

WHIMS2 new homozygous variant

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Case Report

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Abstract

Background

WHIM syndrome type 2 (WHIMS2; OMIM #619407) is an ultra-rare autosomal recessive primary immunodeficiency caused by biallelic loss-of-function (LOF) variants in *CXCR2*. Fewer than twelve patients have been molecularly confirmed worldwide. G-CSF represents the only available standard therapy, but its mechanistic efficacy may be inherently limited by *CXCR2*-dependent neutrophil mobilisation pathways.

Case Presentation:

A 31-year-old Spanish woman with lifelong chronic moderate-to-severe neutropenia and recurrent bacterial infections underwent whole exome sequencing, identifying a novel homozygous nonsense variant in *CXCR2* exon 3 (c.550C > T, p.Arg184*; NM_001557.4; depth 126×; VAF 100%), classified Likely Pathogenic (ACMG/AMP 2015: PVS1/PM2/PP5; ClinVar VCV001372109). After five years of cumulative G-CSF exposure, the patient developed anaphylaxis to filgrastim confirmed by the Allergy service – the first documented case in WHIMS2. Bone marrow aspirate demonstrated preserved trilineage maturation without myelokathexis, extending the genotype-phenotype spectrum of complete *CXCR2* LOF. Absolute neutrophil count (ANC) nadirs showed consistent temporal correlation with menstrual onset, an unreported WHIMS2 feature.

Conclusions

This is the thirteenth molecularly confirmed WHIMS2 patient and the first with documented filgrastim anaphylaxis, eliminating standard therapy and creating the strongest published rationale for *CXCR4* antagonism as the only viable therapeutic option. The patient has been referred to the 4WARD phase 3 trial (NCT06056297) evaluating mavorixafor in chronic neutropenia including *CXCR2* deficiency.

Key Points

- We report the thirteenth molecularly confirmed WHIMS2 patient, bearing a novel homozygous nonsense variant p.(Arg184*) classified Likely Pathogenic (ACMG PVS1/PM2/PP5), causing complete receptor loss of function by TM4 truncation.
- Filgrastim anaphylaxis – the first documented in WHIMS2 – eliminates standard G-CSF therapy; combined with the *CXCR2*-dependence of G-CSF mobilisation, this creates compelling rationale for *CXCR4* antagonism (mavorixafor, off-label) as the only mechanistically sound therapeutic alternative.
- Bone marrow aspirate showed no myelokathexis despite predicted complete LOF, demonstrating this morphological feature is not obligatory in WHIMS2 and should not be required for diagnosis.
- Consistent ANC nadir at menstrual onset represents an unreported WHIMS2 clinical feature warranting prospective investigation.

1. Background

WHIM syndrome type 2 (WHIMS2; OMIM #619407) is a recently delineated autosomal recessive (AR) primary immunodeficiency caused by biallelic loss-of-function (LOF) variants in *CXCR2* (chromosome 2q35), the gene encoding C-X-C chemokine receptor 2 (interleukin-8 receptor B). *CXCR2* mediates neutrophil egress from bone marrow (BM) through activation by its CXCL8-subfamily ligands (CXCL1, CXCL2, CXCL8), acting in physiological opposition to the dominant *CXCR4*/*CXCL12* retention axis [1]. Biallelic LOF disrupts this balance, resulting in mature neutrophil accumulation in BM,

peripheral neutropenia, and susceptibility to bacterial infections without the warts, hypogammaglobulinemia, or lymphopenia that characterise WHIM syndrome type 1 (WHIMS1; *CXCR4* gain-of-function, autosomal dominant) [2].

Fewer than twelve patients have been molecularly confirmed across four published series (Auer 2014, Marin-Esteban 2022, Klimiankou 2024) [2–4], with variants including a frameshift (c.968delA), complete gene deletion, and missense substitutions (p.Arg212Trp, p.Arg144His, p.Lys240AsnfsTer45). No randomised controlled trial has been conducted in WHIMS2, and management is entirely extrapolated from WHIMS1 and severe congenital neutropenia (SCN) protocols, primarily using G-CSF. However, G-CSF-mediated neutrophil mobilisation depends mechanistically on CXCR2 signalling — a pathway abolished in CXCR2-deficient BM chimeric mice [5] — suggesting inherent therapeutic limitations beyond immunological intolerance.

