의학박사 학위논문

# Whole exome sequencing on congenital neutropenia in Korean patients: Genetic, phenotypic and histologic correlations

선천성 호중구 감소증 환자의
전체엑솜염기서열분석: 유전형, 표현형 및 골수
조직 소견 간의 관계

2022년 8월

서울대학교 대학원
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2022년 4월

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# Abstract

**Introduction:** Congenital neutropenia (CN) is a hematological disease heterogeneous in its genetic, phenotypic and histologic aspects. We aimed to identify the genetic etiology of Korean CN patients in the context of bone marrow (BM) histology and clinical phenotype.

**Materials and Methods:** Whole-exome sequencing (WES) or targeted sequencing was performed on the BM or peripheral blood specimens of 16 patients diagnosed with CN based on BM exam from 2009 to 2018. Absolute count of myeloperoxidase (MPO)-positive cells was calculated using ImageJ software. Semi-quantitation of MPO-positive cells in BM sections was performed by MPO grading (grades 0–3). Comprehensive retrospective review on real-world data of 345 pediatric patients with neutropenia including 16 patients in this study during the same period was performed.

**Results:** Seven disease-causing variants were identified in *ELANE*, *G6PC3* and *CXCR4* in 7 patients. A novel homozygous *G6PC3* variant (K72fs) of which the mechanism was copy-neutral loss of heterozygosity was detected in two brothers. A low myeloid-to-erythroid ratio (0.5–1.5) was consistently observed in patients with *ELANE* mutations, while MPO-positive cells (40%–50%) with MPO grade 1 or 2 were detected in myelokathexis caused by *G6PC3* and *CXCR4* mutations. Meanwhile, disease-causing variants were detected in *ELANE*, *TAZ* and *SLC37A4* in 5 patients by retrospective review of medical records.

**Conclusion:** Our results suggest that following the immunological study and BM exam, WES or an expanded next generation sequencing panel that covers genes related to immunodeficiency and other inherited bone marrow failures as well as

CN is recommended for neutropenia patient diagnosis.

**Keyword :** Congenital neutropenia, Whole exome sequencing, Neutropenia

**Student Number :** 2020-35277

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# 1. Introduction

Congenital neutropenia (CN) is a hematological disease heterogeneous in its phenotypic, histologic and molecular aspects. CN can manifest as isolated neutropenia or neutropenia with extra-hematopoietic abnormalities, immunodeficiency or metabolic diseases. Mutations in more than 20 genes have been demonstrated to cause CN, some of which cause complex phenotypes. Some CN-causing genes show characteristic bone marrow (BM) histologic features such as maturation arrest of granulopoiesis or myelokathexis [1-3].

Relationship among the clinical phenotype, BM histology and genotype have been documented in many studies. Also, different genes are associated with different inheritance patterns: autosomal dominant (AD), autosomal recessive (AR) or X-linked recessive (XR). For example, CN without extra-hematopoietic abnormalities can result from *ELANE* mutations (AD inheritance), whereas pathogenic variants of *HAX1*, *G6PC3* and *VPS13B* (AR inheritance) can lead to syndromic features affecting multiple organ systems. Variable BM histologic features can be observed in patients carrying each causative gene variant. Maturation arrest at the promyelocyte or myelocyte stage can be caused by *ELANE*, *GFI1* (AD inheritance), *WAS* (XR inheritance), *HAX1* and *G6PC3* mutations [4-10]. Myelokathexis can be observed in patients with *CXCR4* (AD inheritance), *CXCR2* (AR inheritance) or *G6PC3* mutations [11-13]. Mutations in *SBDS*, *EFL1* or *USB1* (AR inheritance) may result in dysplastic hematopoietic cells [3].

Although clinical features and BM histologies provide some clues to the diagnosis of CN, the same characteristics can be present in other diseases. Some immunodeficiency syndromes, which are often associated with hematologic

abnormalities, might be responsible for neutropenia. Mutations in the *ADA2* gene, which encodes one of the two adenosine deaminases, show overlapping features of immunodeficiency and bone marrow failure, both of which contribute to cytopenia [14].

Differential diagnosis of CN from acquired neutropenia including autoimmune neutropenia is crucial because the clinical and prognostic implications are different: the former is a pre-leukemic disorder with an increased risk of transformation to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) or recurrent chronic and life-threatening infections, whereas the latter usually shows a benign clinical course with rare infectious complications [15]. Several algorithms for the diagnosis of CN have been proposed, which commonly include processes for ruling out acquired neutropenia. Thorough investigation of medical history, repeated complete blood count (CBC) with immunological work up such as immunoglobulin (Ig) measurement, anti-neutrophil antibodies and lymphocyte subset analysis followed by a BM exam have been suggested. Then, genetic study was recommended depending on the context [1,3].

CN patients may benefit from early and timely genetic tests in terms of prognostic perspective. Early hematopoietic stem cell transplantation (HSCT) is known to lower the risk of leukemia development in *ELANE*-mutation patients [16]. It can also reduce the exposure of CN patients to granulocyte-colony stimulating factor (G-CSF) whose cumulative dose is one of the main causes of leukemia development [17]. Early HSCT can reduce the mortality of CN patients by precluding severe infections to which they are predisposed because of low absolute neutrophil count (ANC). Consequently, elucidating the genetic etiology of CN reduces the risk of death and leukemic progression and allows physicians to

establish patients' long-term management plan and familial genetic counseling.

Research on congenital neutropenia has been published by large international registries such as Severe Chronic Neutropenia International Registry or French Congenital Neutropenia Registry. An *ELANE* mutation has been reported to be the most common genetic etiology of CN in patients registered in the Europeans and North American branches of the Severe Chronic Neutropenia International Registry [2]. Alternatively, study results on patients with *ELANE*, *G6PC3*, *CXCR4*, *HAX1*, *GATA2*, *SRP54* and *SRP68* have been reported by French Congenital Neutropenia Registry [18-24].

Meanwhile, whole-exome sequencing (WES) performed on 3 patients and 1 family identified heterozygous *SRP54* gene mutations in CN patients [23]. WES on 27 CN patients from Poland and Sweden revealed homozygous *JAGN1* gene mutations in 3 patients with Kostmann-like phenotype [25].

Some CN-causing gene mutations are known to be closely linked to geographic origin. CN caused by a *HAX1* mutation is prevalent in Iran (41%) and Sweden (19%), whereas CN due to mutated *G6PC3* is frequently identified in Israel (19%) [26-28]. In Korea, a few sporadic cases have been reported which include mutations in *ELANE* (NM_001972.4:c.607G>C, p.(G203R) and c.597+1G > A) and *CXCR4* (NM_003467.2:c.966_967delAG, p.(G323fs)), as revealed by Sanger sequencing [29-31]. However, no extensive molecular study of Korean CN patients has been conducted so far.

Herein, we aimed to present the comprehensive genetic data of Korean CN patients in the context of clinical phenotype and BM histology. WES or targeted sequencing (TS) was performed on 16 pediatric patients who were diagnosed with CN based on BM exam so that we could detect novel variants and establish the

Korean CN molecular data, which is critical for efficient diagnosis of CN.

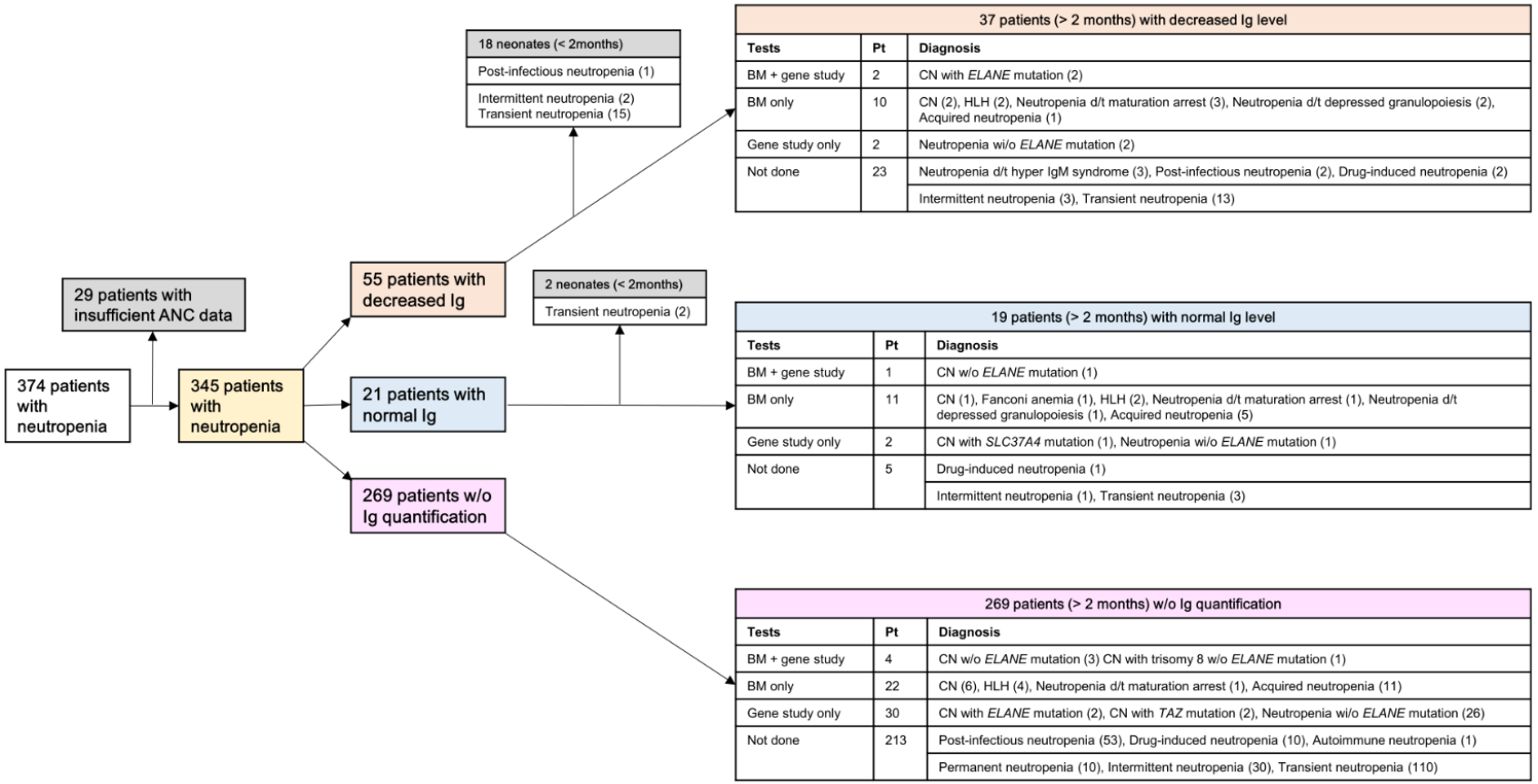
# 2. Materials and Methods

## 2.1. Patients

A total of 16 patients who visited Seoul National University Children's Hospital from 2009 to 2018 and were diagnosed with CN based on BM histology and clinical information were enrolled. Fifteen BM aspirates and one peripheral blood sample were retrospectively collected from the 16 pediatric patients. Data on patients' clinical course, family history and laboratory results such as CBC and Ig levels were retrospectively reviewed using electronic medical records.

Meanwhile, comprehensive review on real-world data of 345 pediatric patients with neutropenia including 16 patients in this study during the same period was performed. Ig levels were measured in 76 out of 345 (22.0%) patients. The patients were classified into 4 groups: patients who underwent both BM and genetic study, only BM exam, only genetic test and those who underwent none of the tests. Sanger sequencing was performed on *ELANE* in 38 patients, *TAZ* in 1 patient and *SLC37A4* in 1 patient. Meanwhile, targeted next generation sequencing of which panels included *ELANE* or *TAZ* was performed on 2 patients (**Figure 1**).

This study was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB No. 2001-139-1096). The research was performed in accordance with the Declaration of Helsinki. The requirement for obtaining informed consent was waived due to the retrospective nature of this study by the IRB of Seoul National University Hospital.




**37 patients (> 2 months) with decreased Ig level**

| Tests | Pt | Diagnosis |
|---|---|---|
| BM + gene study | 2 | CN with *ELANE* mutation (2) |
| BM only | 10 | CN (2), HLH (2), Neutropenia d/t maturation arrest (3), Neutropenia d/t depressed granulopoiesis (2), Acquired neutropenia (1) |
| Gene study only | 2 | Neutropenia wi/o *ELANE* mutation (2) |
| Not done | 23 | Neutropenia d/t hyper IgM syndrome (3), Post-infectious neutropenia (2), Drug-induced neutropenia (2) |
| | | Intermittent neutropenia (3), Transient neutropenia (13) |

**19 patients (> 2 months) with normal Ig level**

| Tests | Pt | Diagnosis |
|---|---|---|
| BM + gene study | 1 | CN w/o *ELANE* mutation (1) |
| BM only | 11 | CN (1), Fanconi anemia (1), HLH (2), Neutropenia d/t maturation arrest (1), Neutropenia d/t depressed granulopoiesis (1), Acquired neutropenia (5) |
| Gene study only | 2 | CN with *SLC37A4* mutation (1), Neutropenia wi/o *ELANE* mutation (1) |
| Not done | 5 | Drug-induced neutropenia (1) |
| | | Intermittent neutropenia (1), Transient neutropenia (3) |

**269 patients (> 2 months) w/o Ig quantification**

| Tests | Pt | Diagnosis |
|---|---|---|
| BM + gene study | 4 | CN w/o *ELANE* mutation (3) CN with trisomy 8 w/o *ELANE* mutation (1) |
| BM only | 22 | CN (6), HLH (4), Neutropenia d/t maturation arrest (1), Acquired neutropenia (11) |
| Gene study only | 30 | CN with *ELANE* mutation (2), CN with *TAZ* mutation (2), Neutropenia wi/o *ELANE* mutation (26) |
| Not done | 213 | Post-infectious neutropenia (53), Drug-induced neutropenia (10), Autoimmune neutropenia (1) |
| | | Permanent neutropenia (10), Intermittent neutropenia (30), Transient neutropenia (110) |

**Figure 1. Real-world data on diagnostic work-up algorithms for neutropenia patients in Seoul National University**

**Children's Hospital from 2009 to 2018.** ANC, absolute neutrophil count; BM, bone marrow; CN, congenital neutropenia; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin.

## 2.2. Immunohistochemical staining for myeloperoxidase

Myeloperoxidase (MPO) was stained in BM biopsy specimens. A paraffin-embedded tissue block was trimmed and sliced into 2-μm sections. The tissues on slides were incubated at 56°C for 30 min and hydrated with xylene, 100% ethanol (EtOH), 95% EtOH and 70% EtOH. Each slide was then stained with Ventana BenchMark ULTRA (Ventana Medical Systems Inc., Tucson, AZ, USA). Polyclonal rabbit anti-human MPO antibody (DAKO, Glostrup, Denmark) was applied for 15 min at room temperature. Subsequently, the slides were dehydrated using 70% EtOH, 95% EtOH, 100% EtOH and xylene.

## 2.3. MPO-positive cell count

Digital images of MPO-stained BM sections (200×) were captured with a Zeiss AxioCAM microscope (Zeiss, Oberkochen, Germany). MPO-positive cells were counted using ImageJ software (https://imagej.nih.gov/ij/). Two or three images per patient were analyzed to minimize the bias from site variation or suboptimal BM section quality. On average, 7,151 nucleated cells (range, 4,369–11,513) per patient were counted. MPO-positive cells were detected by analyzing particle counts. The minimum size of an MPO-positive cell was set from 8 to 40 $pixel^2$ depending on the individual cell size variations; the minimum size of a BM nucleated cell was set to 10–20 $pixel^2$. The maximum size of cells was set to 20,000 $pixel^2$ to exclude non-cell components such as fat or trabecular bone. Hue, saturation and brightness were adjusted to accurately call MPO-positive cells as a numerator and nucleated cells as a denominator. The percentage of MPO-positive cells was calculated by dividing the number of MPO-positive cells by that of

nucleated cells and multiplying the result by 100. Non-specific signals were excluded (**Figure 2**). Meanwhile, MPO-positive cells were manually counted on the same BM section images analyzed by ImageJ, which showed strong correlation (Spearman's rho = 0.930, P <0.001) (**Table 1**).

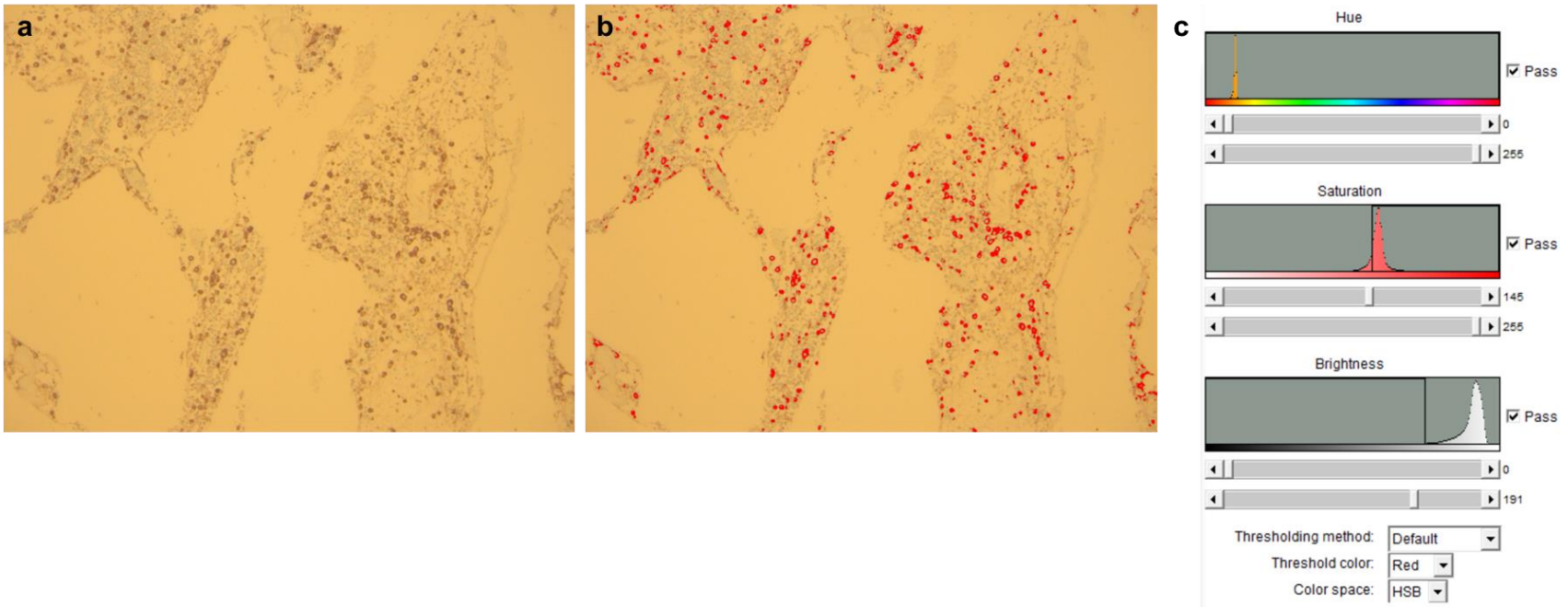



**Figure 2. MPO-positive cell count using ImageJ.** (a) MPO-positive cells with brown cytoplasm. (b) MPO-positive cells with red cytoplasm marked using ImageJ (1388 × 1040 pixels). (c) Threshold color setting of hue, saturation and brightness for image analysis using ImageJ. (a-b) MPO stain, ×200. MPO, myeloperoxidase.

