Biallelic *CXCR2* loss-of-function mutations define a distinct congenital neutropenia entity

Neutrophil homeostasis results from a balance between neutrophil production, release from the bone marrow and clearance from the circulation, where chemokines and their receptors play central roles.[1,2] Studies on mice demonstrated that CXCR4 and CXCR2 receptors antagonistically regulate bone marrow neutrophil release.[2] While CXCR4 and its chemokine CXCL12, which is constitutively expressed in the bone marrow, provide key signals for neutrophil retention, CXCR2 activation by the CXCL8 subfamily of chemokines promotes their release from the bone marrow.[1,2] Those events were shown in patients carrying heterozygous *CXCR4* gain-of-function mutations causing the rare autosomal dominant WHIM syndrome, characterized by human papillomavirus-induced warts, hypogammaglobulinemia, recurrent bacterial infections and myelokathexis reflecting an accumulation of senescent neutrophils in the bone marrow.[3] Profound neutropenia associated with myelokathexis was previously reported in two siblings carrying a homozygous truncating *CXCR2* loss-of-function mutation, supporting the importance of CXCR2 signaling in neutrophil mobilization.[4] Myelokathexis and recurrent severe infections[5] in that single pedigree led to it being included in the large series of WHIM syndrome and WHIM syndrome-like cases,[6] and it remains the only published example of CXCR2 deficiency.

Herein, we report biallelic *CXCR2* mutations, including one complete gene deletion, in four patients with chronic neutropenia, harboring a wild-type (WT) *CXCR4* gene.

Patients were diagnosed during childhood with profound neutropenia in the context of recurrent gingivitis and oral ulcerations (Table 1). Bone marrow smears showed no major granulocytic maturation defect. Myelokathexis was present in only patient 1 (P1) and affected 35% of myeloid cells. Values of the other hema-

Table 1. Clinical profile of the four patients with biallelic *CXCR2* loss-of-function mutations.

Characteristic	Patient (Registry ID)				
	P1 (8364)	P2 (6487)	P3 (6902)	P4 (8497)	Reference range
Clinical profile					
Age at diagnosis (years)	2.9	1.9	1.8	1.2	
Oral lesions	Yes	Yes	Yes	Yes	
Severe infections[a] (age)	No	1 cellulitis (13 months)	1 pneumonitis (22 months)	No	
Prophylactic treatment	No	Cotrimoxazole	Cotrimoxazole	No	
G-CSF therapy (dose, period)	Yes (2 μg/kg, 2 years)	No	Yes (5 μg/kg, 1 month)	No	
Age at last follow-up (years)	36	22.5	10	6.5	
Hematologic values at diagnosis					
Neutrophils (x10⁹/L)	**0.56**	**0.6**	**0.18**	**0.6**	1.5-8.0
Monocytes (x10⁹/L)	0.31	0.46	0.52	0.46	0.1-1.0
Lymphocytes (x10⁹/L)	2.0	6.3	6.2	4.6	1.5-6.5
Hemoglobin level (g/dL)	12.4	12.2	11.8	10	11.5-15.5
Platelets (x10⁹/L)	359	371	368	225	150-400
Hematologic values during follow-up					
Blood counts (n)	18	24	23	7	
Neutrophils (x10⁹/L)	**0.57** (0.28-1.8)	**0.45** (0.1-0.85)	**0.54** (0.1-10.8[b])	**0.35** (0.3-1)	1.5-8.0
Monocytes (x10⁹/L)	0.29 (0.02-0.51)	0.43 (0.16-0.68)	0.53 (0.19-1.3)	0.52 (0.39-0.7)	0.1-1.0
Lymphocytes (x10⁹/L)	1.66 (1-2.7)	2.03 (1-6.3)	4.0 (0.97-10.8)	4.58 (1.9-4.8)	1.5-6.5
Hemoglobin (g/dL)	12.6 (11.5 -13.3)	11.5 (9.9-13.2)	12.2 (10.4-13.1)	10.7 (9.6-12.7)	11.5-15.5
Platelets (x10⁹/L)	357 (257-439)	277 (215-572)	324 (167-544)	523 (225-670)	150-400
Differential bone-marrow count					
Myeloblasts	4%	0%	1%	2%	0.3-4%
Promyelocytes & myelocytes	15%	5%	13%	2%	12-25%
Metamyelocytes & mature neutrophils	43%	29%	38%	37%	33-48%
Myelokathexis	35%	0%	0%	0%	
Immunoglobulin levels (g/L)					
IgG	*15.1* (*14.2-20.5*)	*16.7* (*14.3-17.3*)	10.9 (*10.2-11.8*)	*14.8*	5.98-11.1
IgM	0.91 (0.81-1.12)	*1.77* (1.51-2.0)	*2.41* (*2.12-2.53*)	*1.63*	0.56-1.59
IgA	*2.98* (*1.73-3.06*)	*3.75* (*3.14-3.96*)	*1.75* (*1.69-2.56*)	*3.35*	0.49-1.53
Lymphocyte subsets					
Subset determinations (n)	5	10	3	1[c]	
CD3⁺CD4⁺ T cells (x10⁹/L)	0.544 (0.333-0.700)	0.677 (0.611-0.853)	0.920 (0.766-1.075)	**1.456**	0.53-1.3
CD3⁺CD8⁺ T cells (x10⁹/L)	**0.288** (0.170-0.429)	0.501 (0.432-0.629)	0.611 (0.498-0.725)	**1.295**	0.33-0.92
CD19⁺ B cells (x10⁹/L)	0.157 (0.121-0.177)	0.295 (0.240-0.365)	0.468 (0.344-0.591)	*0.769*	0.11-0.57
CD3⁻CD16⁺CD56⁺ NK cells (x10⁹/L)	0.088 (0.078-0.129)	0.171 (0.134-0.209	0.153 (0.134-0.172)	*0.778*	0.07-0.48