2. Case Presentation

2.1 Patient history and clinical timeline

Written informed consent was obtained from the patient (Ethics approval CEIM HCUVA: not required; Declaration of Helsinki 2013). A 31-year-old Spanish woman was referred to the Haematology service of our tertiary academic centre for evaluation of chronic moderate-to-severe neutropenia. From childhood, she experienced recurrent bacterial tonsillitis requiring amygdalectomy and ongoing infections of the upper and lower respiratory tract, urinary tract, and soft tissues. Recombinant G-CSF (filgrastim; Zarzio® and Acofil®) was commenced at age 14 at three injections per week. After five years of cumulative exposure, anaphylaxis occurred (dyspnoea and haemodynamic compromise), confirmed by the Allergy service as a class-specific reaction to filgrastim. Glycosylated G-CSF (lenograstim; Granocyte®) has since been reserved exclusively for acute febrile episodes without recurrence of systemic hypersensitivity.

2.2 Clinical events 2024–2026

Serial complete blood counts showed ANC 470–2,410/μL, with nadirs consistently coinciding with menstrual onset — a cyclic pattern initially suggesting *ELANE*-related cyclic neutropenia, subsequently excluded by WES. Major events included: hospitalisation for *Staphylococcus aureus* bacteraemia (March 2026; positive blood culture March 17th; treated with intravenous levofloxacin), recurrent sinusitis, urinary tract infections (including one requiring parenteral antibiotics), and oral ulcerations during neutropenic nadirs. Menstruation-associated abundant bleeding with severe cramps was documented on Acofil® (November 2025).

2.3 Diagnostic workup

Immunoglobulins (IgG, IgA, IgM)	Normal at all time points. No hypogammaglobulinemia.
ANA / ANCA / anti-FcyRIIb	Negative on repeated testing.
Beta-2-microglobulin	1.54–1.72 mg/L (borderline-elevated, interpreted as reactive).
EPO	7 mU/mL. LDH: 126–174 U/L.
Thyroid / parathyroid / sex hormones	Normal.
Lymphocyte subsets	Within reference range. No persistent lymphopenia.
Peripheral blood film	Activated lymphocytes and monocytes. Anisopoikilocytosis. No blasts. No dysplastic features.
Rheumatology (Sept 2025)	Anti-vasculitis workup (ANCA, ANA, complement): negative.
HR chest CT (May 2025)	Normal. No bronchiectasis or air trapping.
BM aspirate (Feb 2025)	Hypo-normocellular. Trilineage maturation preserved. No blasts. No dysplasia. No myelokathexis morphology.

3. Genetic Findings

Whole exome sequencing (WES; Illumina NextSeq 1000; Twist Human Comprehensive Exome panel, 21,093 genes; reference genome GRCh38/hg38; mean depth 51×; >98.4% target regions at ≥ 20×; bioinformatic pipeline: Sophia DDM; variant annotation: gnomAD v4.1, ClinVar, HGMD 2019.3, Franklin by Genox) identified the following variant:

Primary finding – CXCR2

Variant (HGVS)	c.550C > T, p.(Arg184*) [NM_001557.4]
Type	Nonsense (premature stop codon)
Zygosity	Homozygous
Chromosome / Exon	2q35 / Exon 3
Read depth / VAF	126 reads / 100%
gnomAD v4.1	9 / 1,614,178 alleles (AF = 5.57×10 ⁻⁶)
ClinVar	VCV001372109 (associated with congenital neutropenia)
ACMG/AMP 2015	Likely Pathogenic (PVS1: null variant in LOF-disease gene; PM2: extremely low population frequency; PP5: ClinVar association)
OMIM phenotype	WHIM Syndrome Type 2 (#619407)
Inheritance	Autosomal recessive
Secondary findings (84 ACMG genes)	None identified
Parental segregation	Pending – extraction scheduled