## Table 1. Enumeration of MPO-positive cells on bone marrow section using ImageJ and manual count

| Pt | Image 1 | | | | | | Image 2 | | | | | | Image 3 | | | | | | Total images | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Image J analysis | | | Manual count | | | Image J analysis | | | Manual count | | | Image J analysis | | | Manual count | | | Image J analysis | | | Manual count | | |
| | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) | MPO (+) | TNC | MPO (%) |
| 01 | 911 | 2431 | 37.4 | 197 | 515 | 38.3 | 674 | 2489 | 27.1 | 201 | 634 | 31.7 | 993 | 3640 | 27.3 | 186 | 663 | 28.1 | 2578 | 8560 | 30.1 | 584 | 1812 | 32.2 |
| 02 | 1289 | 3377 | 38.2 | 181 | 525 | 34.5 | 1696 | 3820 | 44.4 | 267 | 610 | 43.8 | 2337 | 4316 | 54.2 | 330 | 715 | 45.2 | 5322 | 11513 | 46.2 | 778 | 1850 | 42.1 |
| 03* | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 04 | 1821 | 3244 | 56.1 | 439 | 792 | 55.4 | 1477 | 3144 | 47.0 | 416 | 843 | 49.3 | NT | NT | NT | NT | NT | NT | 3298 | 6388 | 51.6 | 855 | 1635 | 52.3 |
| 05 | 352 | 3616 | 9.7 | 88 | 878 | 10.0 | 523 | 3334 | 15.7 | 66 | 642 | 10.3 | NT | NT | NT | NT | NT | NT | 875 | 6950 | 12.6 | 154 | 1520 | 10.1 |
| 06 | 1326 | 3412 | 38.9 | 222 | 522 | 42.5 | 881 | 2620 | 33.6 | 216 | 569 | 38.0 | 382 | 2070 | 44.1 | 271 | 578 | 46.9 | 3119 | 8102 | 38.5 | 709 | 1669 | 42.5 |
| 07 | 2214 | 5185 | 42.7 | 347 | 627 | 55.3 | 1768 | 3166 | 55.8 | 290 | 546 | 53.1 | NT | NT | NT | NT | NT | NT | 3982 | 8351 | 47.7 | 637 | 1173 | 54.3 |
| 08 | 1184 | 2397 | 49.4 | 264 | 527 | 50.1 | 1687 | 4076 | 41.4 | 237 | 615 | 38.5 | NT | NT | NT | NT | NT | NT | 2871 | 6473 | 44.4 | 501 | 1142 | 43.9 |
| 09 | 1518 | 2647 | 57.4 | 396 | 672 | 58.9 | 1054 | 1722 | 61.2 | 360 | 609 | 59.1 | NT | NT | NT | NT | NT | NT | 2572 | 4369 | 58.9 | 756 | 1281 | 59.0 |
| 10 | 275 | 1692 | 16.3 | 148 | 759 | 19.5 | 316 | 1308 | 24.2 | 209 | 815 | 25.6 | 1831 | 1831 | 20.1 | 63 | 284 | 22.2 | 973 | 4831 | 20.1 | 420 | 1858 | 22.6 |
| 11 | 982 | 1665 | 59.0 | 165 | 306 | 53.9 | 1345 | 3447 | 39.0 | 135 | 350 | 38.6 | NT | NT | NT | NT | NT | NT | 2327 | 5112 | 45.5 | 300 | 656 | 45.7 |
| 12 | 1639 | 3423 | 47.9 | 305 | 576 | 53.0 | 1039 | 3431 | 30.3 | 264 | 589 | 44.8 | NT | NT | NT | NT | NT | NT | 2678 | 6854 | 39.1 | 569 | 1165 | 48.8 |
| 13 | 1794 | 3921 | 45.8 | 244 | 545 | 44.8 | 1383 | 2905 | 47.6 | 262 | 505 | 51.9 | NT | NT | NT | NT | NT | NT | 3177 | 6826 | 46.5 | 506 | 1050 | 48.2 |
| 14 | 1702 | 4178 | 40.7 | 223 | 506 | 44.1 | 549 | 1450 | 37.9 | 195 | 500 | 39.0 | 1834 | 1834 | 41.7 | 270 | 515 | 52.4 | 3015 | 7462 | 40.4 | 688 | 1521 | 45.2 |
| 15 | 600 | 2556 | 23.5 | 143 | 725 | 19.7 | 1498 | 5762 | 26.0 | 177 | 766 | 23.1 | NT | NT | NT | NT | NT | NT | 2098 | 8318 | 25.2 | 320 | 1491 | 21.5 |
| 16† | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

*Paraffin block for MPO immunohistochemical stain was not retrospectively available in P-03.
†Bone marrow section quality of P-16 was inadequate.
Abbreviations: MPO, myeloperoxidase; N/A, not applicable; NT, not tested; TNC, total nucleated cell.

## 2.4. Bone marrow histology

BM aspirates and biopsies of the 16 neutropenia patients were retrospectively reviewed. Maturation arrest of the granulocytic lineage and myelokathexis were assessed according to the pediatric age-specific reference range of BM differential count [32, 33]. Myelokathexis was defined as the BM retention status with an increased sum of band plus segmented neutrophils in comparison with the reference range (**Figure 3**).

MPO grade was arbitrarily defined as the number of layers of MPO-positive cells along the trabecular bones: grade 0, <1 layer; grade 1, <2 layers; grade 2, <3 layers; and grade 3, ≥3 layers (**Figure 4**).

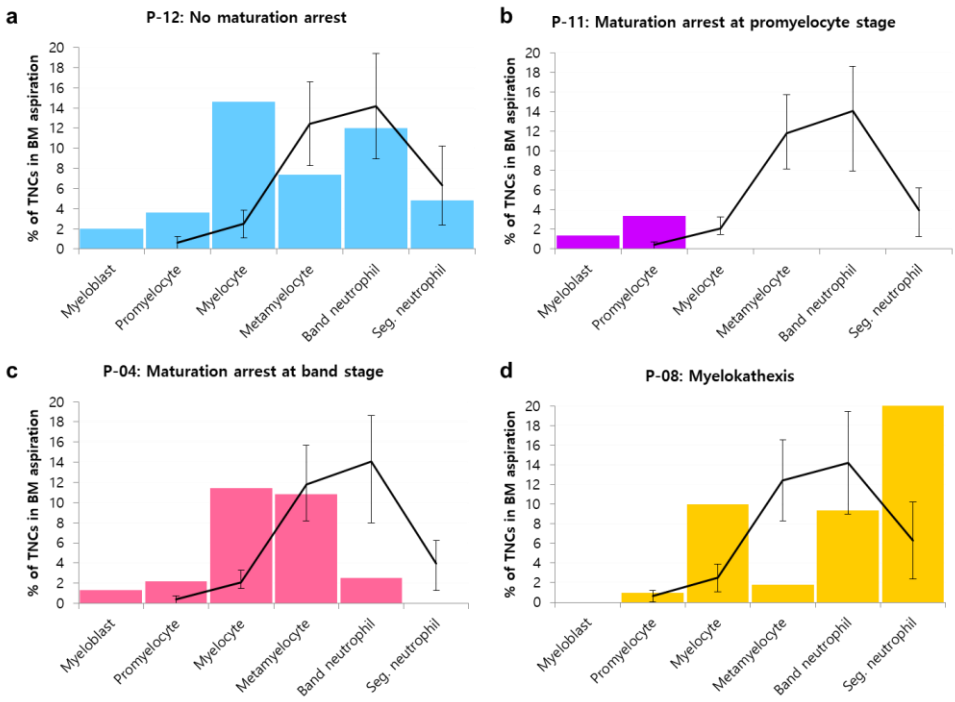



**Figure 3. Maturation arrest and myelokathexis assessment according to the pediatric age–specific reference range of BM differential count**. (a) Normal maturation. (b) Maturation arrest at the promyelocyte stage. (c) Maturation arrest at the band stage. (d) Melokathexis. Black broken lines indicate the median value of the reference range; black vertical lines denote the reference range. BM, bone marrow.

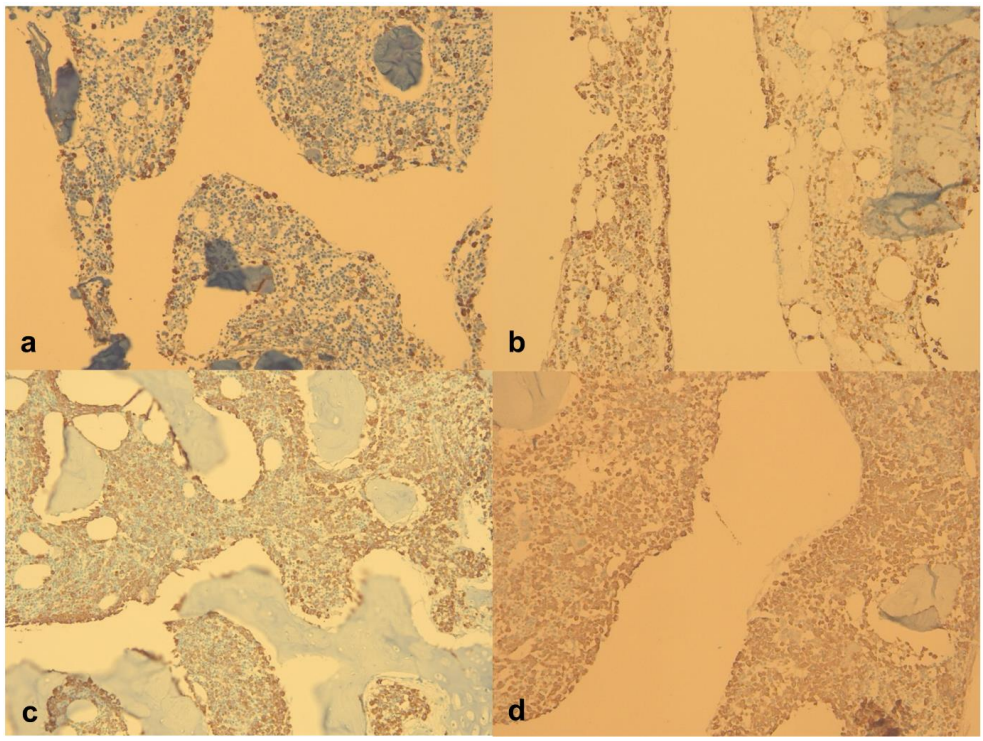



**Figure 4. BM section images showing different MPO grades.** (a-d) BM biopsy images with MPO grade 0, 1, 2 and 3. (a-d) MPO stain, ×200. BM, bone marrow; MPO, myeloperoxidase.

## 2.5. G-banding technique

The heparinized BM samples were collected and white blood cells (WBCs) were sorted by centrifugation and cultured in RPMI-1640 medium (Gibco, USA) at 37℃, in 5% CO2 for 24 hours. Colcemid treatment was done to inhibit the mitosis. The specimen in the medium was centrifuged and the upper layer was decanted. Then, KCl was added at 37℃ for 20 minutes. For fixation, 1 mL of Carnoy's solution was used. After preparation of the slide, Leishman's G-banding stain was performed according to the standard protocol. A minimum of 20 metaphase cells per patient was analyzed using the software Metafer 4 (MetaSystems, Altlussheim, FRG). The karyotype designation was based on the principles of the International System for Human Cytogenetic Nomenclature (ISCN 2016).

## 2.6. Whole exome sequencing

The SureSelectHuman All Exon V5+UTR probe set (Agilent, Santa Clara, CA, USA) included 359,555 exons of 21,522 genes; the size of the total targeted region was 75 Mb. To generate standard exome capture libraries, the Agilent SureSelect Target Enrichment protocol for Illumina paired-end sequencing library (ver. B.3, June 2015) was used with 3 µg of input genomic DNA. The DNA was quantified and its quality was assessed by PicoGreen (Thermo Fisher Scientific, Waltham, MA, USA) and Nanodrop (Thermo Fisher Scientific). Fragmentation of 1 µg of genomic DNA was performed using adaptive focused acoustic technology (AFA; Covaris). The fragmented DNA is repaired, an 'A' is ligated to the 3′ end, and Agilent adapters are then ligated to the fragments. Once ligation had been assessed, the adapter-ligated product is PCR amplified. The final purified product is then quantified using qPCR according to the qPCR Quantification Protocol Guide and

its quality was assessed using the Caliper LabChipHigh Sensitivity DNA kit (PerkinElmer, Waltham, MA, USA). For exome capture, 250 ng of DNA library was mixed with hybridization buffers, blocking mixes, RNase block and 5 μl of the SureSelect all exon capture library according to the standard Agilent SureSelect Target Enrichment protocol. Hybridization to the capture baits was conducted at 65°C using the heated thermal cycler lid option at 105°C for 24 h in a PCR machine. The captured DNA was then amplified. The final purified product was quantified using qPCR according to the qPCR Quantification Protocol Guide and its quality was assessed using the TapeStation DNA ScreenTape (Agilent, Santa Clara, CA, USA). Pooled DNA libraries were then sequenced using the HiSeq 2500 platform (Illumina, San Diego, CA, USA)①.

## 2.7. Targeted sequencing

Targeted sequencing using an in-house panel of 507 genes related to hematologic malignancies and other cancers was performed in one patient (P-08). The panel included 182 out of 500 genes related to CN (20/29, 69.0%), inherited bone marrow failure (IBMF) (41/55, 74.5%), immunodeficiency (80/399, 20.1%) and cancer predisposition (41/77, 53.2%) (**Table 2**).

① Library preparation and sequencing was performed by ByungJoo Min and Ju Han Kim.

## Table 2. List of 500 genes selected for variant analysis

| Gene | Location | Familial syndrome | Inheritance | Category | Reference | WHO 2016 classification | IUIS 2019 gene classification | Targeted sequencing |
|---|---|---|---|---|---|---|---|---|
| *ACKR1* | 1q23.2 | White blood cell count QTL | AR | CN | PMID: 28553950 | no | no | no |
| *AK2* | 1p35.1 | Reticular dysgenesis | AR | CN | PMID: 28593997 | no | yes | yes |
| *AP3B1* | 5q14.1 | Hermansky-Pudlak Syndrome | AR | CN | PMID: 28593997 | no | yes | yes |
| *CD40LG* | Xq26.3 | Immunodeficiency, X-linked, with hyper-IgM | XR | CN | PMID: 28593997 | no | yes | yes |
| *CLPB* | 11q13.4 | 3-methylglutaconic aciduria, type VII, with cataracts, neurologic involvement and neutropenia | AR | CN | PMID: 28593997 | no | yes | no |
| *CSF3R* | 1p34.3 | Neutropenia, severe congenital, 7, autosomal recessive | AR | CN | PMID: 21595885 | yes | yes | yes |
| *CXCR2* | 2q35 | Severe congenital neutropenia | AR | CN | PMID: 28593997 | no | no | no |
| *CXCR4* | 2q22.1 | WHIM syndrome | AD | CN | PMID: 21595885 | no | yes | yes |
| *EIF2AK3* | 2p11.2 | Wolcott-Rallison syndrome | AR | CN | PMID: 28593997 | no | no | no |
| *ELANE* | 19p13.3 | Neutropenia, severe congenital 1, autosomal dominant, Neutropenia, cyclic | AD | CN | PMID: 21595885 | yes | yes | yes |
| *G6PC3* | 17q21.31 | Neutropenia, severe congenital 4, autosomal recessive | AR | CN | PMID: 21595885 | yes | yes | yes |
| *GATA2* | 3q21.3 | Emberger syndrome, Immunodeficiency 21 | AD | CN | PMID: 28593997 | no | yes | yes |
| *GFI1* | 1p22.1 | Neutropenia, severe congenital 2, autosomal dominant, Neutropenia, nonimmune chronic idiopathic, of adults | AD | CN | PMID: 21595885 | yes | yes | yes |
| *HAX1* | 1q21.3 | Neutropenia, severe congenital 3, autosomal recessive | AR | CN | PMID: 21595885 | yes | yes | yes |
| *JAGN1* | 3p25.3 | Neutropenia, severe congenital, 6, autosomal recessive | AR | CN | PMID: 28593997 | no | yes | no |
| *LAMTOR2* | 1q22 | Immunodeficiency due to defect in MAPBP-interacting protein | AR | CN | PMID: 28593997 | no | yes | yes |
| *LYST* | 1q42.3 | Chediak-Higashi syndrome | AR | CN | PMID: 28593997 | no | yes | yes |
| *RAB27A* | 15q21.3 | Griscelli syndrome, type 2 | AR | CN | PMID: 28593997 | no | yes | yes |
| *RMRP* | 9p13.3 | Cartilage-hair hypoplasia | AR | CN | PMID: 21595885 | no | yes | yes |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *SEPTIN6* | Xq24 | Severe congenital neutropenia with tetraploidy, Progressive myelodysplasia and cytogenetic aberrations | | CN | Blood (2018) 132 (Supplement 1): 644. | no | no | no |
| *SLC37A4* | 11q23.3 | Glycogen storage disease Ib | AR | CN | PMID: 21595885 | no | yes | yes |
| *SRP54* | 14q13.2 | Neutropenia, severe congenital, 8, autosomal dominant | AD | CN | PMID: 31953710 | no | yes | no |
| *TAZ* | Xq28 | Barth syndrome | XR | CN | PMID: 21595885 | no | yes | yes |
| *TCIRG1* | 11q13.2 | Osteopetrosis, AR 1 | AR | CN | PMID: 28593997 | no | yes | no |
| *TCN2* | 22q12.2 | Transcobalamin II deficiency | AR | CN | PMID: 28593997 | no | yes | no |
| *USB1* | 16q21 | Poikiloderma with neutropenia | AR | CN | PMID: 28593997 | no | yes | yes |
| *VPS13B* | 8q22.2 | Cohen syndrome | AR | CN | PMID: 21595885 | no | no | yes |
| *VPS45* | 1q21.2 | Neutropenia, severe congenital, 5, AR | AR | CN | PMID: 28593997 | no | yes | yes |
| *WAS* | Xp11.23 | Neutropenia, severe congenital, X-linked | XR | CN | PMID: 21595885 | yes | yes | yes |
| *ACD* | 16q22.1 | Dyskeratosis congenita, autosomal dominant 6, Dyskeratosis congenita, autosomal recessive 7 | AD/AR | IBMF | PMID: 31953710 | no | yes | no |
| *BRCA1* | 17q21.31 | Fanconi anemia type S | AD | IBMF | PMID: 24237972 | no | yes | yes |
| *BRCA2* | 13q13.1 | Fanconi anemia, complementation group D1 | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *BRIP1* | 17q23.2 | Fanconi anemia, complementation group J | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *CTC1* | 17p13.1 | Cerebroretinal microangiopathy with calcifications and cysts | AR | IBMF | PMID: 31953710 | yes | yes | yes |
| *DKC1* | Xq28 | Dyskeratosis congenita | XR | IBMF | PMID: 24237972 | yes | yes | yes |
| *DNAJC21* | 5p13.2 | Bone marrow failure syndrome 3 | AR | IBMF | PMID: 31953710 | no | yes | no |
| *EFL1* | 15q25.2 | Shwachman-Diamond syndrome 2 | AR | IBMF | PMID: 31953710 | no | yes | no |
| *ERCC4* | 16p13.12 | Fanconi anemia, complementation group Q | AR | IBMF | PMID: 31953710 | no | yes | yes |
| *ERCC6L2* | 9q22.32 | Bone marrow failure syndrome 2 | AR | IBMF | PMID: 31953710 | no | yes | no |
| *FANCA* | 16q24.3 | Fanconi anemia, complementation group A | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCB* | Xp22.2 | Fanconi anemia, complementation group B | XR | IBMF | PMID: 24237972 | yes | yes | yes |