Results are expressed as medians (range), unless stated otherwise. Bold type indicates lower values and bold italics indicate higher values compared to the reference range. [a]Intravenous antibiotic-treated infections. [b]At the time of a fever of unknown origin (likely viral), the absolute neutrophil count increased spontaneously. [c]Evaluated at age of 4 years. G-CSF: granulocyte colony-stimulating factor; NK natural killer.

tologic lineages, including lymphocyte subsets, were within their normal ranges. These four patients had high levels of circulating IgG and/or IgA at diagnosis which persisted throughout follow-up.

We investigated a possible genetic etiology using targeted sequencing of genes known to be involved in inherited neutropenia and exome-sequencing. We excluded *CXCR4* mutations and identified a homozygous *CXCR2*-gene deletion in P1, homozygous *CXCR2* missense mutations in P2 and P3, and compound heterozygous *CXCR2* mutations in P4 (Figure 1A, *Online Supplementary Figure S1A, B*). The *CXCR2* deletion was further confirmed by single nucleotide polymorphism-array analysis (*data not shown*) that revealed a homozygous 13.4-kb deletion in 2q35

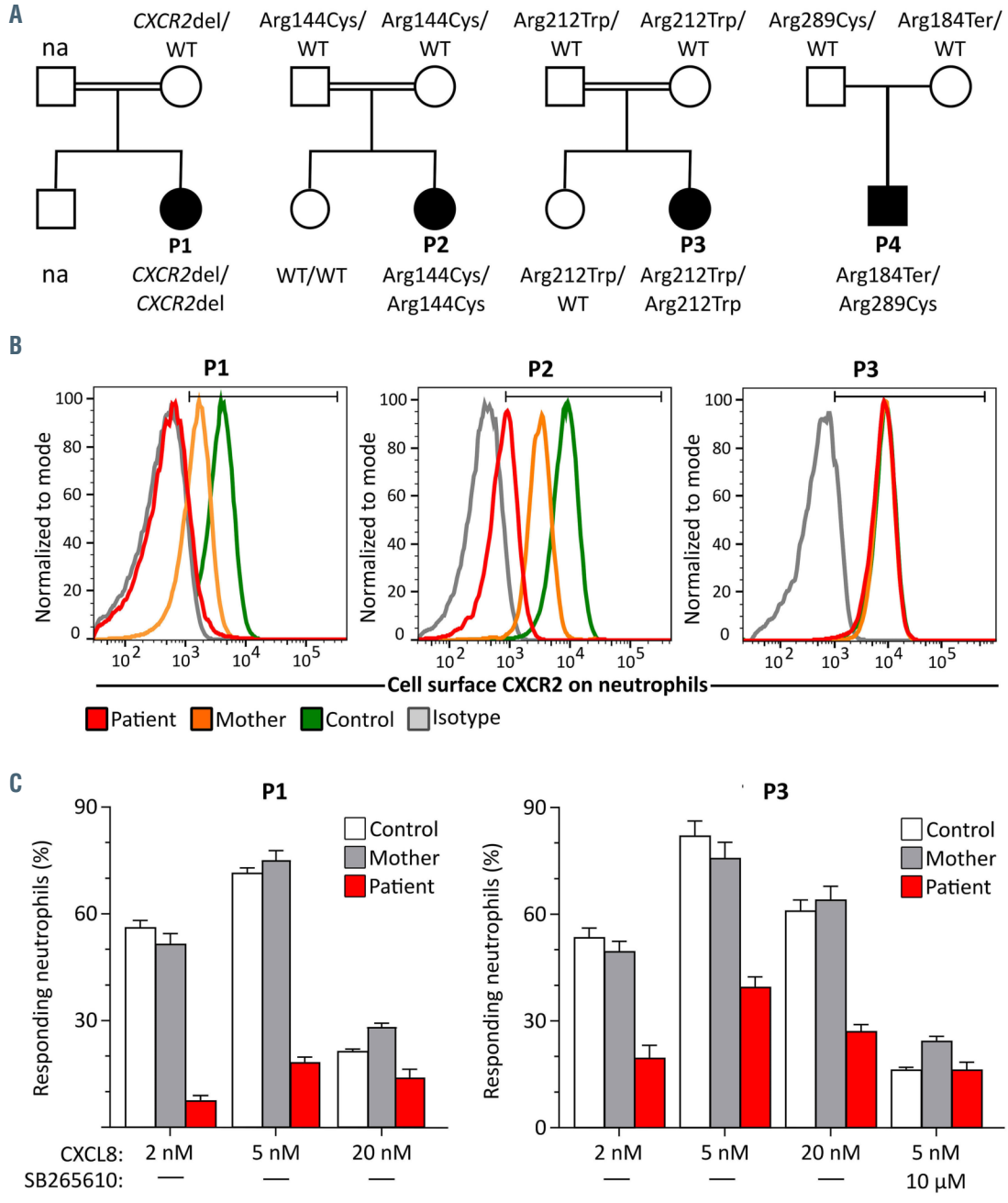