The p.(Arg184*) premature termination codon lies within the predicted fourth transmembrane domain (TM4) of the 360-amino acid CXCR2 receptor (7-transmembrane GPCR). Truncation at this position eliminates TM5, TM6, TM7, the third extracellular loop (ECL3), and the entire C-terminal intracellular tail – domains critical for Gai protein coupling, β-arrestin 1/2 recruitment, GRK2/GRK3-mediated phosphorylation, receptor internalisation, and ERK1/2 / PI3K/AKT downstream signalling.

This constitutes complete receptor LOF by either nonsense-mediated mRNA decay (NMD) or production of a non-functional truncated receptor, analogous in predicted severity to the c.968delA frameshift (Auer et al. [3]).

Table 1
Molecular and clinical comparison of published WHIMS2 cases

Case	Variant	Zyg.	LOF	ANC nadir	Myelokathexis	Warts	Hypogamma	G-CSF
Auer 2014 [3] (n = 2)	c.968delA	Hom	Complete	< 500/ μL	Present	NR	NR	Partial
Marin-Esteban 2022 [2] P1	del CXCR2	Hom	Complete	< 100/ μL	Present	Absent	Absent	Variable
Marin-Esteban 2022 [2] P2-4	p.Arg212Trp	Hom	Partial	~ 500/ μL	Absent	Absent	Absent	Variable
Klimiankou 2024 [4] (3 fam.)	p.Arg144His	Hom/ch	Partial	200–800/ μL	Absent	Absent	Absent	NR
This case	p.(Arg184*)	Hom	Complete	470/ μL	Absent ☒	Absent	Absent	Anaphylaxis ☒

Hom: homozygous; ch: compound heterozygous; LOF: loss of function; NR: not reported; fam: families; ANC: absolute neutrophil count; Hypogamma: hypogammaglobulinemia.

4. Discussion

4.1 Absent myelokathexis despite complete LOF

Prior complete-LOF WHIMS2 variants — frameshift c.968delA [3] and complete gene deletion [2] — exhibited myelokathexis. Our case demonstrates this morphological feature is neither obligatory nor diagnostically required even with predicted null variants. Sampling timing during acute febrile neutropenia, prior G-CSF exposure modifying BM architecture, and potential inter-individual variability in neutrophil retention kinetics may all contribute. BM trephine biopsy with cytogenetics and somatic myeloid panel sequencing is planned prior to 4WARD trial enrolment, and findings will be reported. Clinically, this observation reinforces that WHIMS2 diagnosis should not require myelokathexis — a point with immediate impact given that its absence may delay or preclude correct diagnosis.

4.2 Menstrual cycle–ANC correlation

The consistent temporal correlation between ANC nadir and menstrual onset — which initially directed investigation toward ELANE-related cyclic neutropenia — has not been described previously in WHIMS2. Sex hormone-mediated modulation of CXCR2 expression or downstream neutrophil trafficking represents a plausible but untested mechanism. Progesterone has been shown to modulate CXCL8 signalling in reproductive tissues, and oestrogen fluctuations are associated with systemic inflammatory changes; whether either directly affects CXCR2-dependent neutrophil egress in CXCR2-deficient patients remains unknown. Prospective ANC-menstrual cycle tracking in other WHIMS2 patients may clarify whether this represents a genuine WHIMS2 feature or an incidental finding.