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|---|---|---|---|---|---|---|---|---|
| *FANCC* | 9q22.32 | Fanconi anemia, complementation group C | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCD2* | 3p25.3 | Fanconi anemia, complementation group D2 | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCE* | 6p21.31 | Fanconi anemia, complementation group E | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCF* | 11p14.3 | Fanconi anemia, complementation group F | | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCG* | 9p13.3 | Fanconi anemia, complementation group G | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCI* | 15q26.1 | Fanconi anemia, complementation group I | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCL* | 2p16.1 | Fanconi anemia, complementation group L | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *FANCM* | 14q21.2 | Fanconi anemia, type M | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *GATA1* | Xp11.23 | Anemia, X-linked, with/without neutropenia and/or platelet abnormalities | XR | IBMF | PMID: 10700180, 24453067 | yes | no | yes |
| *LIG4* | 13q33.3 | LIG4 syndrome | AR | IBMF | PMID: 11779494 | no | yes | yes |
| *MAD2L2* | 1p36.22 | Fanconi anemia, complementation group V | AR | IBMF | PMID: 31953710 | no | yes | no |
| *MECOM* | 3q26.2 | Radioulnar synostosis with amegakaryocytic thrombocytopenia 2 | AD | IBMF | PMID: 26581901 | no | no | no |
| *NAF1* | 4q32.2 | Dyskeratosis congenita | AD | IBMF | PMID: 28211564 | no | no | no |
| *NHP2* | 5q35.3 | Dyskeratosis congenita, autosomal recessive 2 | AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *NOP10* | 15q14 | Dyskeratosis congenita, autosomal recessive 1 | AR | IBMF | PMID: 17507419 | yes | yes | yes |
| *PALB2* | 16p12.2 | Fanconi Anemia, Complementation Group N | | IBMF | PMID: 24237972 | yes | yes | yes |
| *PARN* | 16p13.12 | Pulmonary fibrosis and/or bone marrow failure, telomere-related, 4, Dyskeratosis congenita, autosomal recessive 6 | AD/AR | IBMF | PMID: 31953710 | no | yes | no |
| *RAD51* | 15q15.1 | Fanconi anemia, complementation group R | AD | IBMF | PMID: 31953710 | no | yes | no |
| *RAD51C* | 17q22 | Fanconi anemia, complementation group O | AR | IBMF | PMID: 20400963 | yes | yes | yes |
| *RFWD3* | 16q23.1 | Fanconi anemia type W | AR | IBMF | PMID: 31953710 | yes | yes | no |
| *RPL11* | 1p36.11 | Diamond-Blackfan anemia 7 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RPL35A* | 3q29 | Diamond-Blackfan anemia 5 | AD | IBMF | PMID: 24237972 | yes | no | yes |

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|---|---|---|---|---|---|---|---|---|
| *RPL5* | 1p22.1 | Diamond-Blackfan anemia 6 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RPS10* | Xq28 | X-linked syndromic mental retardation-35 | XR | IBMF | PMID: 24237972 | yes | no | yes |
| *RPS17* | 15q25.2 | Diamond-Blackfan anemia 4 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RPS19* | 17q12 | Diamond-Blackfan anemia 1 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RPS24* | 10q22.3 | Diamond-blackfan anemia 3 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RPS26* | 12q13.2 | Diamond-Blackfan anemia 10 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RPS7* | 2p25.3 | Diamond-Blackfan anemia 8 | AD | IBMF | PMID: 24237972 | yes | no | yes |
| *RTEL1* | 20q13.33 | Dyskeratosis congenita, autosomal dominant 4, Dyskeratosis congenita, autosomal recessive 5 | AD/AR | IBMF | PMID: 31953710 | yes | yes | yes |
| *SAMD9* | 7q21.2 | MIRAGE syndrome, Inherited predisposition to myeloid malignancies | AD | IBMF | PMID: 27182967 | no | yes | yes |
| *SAMD9L* | 7q21.2 | Ataxia-pancytopenia syndrome | AD | IBMF | PMID: 31953710 | no | yes | no |
| *SBDS* | 7q11.21 | Shwachman-Diamond syndrome | AR | IBMF | PMID: 21595885 | no | yes | yes |
| *SLX4* | 16p13.3 | Fanconi anemia, complementation group P | AR | IBMF | PMID: 21240277 | yes | yes | yes |
| *SRP72* | 4q12 | Bone marrow failure syndrome 1 | AD | IBMF | PMID: 22541560 | no | yes | yes |
| *STN1* | 10q24.33 | Dyskeratosis congenita | AD | IBMF | PMID: 31953710 | no | yes | no |
| *TERC* | 3q26.2 | Dyskeratosis congenita, autosomal dominant 1 | AD | IBMF | PMID: 24237972 | yes | yes | yes |
| *TERT* | 5p15.33 | Dyskeratosis congenita, autosomal dominant 2, Dyskeratosis congenita, autosomal recessive 4 | AD/AR | IBMF | PMID: 24237972 | yes | yes | yes |
| *TINF2* | 14q12 | Dyskeratosis congenita, autosomal dominant 3, Revesz syndrome | AD | IBMF | PMID: 24237972 | yes | yes | yes |
| *TP53* | 17p13.3 | BMFS5 | AD | IBMF | PMID: 31953710 | no | yes | yes |
| *UBE2T* | 1q32.1 | Fanconi anemia, complementation group T | AR | IBMF | PMID: 31953710 | no | yes | no |
| *WRAP53* | 17p13.1 | Dyskeratosis congenita, autosomal recessive 3 | AR | IBMF | PMID: 31953710 | yes | yes | yes |
| *XRCC2* | 7q36.1 | Fanconi anemia, complementation group U | AR | IBMF | PMID: 31953710 | no | yes | no |
| *ACP5* | 19p13.2 | Spondyloenchondrodysplasia with immune dysregulation | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *ACTB* | 7p22.1 | β actin deficiency | AD | ID | PMID: 31953710 | no | yes | yes |
| *ADA* | 20q13.12 | Severe combined immunodeficiency due to ADA deficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *ADA2* | 22q11.1 | Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *ADAM17* | 2p25.1 | ADAM17 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *ADAR* | 1q21.3 | ADAR1 deficiency, AGS6 | AD | ID | PMID: 31953710 | no | yes | no |
| *AICDA* | 12p13.31 | Immunodeficiency with hyper-IgM, type 2 | AR | ID | PMID: 31953710 | no | yes | no |
| *AIRE* | 21q22.3 | Autoimmune polyendocrinopathy syndrome, type I, with or without reversible metaphyseal dysplasia | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *ALPI* | 2q37.1 | ALPI deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *AP1S3* | 2q36.1 | AP1S3 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *AP3D1* | 19p13.3 | Hermansky-Pudlak syndrome 10 | AR | ID | PMID: 31953710 | no | yes | no |
| *APOL1* | 22q12.3 | Trypanosomiasis | AD | ID | PMID: 31953710 | no | yes | no |
| *ARHGEF1* | 19q13.2 | ARHGEF1 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *ARPC1B* | 7q22.1 | Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease | AR | ID | PMID: 31953710 | no | yes | no |
| *ATM* | 11q22.3 | Ataxia-telangiectasia | AR | ID | PMID: 31953710 | no | yes | yes |
| *ATP6AP1* | Xq28 | ATP6AP1 deficiency | XL | ID | PMID: 31953710 | no | yes | no |
| *B2M* | 15q21.1 | MHC class I deficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *BACH2* | 6q15 | Immunodeficiency 60 | AD | ID | PMID: 31953710 | no | yes | no |
| *BCL10* | 1p22.3 | Immunodeficiency 37 | AR | ID | PMID: 31953710 | no | yes | yes |
| *BCL11B* | 14q32.2 | Immunodeficiency 49 | AD | ID | PMID: 31953710 | no | yes | yes |
| *BLM* | 15q26.1 | Bloom syndrome | AR | ID | PMID: 31953710 | no | yes | yes |
| *BLNK* | 10q24.1 | Agammaglobulinemia 4 | AR | ID | PMID: 31953710 | no | yes | yes |
| *BTK* | Xq22.1 | Agammaglobulinemia, X-linked 1 | XR | ID | PMID: 31953710 | no | yes | yes |

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|---|---|---|---|---|---|---|---|---|
| *C1QA* | 1p36.12 | C1q deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C1QB* | 1p36.12 | C1q deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C1QC* | 1p36.12 | C1q deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C1R* | 12p13.31 | C1r deficiency | AR/AD | ID | PMID: 31953710 | no | yes | no |
| *C1S* | 12p13.31 | C1s deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C2* | 6p21.33 | C2 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C3* | 19p13.3 | C3 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C4A* | 6p21.33 | C4A deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C4B* | 6p21.33 | C4B deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C5* | 9q33.2 | C5 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *C6* | 5p13.1 | C6 deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C7* | 5p13.1 | C7 deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C8A* | 1p32.2 | C8α deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C8B* | 6p21.33 | C8 β deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C8G* | 9q34.3 | C8 γ deficiency | | ID | PMID: 31953710 | no | yes | no |
| *C9* | 5p13.1 | C9 deficiency | | ID | PMID: 31953710 | no | yes | no |
| *CARD11* | 7p22.2 | B-cell expansion with NFKB and T-cell anergy, Immunodeficiency 11A, Immunodeficiency 11B with atopic dermatitis | AD/AR | ID | PMID: 31953710 | no | yes | yes |
| *CARD14* | 17q25.3 | CAMPS (CARD14 mediated psoriasis) | AD | ID | PMID: 31953710 | no | yes | no |
| *CARD9* | 9q34.3 | Candidiasis, familial, 2, autosomal recessive | AR | ID | PMID: 31953710 | no | yes | no |
| *CARMIL2* | 16q22.1 | Immunodeficiency 58 | AR | ID | PMID: 31953710 | no | yes | no |
| *CASP10* | 2q33.1 | Autoimmune lymphoproliferative syndrome | AD | ID | PMID: 31953710 | no | yes | yes |