Figure 1. Characterization of germline biallelic *CXCR2* mutations identified in four patients with chronic neutropenia. (A) Family pedigrees with identified homozygous (patients P1, P2, and P3) or compound heterozygous (P4) *CXCR2* mutations. Healthy parents were heterozygous carriers for the identified mutations. (B) Cell-surface CXCR2 immunostaining on neutrophils from P1, P2, and P3, one heterozygous carrier, and healthy donors. (C) Dose-dependent CXCL8-induced chemotaxis of neutrophils without or with SB265610 (SB), its specific CXCR2 inhibitor. Chemotaxis assays were run in duplicate, with whole blood samples (diluted 1:4 in RPMI with 1% human serum) using 12 mm diameter transwell devises with 5 µm pores. For each assay including patient, parent and control, blood samples were collected concomitantly and treated equally. Samples were added in the upper chamber, CXCL8 in the lower chamber and SB in both chambers. Control wells without chambers were also added to determine the number and phenotype of total seeded cells. After incubation for 1 hour, cells recovered in the lower chambers (responding cells) were counted and identified by flow cytometry. Results are expressed as percentage of responding neutrophils, calculated as [(Number of neutrophils recovered in the lower chamber with CXCL8) - (Number of neutrophils recovered in the lower chamber without CXCL8)] / (Number of total seeded neutrophils) x 100. WT: wild-type; na: not available.

