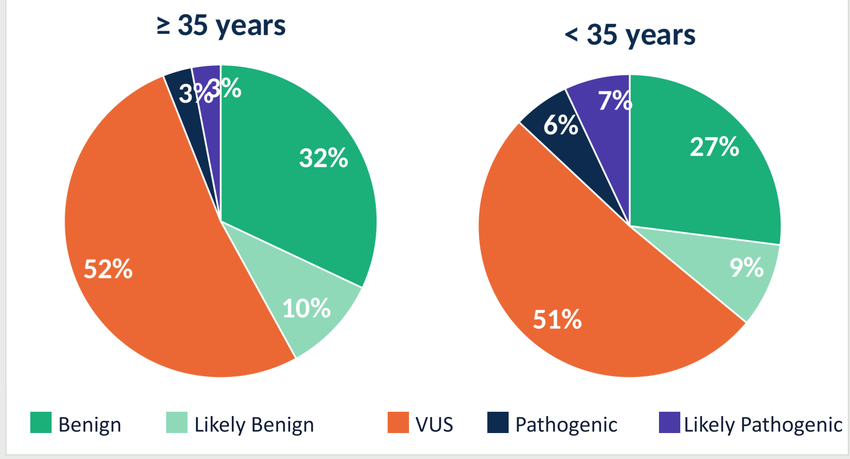
Complement · 6 genes
C6 (P) · C7 (LP) · C2, C3, C8A, C8B (VUS)

Antibody-related genes support B-cell development and class-switching; autoinflammatory genes regulate innate activation; complement genes aid pathogen clearance and immune-complex handling.

Age at Diagnosis & Variant Severity

17 of 38 patients (44.7%) were diagnosed before age 35. youngest: **2 patients at 14 years, 3 at 15 years**.

ACMG classification by age at diagnosis (descriptive)



Homozygous Variants

Gene	Location	Inheritance	ACMG
FANCB	chrX:14,883,140 C>G	X-linked	Likely Benign
CFP	chrX:47,486,217 C>T	X-linked	Benign
LNP1	chr3:100,170,600 (indel)	AR	VUS
METTL22	chr16:8,739,843 (indel)	Somatic	VUS
NFATC2	chr20:50,140,188 G>A	AD/AR	Likely Benign
FANCB	chrX:14,863,004 A>G	X-linked	VUS

Conclusions

- Host genetic factors — including immune-related and DNA-repair-related genes — may predispose to post-BCTT HG, while complement gene variants may relate to the underlying autoimmune disorder.
- The 510-gene IEI panel shows a high VUS burden (51.6%) across antibody and complement pathways.
- Recurrent findings in **CFTR, LRBA, TNFRSF13B** and DNA-repair genes suggest phenotype-relevant subgroups.
- A pilot GWAS identified a **genome-wide-significant locus on chromosome 21** ($p=2.4\times10^{-8}$) — a candidate signal in ICOSLG needing replication.
- Confirmation of putative genetic variants may lead to future implementation of a precision gene panel to assess HG risk and guide BCTT and IgRT.

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CONTACT

- Amera Saadoun, Translational Medicine, Research Department, Sidra Medicine, Doha, Qatar, ⌂ asadoun@sidra.org
- Dr. Mohammed Yousuf Karim, Division Chief – Hematopathology - Hematology, Immunology and Transfusion Div
- ⌂ mkarim@sidra.org

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Abbreviations: BCTT: B-cell targeted therapy · IgRT: immunoglobulin replacement therapy · SV: systemic vasculitis · SLE: systemic lupus erythematosus · WGS: whole-genome sequencing · GWAS: genome-wide association study · IEI: inborn errors of immunity · ACMG: American College of Medical Genetics & Genomics · VUS: variant of uncertain significance · CADD: Combined Annotation Dependent Depletion score · ICOSL: Inducible T-cell Costimulator Ligand