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|---|---|---|---|---|---|---|---|---|
| *CASP8* | 2q33.1 | Autoimmune lymphoproliferative syndrome, type IIB | AR | ID | PMID: 31953710 | no | yes | yes |
| *CCBE1* | 18q21.32 | Hennekam-lymphangiectasia-lymphedema syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *CD19* | 16p11.2 | Immunodeficiency, common variable, 3 | AR | ID | PMID: 31953710 | no | yes | no |
| *CD247* | 1q24.2 | Immunodeficiency 25 | AR | ID | PMID: 31953710 | no | yes | no |
| *CD27* | 12p13.31 | Lymphoproliferative syndrome 2 | AR | ID | PMID: 31953710 | no | yes | yes |
| *CD3D* | 11q23.3 | Immunodeficiency 19 | AR | ID | PMID: 31953710 | no | yes | yes |
| *CD3E* | 11q23.3 | Immunodeficiency 18 | AR | ID | PMID: 31953710 | no | yes | yes |
| *CD3G* | 11q23.3 | Immunodeficiency 17, CD3 gamma deficient | AR | ID | PMID: 31953710 | no | yes | no |
| *CD40* | 20q13.12 | Immunodeficiency with Hyper-IgM | AR | ID | PMID: 31953710 | no | yes | no |
| *CD46* | 1q32.2 | Hemolytic uremic syndrome, atypical | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CD55* | 1q32.2 | Complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy | AR | ID | PMID: 31953710 | no | yes | no |
| *CD70* | 19p13.3 | Lymphoproliferative syndrome 3 | AR | ID | PMID: 31953710 | no | yes | yes |
| *CD79A* | 19q13.2 | Agammaglobulinemia 3 | AR | ID | PMID: 31953710 | no | yes | yes |
| *CD79B* | 17q23.3 | Agammaglobulinemia 6 | AR | ID | PMID: 31953710 | no | yes | yes |
| *CD81* | 11p15.5 | Immunodeficiency, common variable, 6 | AR | ID | PMID: 31953710 | no | yes | no |
| *CD8A* | 2p11.2 | CD8 deficiency, familial | AR | ID | PMID: 31953710 | no | yes | no |
| *CDCA7* | 2q31.1 | Immunodeficiency-centromeric instability-facial anomalies syndrome 3 | AR | ID | PMID: 31953710 | no | yes | no |
| *CEBPE* | 14q11.2 | Specific granule deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *CFB* | 6p21.33 | Complement factor B deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *CFD* | 19p13.3 | Complement factor D deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *CFH* | 1q31.3 | Complement factor H deficiency | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CFHR1* | 1q31.3 | Factor H-related protein deficiencies | AD/AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *CFHR2* | 1q31.3 | Factor H-related protein deficiencies | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CFHR3* | 1q31.3 | Factor H-related protein deficiencies | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CFHR4* | 1q31.3 | Factor H-related protein deficiencies | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CFHR5* | 1q31.3 | Factor H-related protein deficiencies | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CFI* | 4q25 | Complement factor I deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *CFP* | Xp11.23 | Properdin deficiency, X-linked | XR | ID | PMID: 31953710 | no | yes | no |
| *CFTR* | 7q31.2 | Cystic fibrosis | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *CHD7* | 8q12.2 | CHARGE syndrome | AD | ID | PMID: 31953710 | no | yes | no |
| *CIB1* | 15q26.1 | CIB1 deficiency | . | ID | PMID: 31953710 | no | yes | no |
| *CIITA* | 16p13.13 | Bare lymphocyte syndrome, type II, complementation group A | AR | ID | PMID: 31953710 | no | yes | yes |
| *CLCN7* | 16p13.3 | Osteopetrosis, autosomal dominant 2 | AD | ID | PMID: 31953710 | no | yes | no |
| *COLEC11* | 2p25.3 | 3MC syndrome 2 | AR | ID | PMID: 26454309 | no | no | no |
| *COPA* | 1q23.2 | Autoimmune interstitial lung, joint, and kidney disease | AD | ID | PMID: 31953710 | no | yes | no |
| *CORO1A* | 16p11.2 | Immunodeficiency 8 | AR | ID | PMID: 31953710 | no | yes | no |
| *CR2* | 1q32.2 | Immunodeficiency, common variable, 7 | AR | ID | PMID: 31953710 | no | yes | no |
| *CSF2RA* | Xp22.32 | Pulmonary alveolar proteinosis | XL | ID | PMID: 31953710 | no | yes | no |
| *CSFR2B* | 22q12.3 | Pulmonary alveolar proteinosis | AR | ID | PMID: 31953710 | no | yes | no |
| *CTLA4* | 2q33.2 | Autoimmune lymphoproliferative syndrome, type V | AD | ID | PMID: 31953710 | no | yes | no |
| *CTPS1* | 1p34.2 | Immunodeficiency 24 | AR | ID | PMID: 31953710 | no | yes | no |
| *CTSC* | 11q14.2 | Haim-Munk syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *CYBA* | 16q24.2 | Chronic granulomatous disease, autosomal, due to deficiency of CYBA | AR | ID | PMID: 31953710 | no | yes | no |
| *CYBB* | Xp21.1-p11.4 | Chronic granulomatous disease, X-linked, Immunodeficiency 34, mycobacteriosis, X-linked | XR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *CYBC1* | 17q25.3 | Autosomal recessive CGD | AR | ID | PMID: 31953710 | no | yes | no |
| *DBR1* | 3q22.3 | DBR1 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *DCLRE1C* | 10p13 | Omenn syndrome, Severe combined immunodeficiency, Athabascan type | AR | ID | PMID: 31953710 | no | yes | yes |
| *DEF6* | 6p21.31 | DEF6 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *DNASE1L3* | 3p14.3 | Pediatric systemic lupus erythematosus due to DNASE1L3 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *DNASE2* | 19p13.13 | DNAse II deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *DNMT3B* | 20q11.21 | Immunodeficiency-centromeric instability-facial anomalies syndrome 1 | AR | ID | PMID: 31953710 | no | yes | yes |
| *DOCK2* | 5q35.1 | Immunodeficiency 40 | AR | ID | PMID: 31953710 | no | yes | no |
| *DOCK8* | 9p24.3 | Hyper-IgE recurrent infection syndrome, autosomal recessive | AR | ID | PMID: 31953710 | no | yes | no |
| *EPG5* | 18q12.3-q21.1 | Vici syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *ERBIN* | 5q12.3 | ERBIN deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *EXTL3* | 8p21.1 | Immunoskeletal dysplasia with neurodevelopmental abnormalities (ISDNA) | AR | ID | PMID: 31953710 | no | yes | no |
| *FAAP24* | 19q13.11 | FAAP24 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *FADD* | 11q13.3 | Infections, recurrent, with encephalopathy, hepatic dysfunction, and cardiovascular malformations | AR | ID | PMID: 31953710 | no | yes | no |
| *FAS* | 10q23.31 | Autoimmune lymphoproliferative syndrome, type IA | AD/AR | ID | PMID: 31953710 | no | yes | yes |
| *FASLG* | 1q24.3 | Autoimmune lymphoproliferative syndrome, type IB | AD | ID | Phenotype MIM number: 601859 | no | no | yes |
| *FAT4* | 4q28.1 | Hennekam-lymphangiectasia-lymphedema syndrome | AR | ID | PMID: 31953710 | no | yes | yes |
| *FCGR3A* | 1q23.3 | CD16 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *FCHO1* | 19p13.11 | FCHO1 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *FCN3* | 1p36.11 | Ficolin 3 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *FERMT1* | 20p12.3 | FERMT1 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *FERMT3* | 11q13.1 | Leukocyte adhesion deficiency, type III | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *FOXN1* | 17q11.2 | T-cell immunodeficiency, congenital alopecia, and nail dystrophy | AR/AD | ID | PMID: 31953710 | no | yes | yes |
| *FOXP3* | Xp11.23 | Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked | XR | ID | PMID: 31953710 | no | yes | yes |
| *FPR1* | 19q13.41 | Localized juvenile periodontitis | AR | ID | PMID: 31953710 | no | yes | no |
| *G6PD* | Xq28 | G6PD deficiency class I | XL | ID | PMID: 31953710 | no | yes | yes |
| *GINS1* | 20p11.21 | Immunodeficiency 55 | AR | ID | PMID: 31953710 | no | yes | no |
| *HAVCR2* | 5q33.3 | T cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency) | AR | ID | PMID: 31953710 | no | yes | no |
| *HELLS* | 10q23.33 | Immunodeficiency-centromeric instability-facial anomalies syndrome 4 | AR | ID | PMID: 31953710 | no | yes | no |
| *HMOX1* | 22q12.3 | Isolated congenital asplenia (ICA) | AR | ID | PMID: 31953710 | no | yes | no |
| *HYOU1* | 11q23.3 | Immunodeficiency 59 and hypoglycemia | AR | ID | PMID: 31953710 | no | yes | no |
| *ICOS* | 2q33.2 | Immunodeficiency, common variable, 1 | AR | ID | PMID: 31953710 | no | yes | no |
| *ICOSLG* | 21q22.3 | ICOSL deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IFIH1* | 2q24.2 | Singleton-Merten syndrome, Aicardi-Goutieres syndrome 7 | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *IFNAR2* | 21q22.11 | Immunodeficiency 45 | AR | ID | PMID: 31953710 | no | yes | no |
| *IFNGR1* | 6q23.3 | Immunodeficiency 27A, mycobacteriosis, AR, Immunodeficiency 27B, mycobacteriosis, AD | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *IFNGR2* | 21q22.11 | Immunodeficiency 28, mycobacteriosis | AR | ID | PMID: 31953710 | no | yes | no |
| *IGHM* | 14q32.33 | μ heavy chain deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IGKC* | 2p11.2 | Kappa chain deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IGLL1* | 22q11.23 | Agammaglobulinemia 2 | AR | ID | PMID: 31953710 | no | yes | no |
| *IKBKB* | 8p11.21 | Immunodeficiency 15A, Immunodeficiency 15B | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *IKBKG* | Xq28 | EDA-ID due to NEMO/IKBKG deficiency | XL | ID | PMID: 31953710 | no | yes | no |
| *IKZF1* | 7p12.2 | Immunodeficiency, common variable, 13 | AD | ID | PMID: 31953710 | no | yes | yes |
| *IL10* | 1q32.1 | IL-10 deficiency | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *IL10RA* | 11q23.3 | IL-10R deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL10RB* | 21q22.11 | IL-10R deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL12B* | 5q33.3 | Immunodeficiency 29, mycobacteriosis | AR | ID | PMID: 31953710 | no | yes | no |
| *IL12RB1* | 19p13.11 | Immunodeficiency 30 | AR | ID | PMID: 31953710 | no | yes | no |
| *IL12RB2* | 1p31.3 | IL-12Rβ2 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL17F* | 6p12.2 | IL-17F deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *IL17RA* | 22q11.1 | Immunodeficiency 51 | AR | ID | PMID: 31953710 | no | yes | no |
| *IL17RC* | 3p25.3 | Candiasis, familial, 9 | AR | ID | PMID: 31953710 | no | yes | no |
| *IL18BP* | 11q13.4 | IL-18BP deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL1RN* | 2q14.1 | Interleukin 1 receptor antagonist deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL21* | 4q27 | Immunodeficiency, common variable, 11 | AR | ID | PMID: 31953710 | no | yes | no |
| *IL21R* | 16p12.1 | Immunodeficiency 56 | AR | ID | PMID: 31953710 | no | yes | no |
| *IL23R* | 1p31.3 | IL-23R deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL2RA* | 10p15.1 | Immunodeficiency 41 with lymphoproliferation and autoimmunity | AR | ID | PMID: 31953710 | no | yes | no |
| *IL2RB* | 22q12.3 | CD122 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL2RG* | Xq13.1 | Combined immunodeficiency, X-linked, moderate, Severe combined immunodeficiency, X-linked | XL | ID | PMID: 31953710 | no | yes | yes |
| *IL36RN* | 2q14.1 | DITRA (Deficiency of IL-36 receptor antagonist) | AR | ID | PMID: 31953710 | no | yes | no |
| *IL6R* | 1q21.3 | IL6 receptor deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL6ST* | 5q11.2 | IL6 signal transducer (IL6ST) deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IL7R* | 5p13.2 | Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type | AR | ID | PMID: 31953710 | no | yes | yes |
| *INO80* | 15q15.1 | INO80 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IRAK1* | Xq28 | IRAK1 deficiency | XL | ID | PMID: 31953710 | no | yes | yes |

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|---|---|---|---|---|---|---|---|---|
| *IRAK4* | 12q12 | IRAK4 deficiency, Invasive pneumococcal disease, recurrent, isolated, 1 | | ID | PMID: 31953710 | no | yes | no |
| *IRF2BP2* | 1q42.3 | Immunodeficiency, common variable, 14 | AD | ID | PMID: 31953710 | no | yes | no |
| *IRF3* | 19q13.33 | IRF3 deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *IRF4* | 6p25.3 | IRF4 haploinsufficiency | AD | ID | PMID: 31953710 | no | yes | yes |
| *IRF7* | 11p15.5 | IRF7 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *IRF8* | 16q24.1 | Immunodeficiency 32A, mycobacteriosis, autosomal dominant, Immunodeficiency 32B, monocyte and dendritic cell deficiency, autosomal recessive | AD/AR | ID | PMID: 31953710 | no | yes | yes |
| *IRF9* | 14q12 | IRF9 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *ISG15* | 1p36.33 | Immunodeficiency 38 | AR | ID | PMID: 31953710 | no | yes | no |
| *ITCH* | 20q11.22 | ITCH deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *ITGB2* | 21q22.3 | Leukocyte adhesion deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *ITK* | 5q33.3 | Lymphoproliferative syndrome 1 | AR | ID | PMID: 31953710 | no | yes | yes |
| *JAK1* | 1p31.3 | Primary immunodeficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *JAK3* | 19p13.11 | SCID, autosomal recessive, T-negative/B-positive type | AR | ID | PMID: 31953710 | no | yes | yes |
| *KDM6A* | Xp11.3 | Kabuki syndrome (type 1 and 2) | XL | ID | PMID: 31953710 | no | yes | yes |
| *KMT2A* | 11q23.3 | KMT2A deficiency | AD | ID | PMID: 31953710 | no | yes | yes |
| *KMT2D* | 12q13.12 | Kabuki syndrome (type 1 and 2) | AD | ID | PMID: 31953710 | no | yes | yes |
| *KRAS* | 12p12.1 | RAS-associated autoimmune leukoproliferative disorder | AD | ID | PMID: 16474405 | no | no | yes |
| *LAT* | 16q13 | Immunodeficiency 52 | AR | ID | PMID: 31953710 | no | yes | no |
| *LCK* | 1p35.2 | Immunodeficiency 22 | AR | ID | PMID: 31953710 | no | yes | no |
| *LIG1* | 19q13.33 | Ligase I deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *LPIN2* | 18p11.31 | Majeed syndrome | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *LRBA* | 4q31.3 | Immunodeficiency, common variable, 8, with autoimmunity | AR | ID | PMID: 31953710 | no | yes | no |
| *MAGT1* | Xq21.1 | Immunodeficiency, X-linked, with magnesium defect, Epstein-Barr virus infection and neoplasia | XR | ID | PMID: 31953710 | no | yes | yes |
| *MALT1* | 18q21.32 | Immunodeficiency 12 | AR | ID | PMID: 31953710 | no | yes | yes |
| *MAP3K14* | 17q21.31 | Primary immunodeficiency with multifaceted aberrant lymphoid immunity | AR | ID | PMID: 31953710 | no | yes | yes |
| *MASP1* | 3q27.3 | 3MC syndrome 1 | AR | ID | PMID: 26454309 | no | no | no |
| *MASP2* | 1p36.22 | MASP2 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *MCM4* | 8q11.21 | MCM4 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *MEFV* | 16p13.3 | Familial Mediterranean fever | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *MOGS* | 2p13.1 | Congenital disorder of glycosylation, type IIb | AR | ID | PMID: 31953710 | no | yes | no |
| *MRTFA* | 22q13.1-q13.2 | Immunodeficiency 66 | AR | ID | PMID: 31953710 | no | yes | no |
| *MS4A1* | 11q12.2 | CD20 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *MSH6* | 2p16.3 | MSH6 deficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *MSN* | Xq12 | Immunodeficiency 50 | XR | ID | PMID: 31953710 | no | yes | no |
| *MTHFD1* | 14q23.3 | Combined immunodeficiency and megaloblastic anemia with or without hyperhomocysteinemia | AR | ID | PMID: 31953710 | no | yes | no |
| *MVK* | 12q24.11 | Mevalonate kinase deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *MYD88* | 3p22.2 | Pyogenic bacterial infections, recurrent, due to MYD88 deficiency | | ID | PMID: 31953710 | no | yes | yes |
| *MYO5A* | 15q21.2 | Griscelli syndrome, type 1 | AR | ID | Phenotype MIM number: 214450 | no | no | no |
| *MYSM1* | 1p32.1 | MYSM1 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *NBAS* | 2p24.3 | Acute liver failure due to NBAS deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *NBN* | 8q21.3 | Nijmegen breakage syndrome, Non-Hodgkin lymphoma, Acute lymphoblastic leukemia (primarily T cell) | AR | ID | PMID: 31953710 | no | yes | yes |
| *NCF1* | 7q11.23 | Chronic granulomatous disease due to deficiency of NCF-1 | AR | ID | PMID: 31953710 | no | yes | no |
| *NCF2* | 1q25.3 | Chronic granulomatous disease due to deficiency of NCF-2 | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *NCF4* | 22q12.3 | Granulomatous disease, chronic, autosomal recessive, cytochrome b-positive, type III | AR | ID | PMID: 31953710 | no | yes | no |
| *NCSTN* | 1q23.2 | Acne inversa, familial 1 | AD | ID | PMID: 31953710 | no | yes | no |
| *NFAT5* | 16q22.1 | NFAT5 haploinsufficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *NFE2L2* | 2q31.2 | Activating de novo mutations in nuclear factor, erythroid 2-like (NFE2L2) | AD | ID | PMID: 31953710 | no | yes | no |
| *NFKB1* | 4q24 | Immunodeficiency, common variable, 12 | AD | ID | PMID: 26279205 | no | no | no |
| *NFKB2* | 10q24.32 | Immunodeficiency, common variable, 10 | AD | ID | PMID: 31953710 | no | yes | yes |
| *NFKBIA* | 14q13.2 | Ectodermal dysplasia and immunodeficiency 2 | AD | ID | PMID: 31953710 | no | yes | yes |
| *NHEJ1* | 2q35 | Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation | | ID | PMID: 31953710 | no | yes | yes |
| *NLRC4* | 2p22.3 | Autoinflammation with infantile enterocolitis | AD | ID | PMID: 31953710 | no | yes | no |
| *NLRP1* | 17p13.2 | Autoinflammation with arthritis and dyskeratosis | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *NLRP12* | 19q13.42 | Familial cold autoinflammatory syndrome 2 | AD | ID | PMID: 31953710 | no | yes | no |
| *NLRP3* | 1q44 | Chronic infantile neurologic cutaneous articular (CINCA) syndrome | AD | ID | PMID: 31953710 | no | yes | no |
| *NOD2* | 16q12.1 | Blau syndrome | AD | ID | PMID: 31953710 | no | yes | no |
| *NSMCE3* | 15q13.1 | Lung disease, immunodeficiency, and chromosome breakage syndrome (LICS) | AR | ID | PMID: 31953710 | no | yes | no |
| *OAS1* | 12q24.13 | OAS1 deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *ORAI1* | 12q24.31 | Immunodeficiency 9 | AR | ID | PMID: 31953710 | no | yes | yes |
| *OSTM1* | 6q21 | Osteopetrosis | AR | ID | PMID: 31953710 | no | yes | no |
| *OTULIN* | 5p15.2 | Otulipenia/ORAS | AR | ID | PMID: 31953710 | no | yes | no |
| *PEPD* | 19q13.11 | Prolidase deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *PGM3* | 6q14.1 | Immunodeficiency 23 | AR | ID | PMID: 31953710 | no | yes | no |
| *PIK3CD* | 1p36.22 | Immunodeficiency 14 | AD | ID | PMID: 31953710 | no | yes | no |
| *PIK3R1* | 5q13.1 | Immunodeficiency 36, Agammaglobulinemia 7 | AD/AR | ID | PMID: 31953710 | no | yes | yes |

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|---|---|---|---|---|---|---|---|---|
| *PLCG2* | 16q23.3 | Autoinflammation, antibody deficiency, and immune dysregulation syndrome | AD | ID | PMID: 31953710 | no | yes | yes |
| *PLEKHM1* | 17q21.31 | Osteopetrosis | AR | ID | PMID: 31953710 | no | yes | no |
| *PMS2* | 7p22.1 | PMS2 deficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *PNP* | 14q11.2 | Immunodeficiency due to purine nucleoside phosphorylase deficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *POLA1* | Xp22.11-p21.3 | X-linked reticulate pigmentary disorder | XL | ID | PMID: 31953710 | no | yes | no |
| *POLD1* | 19q13.3 | Polymerase and deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *POLD2* | 7p13 | Polymerase and deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *POLE* | 12q24.33 | FILS syndrome, IMAGE-I syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *POLE2* | 14q21.3 | Combined immunodeficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *POLR3A* | 10q22.3 | RNA polymerase III deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *POLR3C* | 1q21.1 | RNA polymerase III deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *POLR3F* | 20p11.23 | RNA polymerase III deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *PRF1* | 10q22.1 | Hemophagocytic lymphohistiocytosis, familial, 2 | AR | ID | PMID: 31953710 | no | yes | yes |
| *PRKCD* | 3p21.1 | Autoimmune lymphoproliferative syndrome type III | AR | ID | PMID: 31953710 | no | yes | no |
| *PRKDC* | 8q11.21 | Immunodeficiency 26, with or without neurologic abnormalities | AR | ID | PMID: 31953710 | no | yes | yes |
| *PSEN1* | 14q24.2 | Hidradenitis suppurativa | AD | ID | PMID: 31953710 | no | yes | no |
| *PSENEN* | 19q13.12 | Hidradenitis suppurativa | AD | ID | PMID: 31953710 | no | yes | no |
| *PSMB8* | 6p21.32 | Proteasome-associated autoinflammatory syndrome 1 and digenic forms | AR | ID | PMID: 31953710 | no | yes | no |
| *PSMG2* | 18p11.21 | CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy) | AR | ID | PMID: 31953710 | no | yes | no |
| *PSTPIP1* | 15q24.3 | Pyogenic sterile arthritis, pyoderma gangrenosum, and acne | AD | ID | PMID: 31953710 | no | yes | no |
| *PTEN* | 10q23.31 | PTEN deficiency (LOF) | AD | ID | PMID: 31953710 | no | yes | yes |
| *PTPRC* | 1q31.3-q32.1 | Severe combined immunodeficiency, T cell-negative, B-cell/natural killer-cell positive | AR | ID | PMID: 31953710 | no | yes | yes |