Table 2. **Comparison of the clinical characteristics of 14 patients with *CXCR4* gain-of-function mutations and four patients with *CXCR2* loss-of-function mutations enrolled in the French Severe Congenital Neutropenia Registry.**

Characteristic	Patients with *CXCR4* mutations	Patients with *CXCR2* mutations	Relevant differences
Number of patients	14	4	
Age at diagnosis (years)	4.9 (0.1-33)	1.8 (1.2-2.9)	
Age at last visit (years)	31.9 (8.9-77)	16.3 (7.2-36.5)	
Oral lesions	3/14	4/4	
Severe infections	10/14	2/4	
Warts	8/14	0/4	
Hematologic values (all available CBC)			
Neutrophils (x10^9/L)	**0.221** (0.13-1.4)	**0.496** (0.18-0.57)	
Monocytes (x10^9/L)	0.156 (0.06-0.44)	0.477 (0.29-0.54)	**
Lymphocytes (x10^9/L)	**0.577** (0.16-1.9)	3.2 (1.6-4.5)	**
Hemoglobin (g/dL)	12.1 (8.6-13.8)	11.8 (10.7-12.6)	
Platelets (x10^9/L)	220 (169-479)	338 (277-523)	*
Myelokathexis	14/14	1/4	*
Bone-marrow myeloid/erythroid ratio	3.5	3	
G-CSF treatment	3/14, poor responses	2/4, good responses	
Immunoglobulin levels (g/L)			
IgG	*8 (4.2-15)*	***16.2** (10.2-20.5)*	**
IgM	*0.64 (0.24-1.7)*	***1.63** (0.81-2.53)*	**
IgA	*0.86 (0.1-2.5)*	***3.33** (1.69-3.96)*	**
Lymphocyte subsets			
CD3$^+$CD4$^+$ T cells (x10^9/L)	**0.37** (0.17-0.51)	0.80 (0.54-1.46)	**
CD3$^+$CD8$^+$ T cells (x10^9/L)	**0.09** (0.04-0.10)	0.50 (0.29-1.29)	**
CD19$^+$ B cells (x10^9/L)	**0.02** (0.01-0.05)	0.38 (0.12-0.77)	**
CD3$^-$CD16$^+$CD56$^+$ NK cells (x10^9/L)	0.12 (0.06-0.16)	0.15 (0.08-0.78)	**
Solid tumors	8/14	0/4	
Tetralogy of Fallot	5/14	0/4	
Deaths	3[a]	0/4	

Results are expressed as medians (range), unless stated otherwise. Bold type indicates lower values and bold italics indicate higher values compared to the reference range. [a]Two deaths occurred between 30 and 40 years of age from vulvar cancer or atypical mycobacteria with liver failure, and one 77-year-old died of pneumonitis. Owing to the very low number of patients to be compared, the most relevant differences are indicated as *P<0.01 or **P<0.001. CBC: complete blood count; G-CSF: granulocyte colony-stimulating factor; NK: natural killer.

(218,988,774_219,002,220) encompassing only *CXCR2*. To exclude other causal variants in P2, P3 and P4, who harbor missense *CXCR2* mutations, DNA from the probands and their parents were subjected to whole-exome sequencing. The mean depth of exome coverage was 74X with 96% covered at least 20X. The *CXCR2* mutations were confirmed and no other potentially causative candidate variants were identified. The homozygous *CXCR2* genotypes of P1, P2, and P3 were consistent with the reported consanguinity of these pedigrees. Parents were heterozygous carriers and their blood-cell counts were within normal ranges. The three *CXCR2* missense mutations (p.Arg144Cys, p.Arg212Trp and p.Arg289Cys) had been entered into the Genome Aggregation Database (gnomAD) with an allele frequency <5x10^{-5} but never as being homozygous. The mutation in P2 affects Arg144 which constitutes the critical DRY motif for G-protein activation.[7] The mutations affect Arg184 in P3, which is highly conserved between CXCR2 and CXCR1, and Arg212 and Arg289 in P4, which belong to domains cooperating with the CXCR2 N-terminal for the efficient docking of the CXCL8-chemokine ligand (*Online Supplementary Figure S1C*).[8]

We then examined cell-surface CXCR2 expression in neutrophils (Figure 1B), monocytes (*Online Supplementary Figure S2A*) and natural killer cells (*data not shown*) from P1, P2 and P3, their parents, and healthy control blood donors. As expected, CXCR2 was not expressed in the different cell populations derived from patient P1, who has a homozygous *CXCR2*-gene deletion. Her mother, who carries a heterozygous *CXCR2* deletion, had intermediate CXCR2 expression between P1 and control values. That mutant-dosage effect was also observed in carriers of *CXCR2* missense mutations, e.g., all pedigree-P2 blood cell populations noted above and pedigree-P3 monocytes (Figure 1B, *Online Supplementary Figure S2A*). Whether the underlying mechanisms implicate altered turnover of the Arg144Cys mutant and, in a more cell-restricted fashion, of the Arg212Trp mutant, remains to be investigated. As expected based on the patients' WT *CXCR4* genotypes, cell-surface CXCR4 expression was within the normal range for all tested blood cell populations as illustrated for P1 and P3 (*Online Supplementary Figure S2B*).