4.3 G-CSF anaphylaxis and the mechanistic case for CXCR4 antagonism

Filgrastim anaphylaxis in WHIMS2 has no prior published precedent. Its occurrence after five years of cumulative exposure is consistent with IgE-mediated sensitisation through repeated dosing, though the immunological mechanism was not further characterised in this case. Beyond the immunological barrier, G-CSF-mediated neutrophil mobilisation depends critically on CXCR2 signalling: G-CSF triggers thrombopoietin release, inducing CXCR2 ligand (CXCL1, CXCL2) upregulation in BM stroma, which drives neutrophil egress [5]. This pathway is abolished in CXCR2-deficient mice, and significantly impaired in *Cxcr2*^{-/-} BM chimeras — suggesting that even without anaphylaxis, G-CSF has intrinsically limited efficacy in complete CXCR2 LOF.

Mavoxifafor (Xolremdi®; X4 Pharmaceuticals), an orally bioavailable selective CXCR4 antagonist, circumvents CXCR2 dependence entirely by blocking the dominant CXCR4/CXCL12 retention pathway — which remains fully functional in WHIMS2. FDA approval was granted for WHIMS1 in April 2024 following the 4WHIM phase 3 RCT (n = 31; significant improvements in time above threshold ANC [TATANC] and lymphocyte count [TATALC] vs. placebo; *P* < 0.0001) [6]; EMA issued a positive opinion in February 2026. In WHIMS2, mavoxifafor remains off-label. Nguyen et al. recently provided the first dedicated preclinical evidence: chronic oral CXCR4 antagonism in a pharmacological CXCR2 LOF murine model normalised peripheral ANC, reversed BM mature neutrophil accumulation and M/E ratio, reduced myelokathexis-like frequency from 43% to 17% of BM neutrophils, and significantly improved survival following *Streptococcus pneumoniae* challenge [7]. These data must be interpreted with caution: the study was fully funded by mavoxifafor's manufacturer (7/9 authors are X4 Pharmaceuticals employees or shareholders), compound 1 is a surrogate CXCR4 antagonist (not mavoxifafor), the model uses pharmacological (not germline) CXCR2 LOF with residual CXCR2 function, and an unresolved discrepancy exists with earlier data demonstrating failure of plerixafor (AMD3100) to mobilise *Cxcr2*^{-/-} BM chimera neutrophils — potentially attributable to pharmacokinetic differences (T_{1/2} compound 1: 6.1h vs. AMD3100: 0.9h) and chronicity of CXCR4 antagonism [1, 7].

4.4 4WARD trial and clinical pathway

The patient has been referred for enrolment in the 4WARD phase 3 randomised, double-blind, placebo-controlled trial (NCT06056297; mavoxifafor ± background G-CSF vs. placebo; n = 176; co-primary endpoints: annual infection rate and ANC response), which includes CXCR2 deficiency among eligible diagnoses. Hospital Universitario Fundación Jiménez Díaz (Madrid; PI: Dr. Nuria Revilla) is the designated enrolment centre. Pre-trial protocol includes BM trephine biopsy, cytogenetics, and somatic myeloid panel sequencing.

5. Conclusions

We describe the thirteenth molecularly confirmed WHIMS2 patient, bearing a novel likely pathogenic homozygous nonsense CXCR2 variant p.(Arg184*), and the first with documented filgrastim anaphylaxis. Four novel observations emerge: complete CXCR2 LOF without myelokathexis; ANC–menstrual cycle correlation; dual mechanical and immunological barrier to G-CSF therapy; and the strongest clinical rationale to date for urgent CXCR4 antagonist access in WHIMS2. Registration in international disease registries (FSCNR, SCNIR, ESID, ERN-EuroBloodNet) is strongly recommended for all WHIMS2 patients, and enrolment in the 4WARD trial should be offered to every eligible patient.

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki (2013 revision). Institutional Review Board approval not required. Written informed consent was obtained from the patient prior to all procedures.

Consent for publication: Written informed consent for publication of identifying information and clinical/genetic data was obtained from the patient. A signed copy is held at the Haematology Service, HCUVA.

Competing interests: The authors declare no competing financial or non-financial interests.

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Data availability: All deidentified clinical data supporting this report are available from the corresponding author upon reasonable request. Genetic data are available in ClinVar (accession VCV001372109).

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