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|---|---|---|---|---|---|---|---|---|
| *RAC2* | 22q13.1 | Neutrophil immunodeficiency syndrome | AD | ID | PMID: 31953710 | no | yes | yes |
| *RAG1* | 11p12 | Omenn syndrome, Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity, Severe combined immunodeficiency, B cell-negative, Combined cellular and humoral immune defects with granulomas | AR | ID | PMID: 31953710 | no | yes | yes |
| *RAG2* | 11p12 | Omenn syndrome, Combined cellular and humoral immune defects with granulomas, Severe combined immunodeficiency, B cell-negative | AR | ID | PMID: 31953710 | no | yes | yes |
| *RANBP2* | 2q13 | Acute necrotizing encephalopathy | AR | ID | PMID: 31953710 | no | yes | no |
| *RASGRP1* | 15q14 | Immunodeficiency 64 | AR | ID | PMID: 31953710 | no | yes | no |
| *RBCK1* | 20p13 | Polyglucosan body myopathy 1 with or without immunodeficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *RECQL4* | 8q24.3 | Baller-Gerold syndrome, RAPADILINO syndrome, Rothmund-Thomson syndrome | AR | ID | PMID: 18716613 | no | no | no |
| *REL* | 2p16.1 | c-Rel deficiency | AR | ID | PMID: 31953710 | no | yes | yes |
| *RELA* | 11q13.1 | RelA haploinsufficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *RELB* | 19q13.32 | RelB deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *RFX5* | 1q21.3 | Bare lymphocyte syndrome, type II, complementation group C, E | AR | ID | PMID: 31953710 | no | yes | no |
| *RFXANK* | 19p13.11 | MHC class II deficiency, complementation group B | AR | ID | PMID: 31953710 | no | yes | no |
| *RFXAP* | 13q13.3 | Bare lymphocyte syndrome, type II, complementation group D | AR | ID | PMID: 31953710 | no | yes | yes |
| *RHOH* | 4p14 | Epidermodysplasia verruciformis, susceptibility to, 4 | AR | ID | PMID: 31953710 | no | yes | no |
| *RIPK1* | 6p25.2 | RIPK1 | AR | ID | PMID: 31953710 | no | yes | yes |
| *RNASEH2A* | 19p13.13 | Aicardi-Goutieres syndrome 4 | AR | ID | PMID: 31953710 | no | yes | no |
| *RNASEH2B* | 13q14.3 | Aicardi-Goutieres syndrome 2 | AR | ID | PMID: 31953710 | no | yes | no |
| *RNASEH2C* | 11q13.1 | Aicardi-Goutieres syndrome 3 | AR | ID | PMID: 31953710 | no | yes | no |
| *RNF168* | 3q29 | RIDDLE syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *RNF31* | 14q12 | HOIP and LUBAC deficiency | AR | ID | PMID: 31953710 | no | yes | no |

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| *RNU4ATAC* | 2q14.2 | Roifman syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *RORC* | 1q21.3 | Immunodeficiency 42 | AR | ID | PMID: 31953710 | no | yes | no |
| *RPSA* | 3p22.1 | Asplenia, isolated congenital | AD | ID | PMID: 31953710 | no | yes | no |
| *SAMHD1* | 20q11.23 | Chilblain lupus 2, Aicardi-Goutières syndrome | AD/AR | ID | PMID: 31953710 | no | yes | yes |
| *SEC61A1* | 3q21.3 | SEC61A1 deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *SEMA3E* | 7q21.11 | CHARGE syndrome | AD | ID | PMID: 31953710 | no | yes | no |
| *SERPING1* | 11q12.1 | Complement component 4, partial deficiency of, Angioedema, hereditary, types I and II | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *SH2D1A* | Xq25 | Lymphoproliferative syndrome | XR | ID | PMID: 31953710 | no | yes | yes |
| *SH3BP2* | 4p16.3 | Cherubism | AD | ID | PMID: 31953710 | no | yes | no |
| *SH3KBP1* | Xp22.12 | SH3KBP1 (CIN85) deficiency | XL | ID | PMID: 31953710 | no | yes | no |
| *SKIV2L* | 6p21.33 | Tricho-Hepato-Enteric Syndrome (THES) | AR | ID | PMID: 31953710 | no | yes | no |
| *SLC29A3* | 10q22.1 | Histiocytosis-lymphadenopathy plus syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *SLC35C1* | 11p11.2 | Congenital disorder of glycosylation, type IIc | AR | ID | PMID: 31953710 | no | yes | no |
| *SLC39A7* | 6p21.32 | SLC39A7 (ZIP7) deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *SLC46A1* | 17q11.2 | Folate malabsorption, hereditary | AR | ID | PMID: 31953710 | no | yes | no |
| *SLC7A7* | 14q11.2 | Lysinuric protein intolerance | AR | ID | PMID: 31953710 | no | yes | yes |
| *SMARCAL1* | 2q35 | Schimke immunoosseous dysplasia | AR | ID | PMID: 31953710 | no | yes | no |
| *SMARCD2* | 17q23.3 | Specific granule defiency 2 | AR | ID | PMID: 31953710 | no | yes | no |
| *SNX10* | 7p15.2 | Osteopetrosis | AR | ID | PMID: 31953710 | no | yes | no |
| *SP110* | 2q37.1 | Hepatic venoocclusive disease with immunodeficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *SPINK5* | 5q32 | Netherton syndrome | AR | ID | PMID: 31953710 | no | yes | no |
| *SPPL2A* | 15q21.2 | SPPL2a deficiency | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *STAT1* | 2q32.2 | Immunodeficiency 31A, 31B, 31C | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *STAT2* | 12q13.3 | Immunodeficiency 44, Pseudo-TORCH syndrome 3 | AR | ID | PMID: 31953710 | no | yes | no |
| *STAT3* | 17q21.2 | Hyper-IgE recurrent infection syndrome, Autoimmune disease, multisystem, infantile onset | AD | ID | PMID: 31953710 | no | yes | yes |
| *STAT5B* | 17q21.2 | Growth hormone insensitivity with immunodeficiency | | ID | PMID: 31953710 | no | yes | yes |
| *STIM1* | 11p15.4 | Stormorken syndrome, Immunodeficiency 10 | AD/AR | ID | PMID: 31953710 | no | yes | yes |
| *STING1* | 5q31.2 | STING-associated vasculopathy, infantile-onsent (SAVI) | AD | ID | PMID: 31953710 | no | yes | no |
| *STK4* | 20q13.12 | T-cell immunodeficiency, recurrent infections, autoimmunity, and cardiac malformations | | ID | PMID: 31953710 | no | yes | no |
| *STX11* | 6q24.2 | Hemophagocytic lymphohistiocytosis, familial, 4 | AR | ID | PMID: 31953710 | no | yes | yes |
| *STXBP2* | 19p13.2 | Hemophagocytic lymphohistiocytosis, familial, 5 | AR | ID | PMID: 31953710 | no | yes | yes |
| *TAP1* | 6p21.32 | Bare lymphocyte syndrome, type I | AR | ID | PMID: 31953710 | no | yes | no |
| *TAP2* | 6p21.32 | Bare lymphocyte syndrome, type I, due to TAP2 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *TAPBP* | 6p21.32 | Bare lymphocyte syndrome, type I | AR | ID | PMID: 31953710 | no | yes | no |
| *TBK1* | 12q14.2 | TBK1 deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *TBX1* | 22q11.21 | DiGeorge syndrome, Velocardiofacial syndrome | AD | ID | PMID: 31953710 | no | yes | yes |
| *TCF3* | 19p13.3 | Agammaglobulinemia 8, autosomal dominant | AD | ID | PMID: 31953710 | no | yes | no |
| *TFRC* | 3q29 | Immunodeficiency 46 | AR | ID | PMID: 31953710 | no | yes | no |
| *TGFBR1* | 9q22.33 | Loeys-Dietz syndrome (TGFBR deficiency) | AD | ID | PMID: 31953710 | no | yes | no |
| *TGFBR2* | 3p24.1 | Loeys-Dietz syndrome (TGFBR deficiency) | AD | ID | PMID: 31953710 | no | yes | no |
| *THBD* | 20p11.21 | Thrombomodulin deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *TICAM1* | 19p13.3 | TRIF deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *TIRAP* | 11q24.2 | TIRAP deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *TLR3* | 4q35.1 | TLR3 deficiency | AD/AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *TMC6* | 17q25.3 | Epidermodysplasia verruciformis | AR | ID | PMID: 31953710 | no | yes | no |
| *TMC8* | 17q25.3 | Epidermodysplasia verruciformis | AR | ID | PMID: 31953710 | no | yes | no |
| *TNFAIP3* | 6q23.3 | Autoinflammatory syndrome, familial, Behcet-like | AD | ID | PMID: 31953710 | no | yes | yes |
| *TNFRSF11A* | 18q21.33 | Osteopetrosis | AR | ID | PMID: 31953710 | no | yes | no |
| *TNFRSF13B* | 17p11.2 | Immunodeficiency, common variable, 2, Immunoglobulin A deficiency 2 | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *TNFRSF13C* | 22q13.2 | BAFF receptor deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *TNFRSF1A* | 12p13.31 | Periodic fever, familial | AD | ID | Phenotype MIM number: 142680 | no | no | no |
| *TNFRSF1A* | 12p13.31 | TNF receptor-associated periodic syndrome (TRAPS) | AD | ID | PMID: 31953710 | no | yes | no |
| *TNFRSF4* | 1p36.33 | Immunodeficiency 16 | AR | ID | PMID: 31953710 | no | yes | no |
| *TNFRSF9* | 1p36.23 | CD137 deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *TNFSF11* | 13q14 | Osteopetrosis | AR | ID | PMID: 31953710 | no | yes | no |
| *TNFSF12* | 17p13.1 | TWEAK deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *TOP2B* | 3p24.2 | Hoffman syndrome/TOP2B deficiency | AD | ID | PMID: 31953710 | no | yes | no |
| *TPP2* | 13q33.1 | Tripeptidyl-peptidase II deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *TRAC* | 14q11.2 | TCRa deficiency | AR | ID | PMID: 31953710 | no | yes | no |
| *TRAF3* | 14q32.32 | TRAF3 deficiency | AD | ID | PMID: 31953710 | no | yes | yes |
| *TRAF3IP2* | 6q21 | Candidiasis, familial, 8 | AR | ID | PMID: 31953710 | no | yes | no |
| *TREX1* | 3p21.31 | Aicardi-Goutieres syndrome 1, dominant and recessive | AD/AR | ID | PMID: 31953710 | no | yes | no |
| *TRIM22* | 11p15.4 | TRIM22 | AR | ID | PMID: 31953710 | no | yes | no |
| *TRNT1* | 3p26.2 | Sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay | AR | ID | PMID: 31953710 | no | yes | no |
| *TTC37* | 5q15 | Tricho-Hepato-Enteric Syndrome (THES) | AR | ID | PMID: 31953710 | no | yes | no |
| *TTC7A* | 2p21 | Gastrointestinal defects and immunodeficiency syndrome | AR | ID | PMID: 31953710 | no | yes | no |

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|---|---|---|---|---|---|---|---|---|
| *TYK2* | 19p13.2 | Immunodeficiency 35 | AR | ID | PMID: 31953710 | no | yes | yes |
| *UNC119* | 17q11.2 | Immunodeficiency 13 | AR | ID | PMID: 22184408 | no | no | no |
| *UNC13D* | 17q25.1 | Hemophagocytic lymphohistiocytosis, familial, 3 | AR | ID | PMID: 31953710 | no | yes | yes |
| *UNC93B1* | 11q13.2 | Encephalopathy, acute, infection-induced (herpes-specific), susceptibility to, 1 | | ID | PMID: 31953710 | no | yes | no |
| *UNG* | 12q24.11 | Immunodeficiency with hyper-IgM, type 5 | AR | ID | PMID: 31953710 | no | yes | no |
| *USP18* | 22q11.21 | Pseudo-TORCH syndrome 2 | AR | ID | PMID: 31953710 | no | yes | no |
| *WDR1* | 4p16.1 | Immunodeficiency/autoinflammatory syndrome with aberrant morphology and function of myeloid cells | | ID | PMID: 31953710 | no | yes | no |
| *WIPF1* | 2q31.1 | Wiskott-Aldrich syndrome 2 | | ID | PMID: 31953710 | no | yes | yes |
| *XIAP* | Xq25 | Lymphoproliferative syndrome, X-linked, 2 | XR | ID | PMID: 31953710 | no | yes | yes |
| *ZAP70* | 2q11.2 | Immunodeficiency 48, Autoimmune disease, multisystem, infantile-onset, 2 | AR | ID | PMID: 31953710 | no | yes | yes |
| *ZBTB24* | 6q21 | Immunodeficiency-centromeric instability-facial anomalies syndrome 2 | AR | ID | PMID: 31953710 | no | yes | no |
| *ZNF341* | 20q11.22 | Hyper-IgE recurrent infection syndrome 3, autosomal recessive | AR | ID | PMID: 31953710 | no | yes | no |
| *AKT1* | 14q32.33 | Cowden syndrome 6 | | Cancer predisposition | Phenotype MIM number: 615109 | no | no | no |
| *ANKRD26* | 10p12.1 | ANKRD26-related thrombocytopenia | AD | Cancer predisposition | PMID: 29927566 | yes | no | yes |
| *APC* | 5q22.2 | Familial adenomatous polyposis | AD | Cancer predisposition | PMID: 11135435 | no | no | yes |
| *ASXL1* | 20q11.1 | Bohring-Opitz syndrome | AD | Cancer predisposition | PMID: 21706002 | no | no | yes |
| *ATG2B* | 14q32.2 | Predisposition to familial myeloid malignancie | | Cancer predisposition | PMID: 27308616 | no | no | no |
| *ATR* | 3q23 | Cutaneous telangiectasia and cancer syndrome | AD | Cancer predisposition | PMID: 22341969 | no | no | yes |
| *BAP1* | 3p21.1 | Tumor predisposition syndrome | AD | Cancer predisposition | Phenotype MIM number: 614327 | no | no | no |
| *BARD1* | 2q35 | Familial cancer of breast | AD | Cancer predisposition | PMID: 15342711 | no | no | yes |
| *BMPR1A* | 10q23.2 | Juvenile polyposis syndrome | AD | Cancer predisposition | PMID: 11381269 | no | no | yes |
| *CBL* | 11q23.3 | Juvenile myelomonocytic leukemia, Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia | AD | Cancer predisposition | Phenotype MIM number: 607785 | no | no | yes |

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|---|---|---|---|---|---|---|---|---|
| *CDC73* | 1q31.2 | Hyperparathyroidism-jaw tumor syndrome | AD | Cancer predisposition | PMID: 12434154 | no | no | yes |
| *CDH1* | 16q22.1 | Hereditary diffuse gastric cancer, Familial cancer of breast | AD | Cancer predisposition | 9537325, 17660459 | no | no | yes |
| *CDK4* | 12q14.1 | Melanoma, cutaneous malignant, 3 | AD | Cancer predisposition | PMID: 21051013 | no | no | no |
| *CDKN2A* | 9p21.3 | Pancreatic cancer/melanoma syndrome | AD | Cancer predisposition | PMID: 7666917 | no | no | yes |
| *CEBPA* | 19q13.1 | CEBPA-Associated Familial Acute Myeloid Leukemia | AD | Cancer predisposition | PMID: 15575056 | yes | no | yes |
| *CHEK2* | 22q12.1 | Li-Fraumeni syndrome | AD | Cancer predisposition | PMID: 10617473 | no | no | yes |
| *CREBBP* | 16p13.3 | Rubinstein-Taybi syndrome | AD | Cancer predisposition | PMID: 9294190 | no | no | yes |
| *DDX41* | 5q35.3 | Familial myeloproliferative/lymphoproliferative neoplasms | AD | Cancer predisposition | PMID: 25920683 | yes | no | yes |
| *DICER1* | 14q32.13 | Pleuropulmonary blastoma, Rhabdomyosarcoma, embryonal, 2 | AD | Cancer predisposition | Phenotype MIM number: 180295 | no | no | no |
| *EP300* | 22q13.2 | Rubinstein-Taybi syndrome | AD | Cancer predisposition | PMID: 15706485 | no | no | yes |
| *EPCAM* | 2p21 | Colorectal cancer, hereditary nonpolyposis, type 8 | | Cancer predisposition | Phenotype MIM number: 613244 | no | no | no |
| *ERBB3* | 12q13.2 | Erythroleukemia, familial, susceptibility to | AD | Cancer predisposition | Phenotype MIM number: 133180 | no | no | no |
| *ERCC6* | 10q11.23 | Lung cancer, susceptibility to | AD | Cancer predisposition | Phenotype MIM number: 211980 | no | no | yes |
| *ETV6* | 12p13.2 | Thrombocytopenia 5 | AD | Cancer predisposition | PMID: 25581430 | yes | no | yes |
| *EZH2* | 7q36.1 | Weaver syndrome | AD | Cancer predisposition | PMID: 22177091 | no | no | yes |
| *FH* | 1q43 | Leiomyomatosis and renal cell cancer | AD | Cancer predisposition | Phenotype MIM number: 150800 | no | no | no |
| *FLCN* | 17p11.2 | Birt-Hogg-Dube syndrome | AD | Cancer predisposition | PMID: 28970150 | no | no | no |
| *GALNT12* | 9q22.33 | Colorectal cancer, susceptibility to, 1 | | Cancer predisposition | Phenotype MIM number: 608812 | no | no | no |
| *GREM1* | 15q13.3 | Predisposition to colorectal cancer | | Cancer predisposition | PMID: 30584801 | no | no | no |
| *GSKIP* | 14q32.2 | Predisposition to familial myeloid malignancie | | Cancer predisposition | PMID: 27308616 | no | no | no |
| *HLTF* | 3q24 | DNA damage accumulation in familial MDS | | Cancer predisposition | PMID: 30696947 | no | no | no |
| *HOXB13* | 17q21.32 | Prostate cancer, hereditary, 9 | | Cancer predisposition | Phenotype MIM number: 6610997 | no | no | no |