We evaluated the potential impact of *CXCR2* mutations on the CXCL8-driven chemotactic response of blood neutrophils derived from P1 and P3 pedigrees (Figure 1C). In transwell migration assays, healthy donors' neutrophils responded to CXCL8, yielding a typical bell-shaped, dose-dependent, chemotaxis-response curve. Blockade with the specific CXCR2 inhibitor SB265610 confirmed the involvement of CXCR2 in the observed chemotaxis. Neutrophils from parents migrated similarly to controls despite lower cell-surface CXCR2 expression, supporting the reported dissociation between the expression level of chemokines-receptors and their

functions.[9] In contrast, efficacy of the CXCL8-induced chemotaxis for P1-derived neutrophils was drastically reduced (up to 86%) for all tested CXCL8 concentrations. For P3-derived neutrophils, this response was more weakly lowered (up to 59%) indicating that the Arg212Trp CXCR2 mutation only partially abrogates CXCR2 function. This was further confirmed by the SB265610-mediated inhibition of the remaining Arg212Trp CXCR2-driven chemotaxis (Figure 1C). P3-derived neutrophils expressed similar levels of CXCR2 than control neutrophils (Figure 1B) and their remaining chemotactic responses toward CXCL8 were out of the range of the ones provided by control neutrophils (*Online Supplementary Figure S3A*), further supporting the *CXCR2* loss-of-function phenotype. We extrapolated that this loss-of-function phenotype would be similarly conferred by P2's and P4's *CXCR2* missense mutations, affecting the protein's critical DRY domain[7] or N-terminal domain,[8] respectively. CXCR1 could account for the remaining migration of P1's neutrophils, which were not affected by the inhibitor SB265610.[10] Indeed, although CXCR1 and CXCR2 have closely linked actions, they differ notably in their signaling properties and chemokine-ligand spectra, with CXCR1 being engaged by CXCL5 and CXCL6 and having high affinity for CXCL8, while CXCR2 promiscuously binds to all seven CXCL8-family chemokines.[11] CXCR1 expression levels on P1 and control neutrophils were within the same range (*Online Supplementary Figure S3B*), thereby substantiating that hypothesis.

The patients described herein did not experience severe recurrent bacterial infections, suggesting that although CXCR2 actively participated in neutrophil recruitment into inflammatory tissues, this function was largely counterbalanced. Indeed, patients' neutrophils remained responsive to *N*-formylmethionine-leucyl-phenylalanine (fMLP) (*Online Supplementary Figure S3C*), indicating that they might be efficiently guided to inflammatory sites by chemoattractant signals, such as fMLP and possibly others including the C5a complement factor, both abundantly generated in foci of bacterial infection.[12] Likewise, CXCL12-driven migration was equivalent for $CD3^+CD4^+$ cells (*Online Supplementary Figure S3D*) and the other lymphocyte subpopulations (*data not shown*) from P1 and P3, their parents and controls. These findings support the postulate of normal CXCR4 function in patients harboring *CXCR2* mutations acting as drivers of congenital neutropenias although it remains to be experimentally demonstrated.

Different clinical manifestations distinguish these four patients with *CXCR2* mutations from the clinical spectrum of the 14 WHIM syndrome cases enrolled in the French Severe Chronic Neutropenia Registry, as summarized in Table 2. Myelokathexis, a pathognomonic feature of WHIM syndrome,[6] was solely detected in P1, harboring the *CXCR2* gene deletion, thereby extending the description of the two previously reported cases with *CXCR2* loss-of-function mutations.[5] Its absence in the clinical pictures of P2, P3 and P4, together with the partial CXCR2-chemotaxis response retained by Arg212Trp, further suggests that their chronic neutropenia is not the only consequence of a CXCR2-dependent mobilization defect; neutrophil homeostasis also seems to be affected. That hypothesis is supported by the reported association of rare heterozygous *CXCR2* missense variants, including the one carried by P4, with low white blood-cell counts.[4]