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|---|---|---|---|---|---|---|---|---|
| *HRAS* | 11p15.5 | Costello syndrome | AD | Cancer predisposition | PMID: 16170316 | no | no | yes |
| *KDM1A* | 1p36.12 | Susceptibility to multiple myeloma | | Cancer predisposition | PMID: 29559475 | no | no | no |
| *KIT* | 4q12 | Gastrointestinal stromal tumor, familial | | Cancer predisposition | Phenotype MIM number: 606764 | no | no | yes |
| *LAPTM5* | 1p35.2 | Familial Waldenström macroglobulinemia | | Cancer predisposition | PMID: 26903547 | no | no | no |
| *MAX* | 14q23.3 | Pheochromocytoma, susceptibility to | AD | Cancer predisposition | Phenotype MIM number: 171300 | no | no | no |
| *MBD4* | 3q21.3 | Predisposition to uveal melanoma | | Cancer predisposition | PMID: 32239153 | no | no | no |
| *MC1R* | 16q24.3 | Melanoma, cutaneous malignant, 5 | | Cancer predisposition | Phenotype MIM number: 613099 | no | no | no |
| *MEN1* | 11q13.1 | Multiple endocrine neoplasia 1 | AD | Cancer predisposition | PMID: 25099597 | no | no | no |
| *MET* | 7q31.2 | Papillary renal cell carcinoma | | Cancer predisposition | PMID: 9140397 | no | no | yes |
| *MITF* | 3p13 | Melanoma, cutaneous malignant, susceptibility to, 8 | | Cancer predisposition | Phenotype MIM number: 614456 | no | no | no |
| *MLH1* | 3p22.2 | Hereditary non-polyposis colon cancer | | Cancer predisposition | PMID: 7903889 | no | no | yes |
| *MSH2* | 2p21-p16 | Hereditary nonpolyposis colon cancer, type1 | AD | Cancer predisposition | PMID: 8252616 | no | no | yes |
| *MST1R* | 3p21.31 | Nasopharyngeal carcinoma, susceptibility to, 3 | AD | Cancer predisposition | Phenotype MIM number: 617075 | no | no | yes |
| *MUTYH* | 1p34.1 | Familial adenomatous polyposis 2 | AR | Cancer predisposition | PMID: 12393807 | no | no | yes |
| *NF1* | 17q11.2 | Neurofibromatosis, type 1, Juvenile myelomonocytic leukemia | AD | Cancer predisposition | PMID: 9639526 | no | no | yes |
| *NF2* | 22q12.2 | Neurofibromatosis, type 2, predisposition to central and peripheral nervous system tumors (meningiomas, schwannomas, ependymomas), subcutaneous tumors | AD | Cancer predisposition | Phenotype MIM number: 101000 | no | no | no |
| *PAX5* | 9p13.2 | B-cell acute lymphoblastic leukemia-3 | | Cancer predisposition | PMID: 24013638 | no | no | yes |
| *PDGFRA* | 4q12 | Gastrointestinal stromal tumor/GIST-plus syndrome, somatic or familial | | Cancer predisposition | Phenotype MIM number: 175510 | no | no | yes |
| *PIK3CA* | 3q26.32 | Cowden syndrome 5 | | Cancer predisposition | Phenotype MIM number: 615108 | no | no | no |
| *POT1* | 7q31.33 | Glioma susceptibility 9, Melanoma, cutaneous malignant, susceptibility to, 10 | AD | Cancer predisposition | Phenotype MIM number: 616568 | no | no | yes |
| *PTCH1* | 9q22.32 | Basal cell nevus syndrome, Holoprosencephaly 7 | AD | Cancer predisposition | Phenotype MIM number: 109400 | no | no | no |

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|---|---|---|---|---|---|---|---|---|
| *PTPN11* | 12q24.13 | Noonan syndrome | AD | Cancer predisposition | PMID: 11704759 | no | no | yes |
| *RAD51D* | 17q12 | Breast-ovarian cancer, familial, susceptibility to, 4 | | Cancer predisposition | Phenotype MIM number: 614291 | no | no | no |
| *RB1* | 13q14.2 | Retinoblastoma | AD | Cancer predisposition | PMID: 2895471 | no | no | yes |
| *RBBP6* | 16p12.1 | Predisposition to myeloproliferative neoplasms | ? | Cancer predisposition | PMID: 26574608 | no | no | no |
| *RET* | 10q11.21 | Medullary thyroid carcinoma, Multiple endocrine neoplasia IIA, IIB, Pheochromocytoma | AD | Cancer predisposition | Phenotype MIM number: 155240 | no | no | no |
| *RUNX1* | 21q22.12 | Familial platelet disorder with associated myeloid malignancy | AD | Cancer predisposition | PMID: 11830488 | yes | no | yes |
| *SMARCA4* | 19p13.2 | rhabdoid tumor predisposition syndrome-2 | AD | Cancer predisposition | Phenotype MIM number: 613325 | no | no | no |
| *SDHA* | 5p15.33 | Paragangliomas 5 | AD | Cancer predisposition | Phenotype MIM number: 614165 | no | no | no |
| *SDHAF2* | 11q12.2 | Paragangliomas 2 | AD | Cancer predisposition | Phenotype MIM number: 601650 | no | no | no |
| *SDHB* | 1p36.13 | Gastrointestinal stromal tumor, Paragangliomas 4, Pheochromocytoma | AD | Cancer predisposition | Phenotype MIM number: 115310 | no | no | no |
| *SDHC* | 1q23.3 | Gastrointestinal stromal tumor, Paragangliomas 3 | AD | Cancer predisposition | Phenotype MIM number: 605373 | no | no | no |
| *SDHD* | 11q23.1 | Paragangliomas 1, with or without deafness, Pheochromocytoma | AD | Cancer predisposition | Phenotype MIM number: 171300 | no | no | no |
| *SETBP1* | 18q12.3 | Schinzel-Giedion midface retraction syndrome | AD | Cancer predisposition | PMID: 20436468 | no | no | yes |
| *SH2B3* | 12q24.12 | Predisposition to acute lymphoblastic leukemia | | Cancer predisposition | PMID: 23908464 | no | no | yes |
| *SMAD4* | 18q21.2 | Juvenile polyposis syndrome | AD | Cancer predisposition | PMID: 9545410 | no | no | yes |
| *SMARCA4* | 19p13.2 | Rhabdoid tumor predisposition syndrome 2 | AD | Cancer predisposition | PMID: 20137775 | no | no | yes |
| *SMARCB1* | 22q11.23 | Rhabdoid tumor predisposition syndrome 1 | AD | Cancer predisposition | PMID: 10521299 | no | no | yes |
| *SOS1* | 2p22.1 | Noonan syndrome 4 | AD | Cancer predisposition | PMID: 610733 | no | no | yes |
| *STK11* | 19p13.3 | Peutz-Jeghers syndrome | AD | Cancer predisposition | Phenotype MIM number: 175200 | no | no | yes |
| *TERF2IP* | 16q23.1 | Familial chronic lymphocytic leukemia | | Cancer predisposition | PMID: 27528712 | no | no | no |
| *TMEM127* | 2q11.2 | Pheochromocytoma, susceptibility to | AD | Cancer predisposition | Phenotype MIM number: 171300 | no | no | no |
| *VHL* | 3p25.3 | von Hippel-Lindau syndrome | AD | Cancer predisposition | PMID: 8493574 | no | no | yes |

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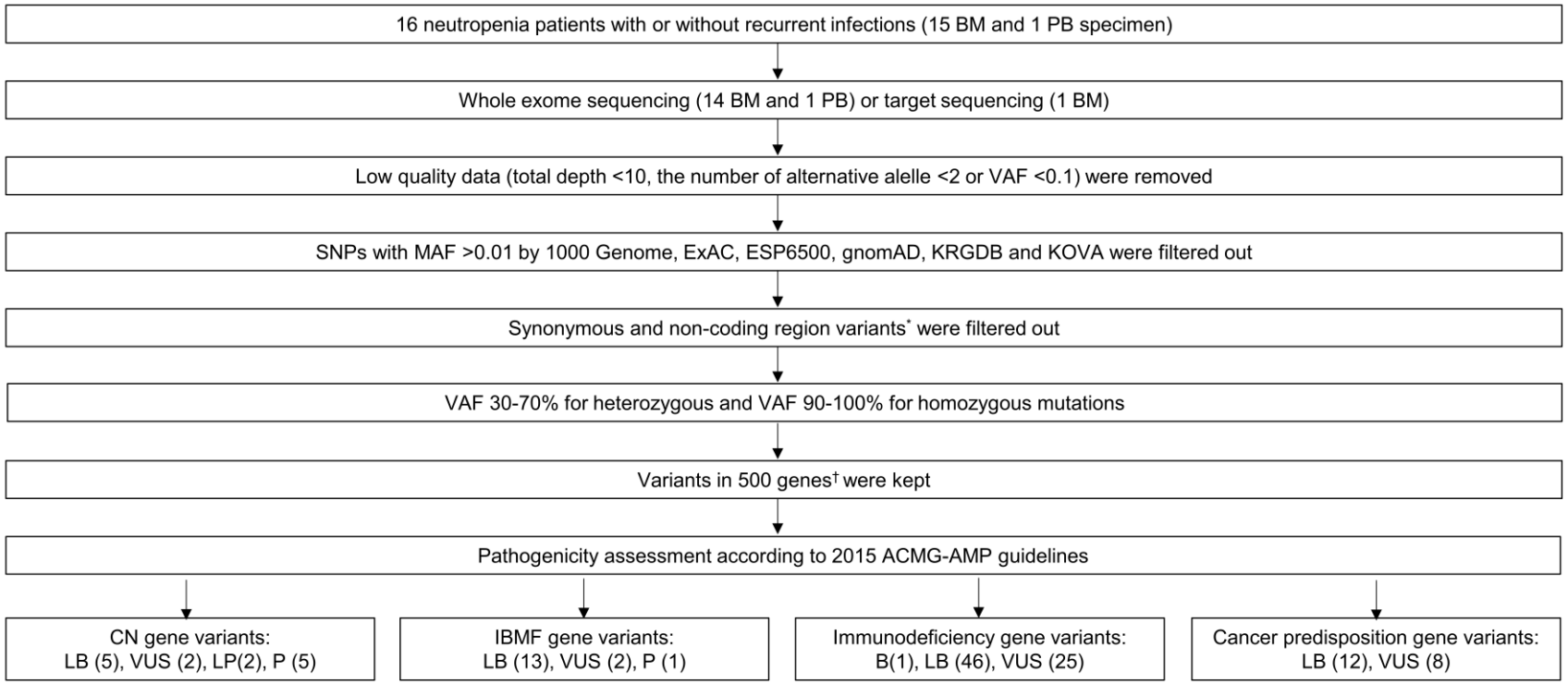
|---|---|---|---|---|---|---|---|---|
| *WRN* | 8p12 | Werner syndrome, Exocrine pancreatic cancer | AR | Cancer predisposition | PMID: 20657174 | no | no | no |
| *WT1* | 11p13 | Wilms tumor, type 1 | AD | Cancer predisposition | PMID: 15150775 | no | no | yes |

*Genes related to CN or IBMF introduced by WHO (WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th Edition)
†Immunodeficiency-related genes reported by IUIS (J Clin Immunol. 2020 Jan;40(1):24-64)
‡Targeted sequencing using an in-house panel of 507 genes was performed on one patient (P-08).
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; IBMF, inherited bone marrow failure; IUIS, International Union of Immunological Societies; WHO, World Health Organization; XR, X-linked recessive.

## 2.8. Variant analysis strategies

Low-quality data with a total depth of <10, the number of reads with alternative allele of <2 or variant allele frequency <0.1 were removed. Variants with minor allele frequency of >0.01 were filtered out based on the 1000 Genome, Exome Aggregation Consortium, Exome Sequencing Project v. 6500, Genome Aggregation Database, Korean Reference Genome Database and Korean Variant Archive. Synonymous and non-coding region variants were also eliminated while invariant splice site variants which are located on ±2 base position from exons were kept. Variant allele frequencies of 30%–70% and 90%–100% were considered as indicative of candidate heterozygous and homozygous variants, respectively. A total of 500 genes were used for filtering in candidate variants: 29 genes known to cause CN, 55 genes related to IBMF, 339 genes associated with immunodeficiency and 77 cancer predisposition genes (**Table 2**). Pathogenicity was assessed according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines [34] (**Figure 5**).




*invariant splice site variants which are located in ±2 base position from exons were kept.
†Refer to Table 2.

**Figure 5. Strategies for whole exome or targeted sequencing variant analysis to search for disease-causing variants in 16 neutropenia**

**patients.** B, benign; BM, bone marrow; CN, congenital neutropenia; IBMF, inherited bone marrow failure; LB, likely benign; LP, likely pathogenic; MAF, minor allele frequency; PB, peripheral blood; SNP, single nucleotide polymorphism; VAF, variant allele frequency; VUS, variant of unknown significance; WES, whole-exome sequencing.

## 2.9. Copy-number variant analysis

CNV analysis of the 15 patients who underwent WES was conducted using Nexus Copy Number (version 10.0, BioDiscovery). A reference file was made by MUltiScale BAM Reference Builder. Using BAM files of the 4 male patients with *ELANE* pathogenic mutations as controls, CNV analysis of the other 11 patients was carried out. A total of 3,997 autosomal and sex-chromosomal CNVs, which included copy number gain, copy number loss, high copy number gain and homozygous copy loss, were called automatically by using pre-set thresholds provided by the software. We used strict probe median values for filtering in the candidate CNVs (**Figure 6**).

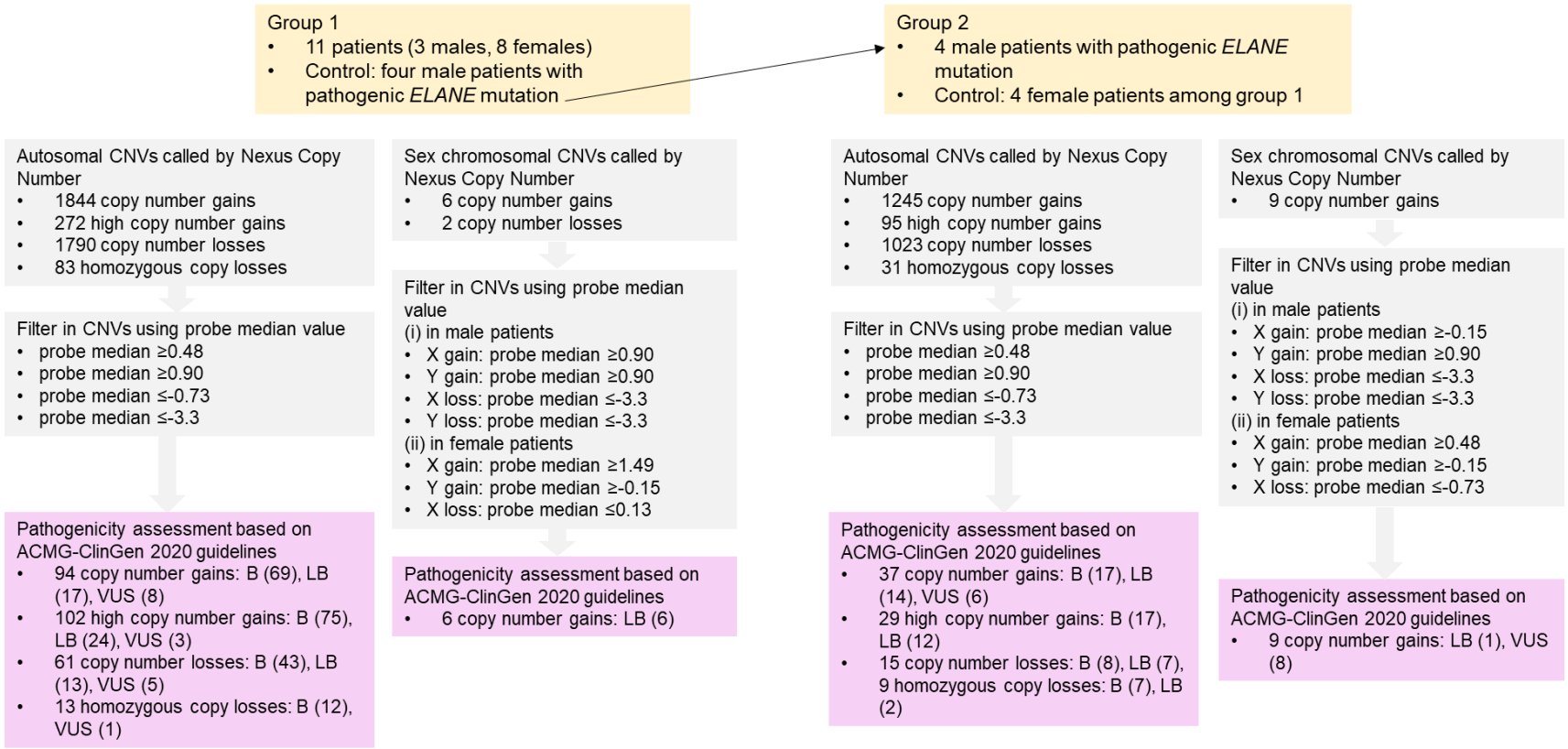



**Figure 6. CNV analysis strategies in 15 congenital neutropenia patients who underwent WES.** B, benign; CNV, copy-number variant; LB, likely benign; LP, likely pathogenic; VUS, variant of unknown significance; WES, whole-exome sequencing.

Consequently, 100 copy number gains, 63 copy number losses, 102 high copy number gains and 13 homozygous losses in autosomal and sex chromosomes were detected. The pathogenicity of each CNV was assessed according to the American College of Medical Genetics and Genomics and the Clinical Genome Resource guidelines [35]. Conversely, BAM files of 4 female patients (P-02, P-04, P-06 and P-07) were used as controls to analyze the CNVs of the 4 patients with *ELANE* pathogenic mutations. Using the same methods as above, 46 copy number gains, 15 copy number losses, 29 high copy number gains and 9 homozygous losses in autosomal and sex chromosomes were detected **(Figure 6**). In the case of suspected LOH, manual inspection of the B-allele frequency plots of the chromosomal region was performed.

## 2.10. Statistical analysis

Continuous data were presented as medians and interquartile ranges (IQRs). For comparisons of continuous variables, Mann–Whitney and Kruskal–Wallis tests were performed. Chi-square test was used for comparisons of non-continuous variables between groups. Correlation analysis was carried out using Spearman's correlation. Statistical significance was defined as $P$ <0.05. The SPSS version 25.0 software program (SPSS Inc., Chicago, IL, USA), GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA) and R package version 4.0.1 were used.

# 3. Results

## 3.1. Patients

The median age at the initial presentation of neutropenia was 7.1 months (IQR, 3.8–15.3) and the median age when an initial BM exam was performed was 11.7 months (IQR, 6.8–20.9). The male-to-female ratio was 1:1. Seven (43.8%) patients had a family history of cancer or recurrent infections. Six (37.5%) patients had organomegaly: hepatomegaly in 3, splenomegaly in 1 and hepatosplenomegaly in 2 patients. Fourteen (87.5%) patients experienced infectious complications and half of them suffered from severe infections. Five (31.3%) patients displayed extra-hematopoietic abnormalities in central nervous system, heart and other organs. Permanent and intermittent neutropenia was found in 5 (31.3%) and 11 (68.8%) patients, respectively. Neutropenia was severe in 15 patients (93.8%) and moderate in 1 patient (6.3%). No one exhibited a cyclic pattern of neutropenia. Filgrastim (Grasin; Jeil Pharm, Seoul, Korea) or lenograstim (Neutrogin; Chungai, Seoul, Korea) was administered to 12 (75.0%) patients. Five out of 12 (41.7%) patients responded to G-CSF, while 7 (58.3%) did not. One of the G-CSF responder (P-08) became a G-CSF non-responder later. Five (31.3%) patients underwent allogeneic peripheral blood stem cell transplantation (PBSCT): 4 unrelated PBSCT (uPBSCT) and one haploidentical PBSCT (hPBSCT) from father. Four out of 5 (80.0%) patients had successful PBSCT while one patient (P-05) died despite two successive uPBSCT (**Table 3**). Alternatively, 3 patients were observed without any treatment. No patients evolved to MDS or AML during the follow-up period (median, 48.6 months; IQR, 20.9–72.7).

## Table 3. Clinical, histologic, cytogenetic and molecular characteristics of 16 neutropenia patients

| P | Age* | Hb (g/dl) | WBC ($\times 10^9$/l) | PLT ($\times 10^9$/l) | ANC ($\times 10^9$/l) | Neutropenia | Recurrent infection | Extra-hematopoietic features | G-CSF | G-CSF response | PBSCT | IgG/A/M (mg/dl) | Cellularity (%) | Maturation arrest† | Myelo-kathexis† | MPO (%)‡ | MPO grade‡ | Likely pathogenic or pathogenic Variants§ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 01 | 16 | 13.7 | 7000 | 305 | 146 | Intermittent | Yes | None | Grasin 75mcg × 9 for 1341 days | No | No | N/A | 91-100 | Band stage | None | 30.1 | 1 | None |
| 02 | 18 | 11.9 | 11530 | 142 | 189 | Intermittent | No | None | Grasin 75mcg × 2 for 3 days | Yes | No | N/A | 81-90 | Band stage | None | 46.2 | 2 | None |
| 03 | 0.5 | 8.3 | 10340 | 565 | 0 | Permanent | Yes | High arched palate | Grasin 75mcg × 13 for 24 days | No | No | 1570/85/215 | 61-70 | Myelocyte stage | None | N/A | N/A | *ELANE* (NM_001972.2):c.452G>A, p.(C151Y), heterozygous |
| 04 | 8 | 10.1 | 9190 | 457 | 254 | Intermittent | Yes | None | Grasin 75mcg × 11 for 428 days | Yes | No | N/A | 91-100 | Band stage | None | 51.6 | 3 | None |
| 05 | 3 | 12.4 | 5590 | 244 | 102 | Permanent | Yes | None | N/A | N/A | uPBSCT x2‖ | 1074/183/62 | 81-90 | N/A | N/A | 12.6 | 0 | *ELANE* (NM_001972.2):c.640G>A, p.(G214R), heterozygous |
| 06 | 18 | 11.2 | 2300 | 140 | 125 | Intermittent | Yes | None | Neutrogin 50mcg × 2 for 2 days | No | No | N/A | 41-50 | None | None | 38.5 | 3 | None |
| 07 | 10 | 11.3 | 5350 | 382 | 0 | Intermittent | Yes | None | N/A | N/A | No | N/A | 91-100 | Band stage | None | 47.7 | 3 | None |
| 08 | 4 | 13.0 | 2950 | 280 | 0 | Permanent | Yes | Incomplete cleft lip, inguinal hernia | Grasin 75mcg × 13 for 410 days | Yes¶ | uPBSCT | 282/19/59 | 91-100 | None | Yes | 44.4 | 2 | *CXCR4* (NM_003467.2)c.978_979del, p.(G323fs), heterozygous |
| 09 | 14 | 10.9 | 4110 | 252 | 0 | Intermittent | Yes | None | Grasin 75mcg × 4 for 302 days | Yes | No | N/A | 71-80 | Band stage | None | 58.9 | 3 | None |
| 10 | 4 | 10.8 | 7460 | 364 | 64 | Intermittent | Yes | Lipomeningomyelocele, pes calcaneous | Grasin 75mcg × 2 for 11 days | Yes | No | N/A | 71-80 | None | None | 20.1 | 0 | None |
| 11 | 0.3 | 10.0 | 8660 | 153 | 0 | Permanent | Yes | None | Grasin 75mcg × 88 for 137 days | No | hPBSCT x2 | 1023/71/52 | 71-80 | Promyelocyte stage | None | 45.5 | 3 | *ELANE* ((NM_001972.2):c.640G>A, p.(G214R), heterozygous |
| 12 | 10 | 11.2 | 5180 | 227 | 825 | Intermittent | Yes | None | N/A | N/A | No | N/A | 71-80 | None | None | 39.4 | 3 | None |
| 13 | 28 | 11.5 | 1430 | 204 | 1301 | Intermittent | Yes | ASD, Crohn's disease, growth retardation, JRA, PTC, nephrocalcinosis | Neutrogin 150mcg × 7 for 11 days<br>Grasin 150mcg × 316 for 3180 days | No | No | 2253/231/143 | | None | Yes | 46.5 | 1 | *G6PC3* (NM_138387.3):c.214delA, p.(K72fs), homozygous |
| 14 | 48 | 11.3 | 3320 | 155 | 958 | Intermittent | Yes | ASD, Crohn's disease, growth retardation, prominent skin vessels, testicular microlithiasis, clinodactyly of both 5th fingers | Neutrogin 100mcg × 14 for 75 days<br>Grasin 150mcg × 316 for 3095 days | No | uPBSCT | 1362/139/59 | 71-80 | None | Yes | 40.4 | 1 | *G6PC3* (NM_138387.3):c.214delA, p.(K72fs), homozygous |
| 15 | 1 | 10.5 | 10090 | 292 | 796 | Permanent | Yes | None | Grasin 75mcg × 19 for 115 days | No | uPBSCT | 1283/89/89 | 81-90 | Promyelocyte stage | None | 25.2 | 1 | *ELANE* (NM_001972.2:c.608G>A, p.(G203D), heterozygous |
| 16 | 3 | 6.7 | 5480 | 40 | 1064 | Intermittent | No | None | N/A | N/A | No | N/A | N/A | None | None | N/A | N/A | None |

[*] Age at initial presentation of neutropenia
[†] One patient with diluted BM aspiration in which reliable differential count could not be made was excluded.
[‡] Two patients were not included due to inadequate BM section quality or retrospectively unavailable BM paraffin block for MPO stain.
[§] Only likely pathogenic or pathogenic variants are documented in this table. Information on all the variants detected including VUS is displayed in Table S3.
[‖] One out of 5 (20.0%) who underwent PBSCT died despite two successive uPBSCT.
[¶] One patient (P-08) initially responded to G-CSF but then became a non-responder.
[#] Haploidentical PBSCT from father
Abbreviations: ANC, absolute neutrophil count; ASD, atrial septal defect; BM, bone marrow; G-CSF, granulocyte-colony stimulating factor; Hb, hemoglobin; hPBSCT, haploidentical peripheral blood stem cell transplantation; JRA, juvenile rheumatoid arthritis; M:E, myeloid to erythroid; MPO, myeloperoxidase; N/A, not applicable; P, patient; PBSCT, peripheral blood stem cell transplantation; PLT, platelet; PTC, papillary thyroid cancer; uPBSCT, unrelated peripheral blood stem cell transplantation; WBC, white blood cell.

## 3.2. Laboratory results

Median CBC values were as follows: hemoglobin 11.2 g/dl (IQR, 10.2–11.8), white blood cell count $5.54\times10^9$/l (IQR, 3.52–9.06) and platelet level $248\times10^9$/l (IQR, 154–349). Median ANC was $0.07\times10^9$/l (IQR, 0.00–0.31), while median absolute monocyte count was $0.56\times10^9$/l (IQR, 0.33–0.89). Median absolute lymphocyte count was $4.76\times10^9$/l (IQR, 2.66–6.83) and median absolute eosinophil count was $0.16\times10^9$/l (IQR, 0.09–0.45). Monocytosis was observed in 2 patients (P-03 and P-11), while eosinophilia was not detected based on the reference range for each patient's age.

Ig levels were retrospectively available only in 7 (43.8%) patients. Median IgG and IgM levels were within the reference range (IgG, 1362 mg/dl, IQR 1179–1797; IgM, 62 mg/dl, IQR 59–116), while IgA was slightly reduced (median 89 mg/dl, IQR 78–161). One patient (P-08) showed decreased levels of both IgG and IgA while two patients (P-11 and P-15) had slightly decreased level of IgA compared to reference range (**Table 3**).

## 3.3. Bone marrow histology

BM of the 16 patients had a median myeloid-to-erythroid (M:E) ratio of 1.9 (IQR, 1.2–3.7) and cellularity of 85% (IQR, 75–90). The BM aspirate of one patient (P-08) revealed dysplastic neutrophils with pyknotic lobes with long filaments and hypolobation. Maturation arrest of granulopoiesis was detected in 8 out of 15 (53.3%) patients whose BM aspirates were of good quality for the assessment. Three (20.0%) of the 15 patients presented maturation arrest at the promyelocyte or myelocyte stage, while in 5 (33.3 %) patients maturation block was observed at the band stage. Myelokathexis was noted in 3 (20.0%) of the 15 patients. No BM fibrosis or histiocytes with hemophagocytic activity were observed in any of the patients.

Median percentage of MPO-positive cells in the 14 patients for whom BM biopsy specimens of adequate quality were available was 42.4% (IQR, 32.2–46.5). The MPO grade was as follows: grade 0 (n = 2, 14.3%), grade 1 (n = 4, 28.6%), grade 2 (n = 2, 14.3%) and grade 3 (n = 6, 42.9%). There was a tendency toward a positive correlation between the MPO grade and the percentage of MPO-positive cells, though it was not statistically significant ($P$ = 0.086). No distinct association between the MPO grade and M:E ratio was observed ($P$ = 0.477) (**Figure 7**).

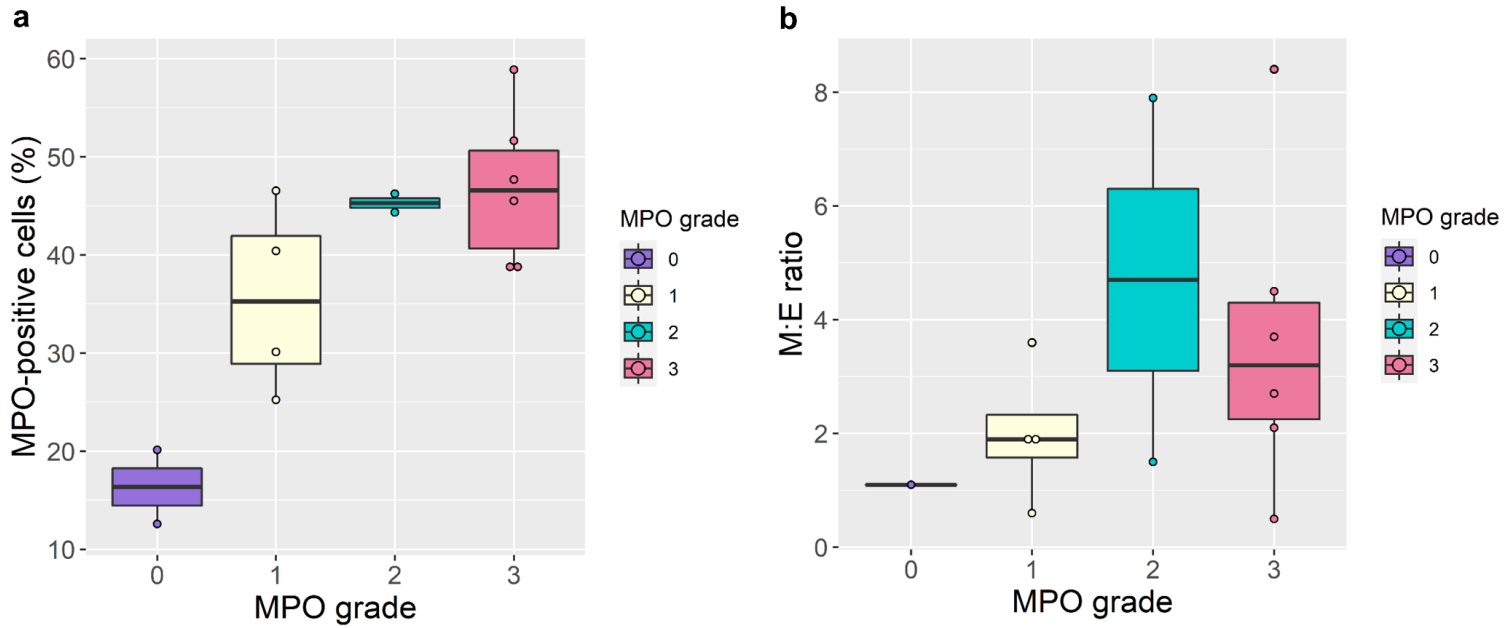



**Figure 7. Distributions of MPO-positive cells analyzed by ImageJ and M:E ratio according to MPO grade.** (a) A tendency toward positive correlation between MPO grade and the percentage of MPO-positive cells ($P$ = 0.086). (b) The absence of distinct association between MPO grade and M:E ratio ($P$ = 0.477). M:E, myeloid-to-erythroid; MPO, myeloperoxidase.

## 3.4. Cytogenetics

Most patients (n = 15, 93.8%) had a normal karyotype, whereas one patient (P-16) carried 46,XX,add(14)(p13).

## 3.5. Results of whole exome sequencing and targeted sequencing

A total of 102 variants in genes related to CN, IBMF, or immunodeficiency were detected in the 16 patients. One benign, 64 likely benign, 29 variants of unknown significance (VUS), 2 likely pathogenic and 6 pathogenic variants were identified. Pathogenic variants in CN-related genes included *ELANE* (NM_001972.2):c.640G>A, p.(G214R) in 2 patients, *G6PC3* (NM_138387.3):c.214delA, p.(K72fs) in 2 brothers, which was a novel variant, and *CXCR4* (NM_003467.2):c.966_967del, p.(R326fs) in 1 patient, which was previously reported [23]. A heterozygous pathogenic variant of *FANCI* (NM_001113378.1:c.3172G>T, p.(E1058X)) was identified in one patient. Likely pathogenic variants in *ELANE* (NM_001972.2: c.452G>A, p.(C151Y) and c.608G>A, p.(G203D)) were found in 2 patients. Twenty-nine VUS were as follows: *SEPTIN6* (NM_015129.5:c.1085A>G, p.(K362R)),

*LRBA* (NM_006726.3:c.3778G>C, p.(A1260P) and c.1408A>T, p.(I470F)) in 2 patients, *IL12RB1* (NM_005535.1:c.1601C>T, p.(P534L)), *SLC7A7* (NM_001126106.1:c.333T>G, p.(F111L)) in 2 patients, *C6* (NM_000065.2:c.449G>A, p.(R150H)), *CFP* (NM_002621.2:c.1366C>G, p.(L456V)), *TCF3* (NM_003200.2:c.1069G>A, p.(V357M)), *LYST* (NM_000081.2:c.5480G>A, p.(C1827Y)), *SMARCAL1* (NM_014140.3:c.1786G>A, p.(A596T)), *LIG1* (NM_000234.1:c.1879C>T,

p.(R627W)), *MAGT1* (NM_032121.5:c.572G>A, p.(R191Q)), *NCF4* (NM_013416.3:c.457C>T, p.(R153C)), *RNASEH2C* (NM_032193.3:c.270G>C, p.(K90N)), *DNASE2* (NM_001375.2:c.319G>A, p.(D107N)), *DOCK2* (NM_004946.2:c.5017C>T, p.(P1673S)), *EPG5* (NM_020964.2:c.7736G>A, p.(R2579Q)), *FANCG* (NM_004629.1:c.70G>A, p.(V24I)), *SPINK5* (NM_006846.3:c.775G>C, p.(A259P)), *IRAK1* (NM_001569.3:c.609T>G, p.(C203W)), *TGFBR2* (NM_003242.5:c.1013C>T, p.(T338M)), *NFE2L2* (NM_006164.3:c.76C>T, p.(R42X)), *CD3G* (NM_000073.2:c.56-1G>A), *CD79B* (NM_000626.2:c.97G>C, p.(E33Q)), *NLRP3* (NM_004895.4:c.200C>G, p.(A67G)), *NSMCE3* (NM_138704.4:c.342C>A, p.(H114Q)) and *SKIV2L* (NM_006929.5:c.151G>A, p.(A51T)).

Meanwhile, 8 cancer predisposition gene mutations which were assessed as VUS were detected in 4 patients: *ANKRD26* (NM_014915.2:c.3086A>T, p.(E1028V)), *BARD1* (NM_000465.2:c.1862T>C, p.(M151T)), *DHX34* (NM_014681.5:c.1831G>A, p.(A611T)), *ERCC6* (NM_000124.2:c.2996A>G, p.(A2996G)), *FH* (NM_000143.3:c.1434T>A, p.(N478K)), *KDM1A* (NM_001009999.2:c.44C>T, p.(A15V)), *MST1R* (NM_002447.2:c.1729delC, p.(H577fs)) and *SMARCA4* (NM_001128849.1:c.4925A>C, p.(K1580T)) (**Table 4**).