Elucidating the mechanisms underlying the relationship between the biallelic *CXCR2* mutations identified herein and neutropenia will require the development of relevant experimental models. Alternative models to mice should be considered, in light of the lack of a murine CXCL8 homologue and the neutrophilia of mice lacking *Cxcr2*.[13,14] However, targeted *Cxcr2* invalidation in mouse neutrophils led to their retention in bone marrow, reproducing a myelokathexis phenotype,[4] thereby suggesting a role for Cxcr2 in the regulation of neutrophil biology and, intrinsically, in neutrophil trafficking. In contrast to patients with WHIM syndrome, who suffer from chronic lymphopenia, often associated with hypogammaglobulinemia,[6,15] patients with *CXCR2* mutations experienced only transient episodes of lymphopenia and had elevated levels of immunoglobulins, mostly IgG and IgA (Table 2). B-lymphocyte counts were normal, unlike those in mice with invalidated *Cxcr2*, which exhibited B-cell expansion,[13] highlighting the limitation of mice to model CXCR2 deficiency. No papilloma virus-induced warts, neoplasia or syndromic features, such as tetralogy of Fallot, observed in WHIM syndrome[15] were noted during the follow-up of the patients. However, we could not exclude incomplete penetrance of these phenotypes, as reported in WHIM syndrome.[6,15]

In conclusion, CXCR2 deficiency seems to be a distinct molecular entity associated with congenital neutropenia with clinical severity and pathogenic mechanisms distinct from those of WHIM syndrome, thereby highlighting the importance of determining *CXCR2* mutational status in patients with chronic neutropenia.

Viviana Marin-Esteban,[1] Jenny Youn,[2] Blandine Beaupain,[3,4] Agnieszka Jaracz-Ros,[1] Vincent Barlogis,[5] Odile Fenneteau,[6] Thierry Leblanc,[7] Florence Bellanger,[8] Philippe Pellet,[8] Julien Buratti,[8] Hélène Lapillonne,[9] Françoise Bachelerie,[1] Jean Donadieu[2,3,4] and Christine Bellanné-Chantelot[4,8,10]

[1]Université Paris-Saclay, Inserm UMR996, Inflammation, Microbiome and Immunosurveillance, Clamart; [2]Sorbonne Université, Service d'Hémato-oncologie Pédiatrique, Assistance Publique–Hopitaux de Paris (AP-HP), Hôpital Trousseau, Paris; [3]Registre Français des Neutropénies Congénitales, Hôpital Trousseau, Paris; [4]Centre de Référence des Neutropénies Chroniques, AP-HP, Hôpital Trousseau, Paris; [5]CHU Marseille, Hôpital La Timone, Service d'Hémato-oncologie Pédiatrique, Assistance Publique–Hôpitaux de Marseille, Marseille; [6]AP-HP, Laboratoire d'Hématologie, Hôpital Robert-Debré, Paris; [7]AP-HP, Hôpital Robert-Debré, Service d'Hématologie Pédiatrique, Paris; [8]Sorbonne Université, Département de Génétique Médicale, AP-HP, Hôpital Pitié–Salpêtrière, Paris; [9]Sorbonne Université, CRSA–Unité INSERM, AP-HP, Hôpital Trousseau, Paris and [10]Inserm U1287, Villejuif, France

Correspondence:
CHRISTINE BELLANNÉ-CHANTELOT
christine.bellanne-chantelot@aphp.fr

VIVIANA MARIN-ESTEBAN
viviana.marin-esteban@universite-paris-saclay.fr

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Contributions: VM-E, FB, JD and CB-C designed the study. VM-E collected and interpreted functional data. JY analyzed clinical data. BB collected biological and clinical data. AJ-R performed chemotaxis assays. VB and TL provided samples and clinical data. OF performed and reviewed bone marrow examinations. FB and PP performed molecular experiments and exome sequencing. JB performed exome annotation. HL performed cytological analysis. JD analyzed clinical data and performed the statistical analysis. CB-C analyzed exome

sequencing and performed variant interpretation; VM-E, FB, JD and CB-C analyzed the data and wrote the manuscript which was reviewed and edited by all authors.

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Data-sharing statement: technical information is available on request in order to assist other laboratories with characterization of CXCR2 variants.

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