## Table 4. Variants detected in the 16 neutropenia patients including VUS

| P | CN/IBMF/ID gene analysis | | | | Cancer predisposition gene analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Variants | VAF | Pathogenicity | Pathogenicity assessment* | Variants | VAF | Pathogenicity | Pathogenicity assessment* |
| P-01 | *SEPTIN6* (NM_015129.5):c.1085A>G, p.(K362R) | 0.48 | VUS | PM2 | *DHX34* (NM_014681.5):c.1831G>A, p.(A611T)) | 0.37 | VUS | PM2 |
| | | | | | *KDM1A* (NM_001009999.2):c.44C>T, p.(A15V) | 0.58 | VUS | PM2 |
| P-02 | *LRBA* (NM_006726.3):c.3778G>C, p.(A1260P) | 0.51 | VUS | PM2+BP1 | *ANKRD26* (NM_014915.2):c.3086A>T, p.(E1029V) | 0.49 | VUS | . |
| | | | | | *ERCC6* (NM_000124.2:c.2996A>G, p.(N999S) | 0.55 | VUS | PM1+PM2+BP1 |
| P-03 | *ELANE* (NM_001972.2):c.452G>A, p.(C151Y) | 0.60 | Likely pathogenic | PM1+PM2+PM5+PP2 +PP3+PP5+PP4 | None | | | |
| P-04 | *IL12RB1* (NM_005535.1):c.1601C>T, p.(P534L) | 0.49 | VUS | PM2 | None | | | |
| P-05 | *ELANE* (NM_001972.2):c.640G>A, p.(G214R) | 0.48 | Pathogenic | PS1+PM1+PM2+PM +PP2+PP3+PP5+PP4 | None | | | |
| | *SLC7A7* (NM_001126106.1):c.333T>G, p.(F111L) | 0.53 | VUS | PM2 | | | | |
| P-06 | *FANCI* (NM_001113378.1):c.3568A>G, p.(I1190V) | 0.46 | VUS | PM2 | None | | | |
| | *C6* (NM_000065.2):c.449G>A, p.(R150H) | 0.66 | VUS | PM2+PP3+BP1 | | | | |
| | *CFP* (NM_002621.2):c.1366C>G, p.(L456V) | 0.49 | VUS | PM2+BP1 | | | | |
| | *TCF3* (NM_003200.2):c.1069G>A, p.(V357M) | 0.49 | VUS | PM2+BP1 | | | | |
| P-07 | *LYST* (NM_000081.2):c.5480G>A, p.(C1827Y) | 0.46 | VUS | PM2+PP3+BP1 | None | | | |
| | *SMARCAL1* (NM_014140.3):c.1786G>A, p.(A596T) | 0.44 | VUS | PM2 | | | | |
| | *LIG1* (NM_000234.1):c.1879C>T, p.(R627W) | 0.48 | VUS | PM2+BP1 | | | | |
| P-08 | *CXCR4* (NM_003467.2):c.966_967del, | 0.50 | Pathogenic | PVS1+PM2+PP4 | None | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | p.(G323fs) | | | | | | | |
| P-09 | *LRBA* (NM_006726.3):c.1408A>T, p.(I470F) | 0.53 | VUS | PM2+BP1 | *BARD1* (NM_000465.2):c.1862T>C, p.(M621T) | 0.48 | VUS | PM2+PP3+BP1 |
| P-10 | *MAGT1* (NM_032121.5):c.572G>A, p.(R191Q) | 0.52 | VUS | PM2+BP1 | None | | | |
| | *NCF4* (NM_013416.3):c.457C>T, p.(R153C) | 0.57 | VUS | PM2+BP1 | | | | |
| | *RNASEH2C* (NM_032193.3):c.270G>C, p.(K90N) | 0.49 | VUS | PM2+BP4 | | | | |
| | *DNASE2* (NM_001375.2):c.319G>A, p.(D107N) | 0.55 | VUS | PM2+PP3 | | | | |
| P-11 | *ELANE* (NM_001972.2):c.640G>A, p.(G214R) | 0.52 | Pathogenic | PS1+PM1+PM2+PM5 +PP2+PP3+PP5+PP4 | None | | | |
| | *SLC7A7* (NM_001126106).1:c.333T>G, p.(F111L) | 0.51 | VUS | PM2+PP3+BP5 | | | | |
| P-12 | *FANCI* (NM_001113378.1):c.3172G>T, p.(E1058X) | 0.40 | Pathogenic | PVS1+PM2+PP3 | None | | | |
| | *DOCK2* (NM_004946.2):c.5017C>T, p.(P1673S) | 0.41 | VUS | PM2+BP1 | | | | |
| | *EPG5* (NM_020964.2):c.7736G>A, p.(R2579Q) | 0.56 | VUS | PM2+BP1 | | | | |
| | *FANCG* (NM_004629.1):c.70G>A, p.(V24I) | 0.46 | VUS | PM2+BP1+PP3 | | | | |
| | *SPINK5* (NM_006846.3):c.775G>C, p.(A259P) | 0.46 | VUS | PM2+BP1 | | | | |
| | *IRAK1* (NM_001569.3):c.609T>G, p.(C203W) | 0.31 | VUS | PM2 | | | | |
| | *TGFBR2* (NM_003242.5):c.1013C>T, p.(T338M) | 0.44 | VUS | PM2+PP2 | | | | |
| P-13 | *G6PC3* (NM_138387.3):c.214delA, p.(K72fs) | 1.00 | Pathogenic | PVS1+PM2+PP4 | None | | | |
| P-14 | *G6PC3* (NM_138387.3):c.214delA, p.(K72fs) | 1.00 | Pathogenic | PVS1+PM2+PP4 | None | | | |
| P-15 | *ELANE* (NM_001972.2:c.608G>A), p.(G203D) | 0.53 | Likely pathogenic | PM1+PM2+PM5+PP2 +PP3+PP5+PP4 | *MST1R* (NM_002447.2):c.1729delC, p.(H577fs) | 0.48 | VUS | PM2 |
| | *NFE2L2* (NM_006164.3):c.76C>T, p.(R42X) | 0.36 | VUS | PM2+BP5 | *FH* (NM_000143.3):c.1434T>A, p.(N478K) | 0.48 | VUS | PM2 |
| | | | | | *SMARCA4* (NM_001128849.1):c.4925A>C, p.(K1642T) | 0.62 | VUS | PM2 |

| | | | | | |
|---|---|---|---|---|---|
| P-16 | *CD3G* (NM_000073.2):c.56-1G>A | 0.44 | VUS | PVS1 | None |
| | *CD79B* (NM_000626.2):c.97G>C, p.(E33Q) | 0.52 | VUS | PM2+BP4 | |
| | *NLRP3* (NM_004895.4):c.200C>G, p.(A67G) | 0.38 | VUS | PP2 | |
| | *NSMCE3* (NM_138704.4):c.342C>A, p.(H114Q) | 0.45 | VUS | PM2 | |
| | *SKIV2L* (NM_006929.5):c.151G>A, p.(A51T) | 0.45 | VUS | PM2+BP1 | |

*Pathogenicity of each variant was assessed according to 2015 ACMG-AMP guidelines for the interpretation of sequence variants [26].
Abbreviations: CN, congenital neutropenia; IBMF, inherited bone marrow failure; ID, immunodeficiency; LP, likely pathogenic; P, patient; VAF, variant allele frequency; VUS, variant of unknown significance

## 3.6. Results of copy-number variant analysis

A total of 31 copy-number variants (CNV) in 11 patients were assessed as VUS, none of which involved regions including genes associated with CN, IBMF or immunodeficiency. No pathogenic CNVs were identified (**Table 5**). Copy-neutral loss of heterozygosity (CN-LOH) at 17q21.31[②] was revealed in 2 brothers (P-13 and P-14) with pathogenic homozygous mutations in G6PC3 (NM_138387.3:c.214delA, c.214delA, p.K72fs) (**Figure 8**).

[②] CN-LOH at 17q21.31 was detected by Sung-Min and Young Seok Ju.

## Table 5. CNV analysis of 15 patients for whom WES was performed

| Patient | Sex | Control | Chromosome region | Cytoband | Event | Length | Probe median | Pathogenicity | Pathogenicity assessment‡ |
|---|---|---|---|---|---|---|---|---|---|
| P-02 | F | M* | chr15:76,678,281-77,271,846 | q24.3 | CN gain | 593,566 | 0.48340754 | VUS | 1A+3B |
| P-02 | F | M* | chr17:58,260,605-59,433,505 | q23.1 - q23.2 | CN gain | 1,172,901 | 0.48906463 | VUS | 1A+2J+3A |
| P-02 | F | M* | chr7:100,494,267-100,624,831 | q22.1 | High copy gain | 130,565 | 1.18507564 | VUS | 1A+2J+3A |
| P-02 | F | M* | chr17:62,385,805-62,486,400 | q23.3 | High copy gain | 100,596 | 0.92298582 | VUS | 1A+3A |
| P-03 | M | F† | chr17:12,872,505-13,262,605 | p12 | CN gain | 390,101 | 0.49955885 | VUS | 1A+2J |
| P-03 | M | F† | chrY:12,500,000-16,936,081 | q11.1 - q11.221 | CN gain | 4,436,082 | 1.13695192 | VUS | 1A+2L+3B |
| P-03 | M | F† | chrY:2,655,180-10,037,833 | p11.31 - p11.2 | CN gain | 7,382,654 | 1.29101992 | VUS | 1A+2L+3A |
| P-04 | F | M* | chr9:133,048,608-133,240,215 | q34.11 | CN gain | 191,608 | 0.49118426 | VUS | 1A+2L |
| P-04 | F | M* | chr11:1,151,752-1,221,908 | p15.5 | CN gain | 70,157 | 0.54887050 | VUS | 1A+3A |
| P-04 | F | M* | chr12:7,172,497-7,260,947 | p13.31 | CN gain | 88,451 | 0.50153291 | VUS | 1A+3A |
| P-05 | M | F† | chr17:45,186,449-45,287,005 | p11.31 - p11.2 | CN gain | 100,557 | 0.52129602 | VUS | 1A+2L |
| P-05 | M | F† | chrY:2,655,180-10,037,833 | p21.1 | CN gain | 7,382,654 | 1.33612883 | VUS | 1A+2L+3A |
| P-06 | F | M* | chr1:104,162,210-104,469,210 | p21.1 | CN loss | 307,001 | -0.85330367 | VUS | 1A+3A |
| P-09 | F | M* | chr7:100,549,731-100,691,231 | q22.1 | CN gain | 141,501 | 0.52355498 | VUS | 1A+2L+3A |
| P-09 | F | M* | chr12:0-176,247 | p13.33 | CN loss | 176,248 | -0.86360770 | VUS | 1A+2C-1+4N |
| P-09 | F | M* | chr11:1,263,708-1,273,708 | p15.5 | High copy gain | 10,001 | 1.31133997 | VUS | 2I |
| P-10 | F | M* | chr1:104,166,710-104,616,110 | p21.1 | CN gain | 449,401 | 0.52691755 | VUS | 1A+2L+2G+3A |
| P-10 | F | M* | chr3:196,510,115-196,554,315 | q29 | CN loss | 44,201 | -0.77570057 | VUS | 2E |
| P-10 | F | M* | chr12:0-187,947 | p13.33 | CN loss | 187,948 | -0.82084373 | VUS | 1A+2C-1+4N |
| P-10 | F | M* | chr12:9,626,047-9,751,283 | p13.31 | Homozygous copy loss | 125,237 | -3.49378848 | VUS | 1A+3A+4D |
| P-11 | M | F† | chr6:133,562,733-133,849,149 | q23.2 | CN gain | 286,417 | 0.51672930 | VUS | 1A+2L+3A |
| P-11 | M | F† | chr8:113,237,828-114,736,511 | q23.3 | CN gain | 1,498,684 | 0.48284447 | VUS | 1A+2J |
| P-11 | M | F† | chrY:2,655,180-10,037,833 | p11.31 - p11.2 | CN gain | 7,382,654 | 0.95616442 | VUS | 1A+2L+3A |
| P-11 | M | F† | chrY:2,655,180-10,037,833 | q11.1 - q11.221 | CN gain | 4,436,082 | 1.16044438 | VUS | 1A+2L+3B |
| P-12 | M | M* | chr12:7,982,347-8,205,185 | p13.31 | CN loss | 222,839 | -0.84832293 | VUS | 1A+2C-1+4N |
| P-13 | M | M* | chr17:45,287,005-48,276,944 | q21.32 - q21.33 | CN-LOH | 2,989,940 | -0.05550943 | N/A | N/A |
| P-14 | M | M* | chr17:44,771,405-48,276,944 | q21.31 - q21.33 | CN-LOH | 3,505,540 | -0.06042904 | N/A | N/A |
| P-14 | M | M* | chr1:104,120,510-104,469,210 | p21.1 | CN gain | 348,701 | 0.50930575 | VUS | 1A+2G+2L+3A |
| P-15 | M | F† | chr5:92,920,830-92,929,730 | q15 | CN gain | 8,901 | 0.52647978 | VUS | 1A+2L+3A+2L |
| P-15 | M | F† | chr15:96,831,446-96,880,946 | q26.2 | CN gain | 49,501 | 0.49010783 | VUS | 1A+2J |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| P-15 | M | F† | chrX:155,001,830-155,270,560 | q28 | CN gain | 268,731 | 0.18132728 | VUS | 1A+2L |
| P-15 | M | F† | chrY:12,500,000-16,936,081 | q11.1 - q11.221 | CN gain | 4,436,082 | 0.92853528 | VUS | 1A+2L+3B |
| P-15 | M | F† | chrY:2,655,180-10,037,833 | p11.31 - p11.2 | CN gain | 7,382,654 | 1.395358 | VUS | 3A+1A+2L |

*Four male patients with likely pathogenic or pathogenic *ELANE* variants were used as controls for the copy-number variant analysis.
†Four female patients without likely pathogenic or pathogenic variants who were re-diagnosed with autoimmune neutropenia were used as controls for the copy-number variant analysis.
‡Pathogenicity of each copy-number variant was assessed according to 2020 ACMG-ClinGen guidelines for the interpretation and reporting of constitutional copy-number variants [34].
Abbreviations: CN, copy number; CNV, copy number variant; N/A, not applicable; VUS, variant of unknown significance; WES, whole-exome sequencing.


**Figure 8. The log R ratio and B allele frequency plots of chromosome 17 in two brothers (P-13 and P-14) with the same *G6PC3* mutation (NM_138387.3:c.214delA, p.(K72fs)).** CN-LOH, copy-neutral loss of heterozygosity.

## 3.7. Sixteen neutropenia patients: clinical, histologic and molecular features

In the 16 neutropenia patients, an average of 2.4 variants, including VUS, per patient were detected in genes related to CN, IBMF or immunodeficiency. An average of 2.9 variants, including VUS, per patient were identified in genes related to CN, IBMF, immunodeficiency or cancer predisposition. Detailed information on the clinical features of the neutropenia, recurrent infections, extra-hematopoietic features, G-CSF doses, G-CSF response, PBSCT, Ig levels, BM histology of maturation arrest, myelokathexis, MPO-positive cell percentage and MPO grade, and variants detected by WES or TS in each patient is described in **Table 3** and **Table 4**.

## 3.8. Congenital neutropenia with causal pathogenic variants

The 4 patients who harbored likely pathogenic or pathogenic *ELANE* mutations showed common features of permanent neutropenia, recurrent infections with several neutropenic fever events, G-CSF non-responsiveness and maturation arrest at the promyelocyte or myelocyte stage with no dysplastic hematopoietic cells. Three out of 4 (75.0%) patients had organomegaly: 2 had hepatosplenomegaly and 1 had splenomegaly. One patient had an extra-hematopoietic feature of a high arched palate and family history of liver and gastric cancer in his maternal grandfather. Monocytosis was observed in 2 (50.0%) patients. The 4 patients displayed a variable percentage of MPO-positive cells (range, 12.6%–45.5%) and MPO grade (range, 0–3). Two patients (P-05 and P-11) harbored the same pathogenic *ELANE* mutation (NM_001972.2:c.640G>A, p.(G214R)) but their BM histology and clinical outcomes were totally different:

BM biopsy revealed 12.6% of MPO-positive cells and MPO grade 0 in P-05 but 45.5% of MPO-positive cells and MPO grade 3 in P-11 (**Figure 9**). The former underwent two uPBSCT, but he died of sepsis. The latter patient had successful second hPBSCT, which led to the correction of the ANC level. (**Figure 10**).

The patient (P-08) with a pathogenic *CXCR4* mutation (NM_003467.2:c.966_967del, p.(R326fs)) showed permanent neutropenia, several neutropenic fever events with or without infections, inguinal hernia, incomplete cleft lip and serum IgG and IgA deficiencies. Myelokathexis was the most representative histologic feature with increased M:E ratio of 7.9, MPO grade 2 and 44.4% of MPO-positive cells on a BM section (**Figure 11**). An ANC of $>1.00\times10^9$/l has been maintained after he had uPBSCT (**Figure 12**).

Clinical manifestations and BM histologies were very similar in the P-13 and P-14 brothers. Both presented intermittent neutropenia and suffered from numerous infectious events from mild to severe with neutropenic or non-neutropenic fever (**Figure 13**). They showed similar extra-hematological involvement such as an atrial septum defect, Crohn's disease and growth retardation. Meanwhile, some different features were noted: P-13 suffered from juvenile rheumatoid arthritis, papillary thyroid carcinoma and medullary nephrocalcinosis with multiple cysts, whereas P-14 showed prominent skin vessels, bilateral testicular microlithiasis, necrotizing enterocolitis and clinodactyly of both 5th fingers. Both were G-CSF non-responders. Myelokathexis with prominently increased hypermature segmented neutrophils was observed with MPO grade 1 and 40.4%–46.5% MPO-positive cells on BM sections (**Figure 14**). In contrast to BM of the patient with the *CXCR4* (R326fs) mutation, who exhibited myelokathexis with an overall increase in the number of myeloid cells at each stage, BM of

patients with the *G6PC3* (K72fs) mutation displayed a prominent increase in the number of segmented neutrophils but not of the other kinds of myeloid cells (**Figure 10**).

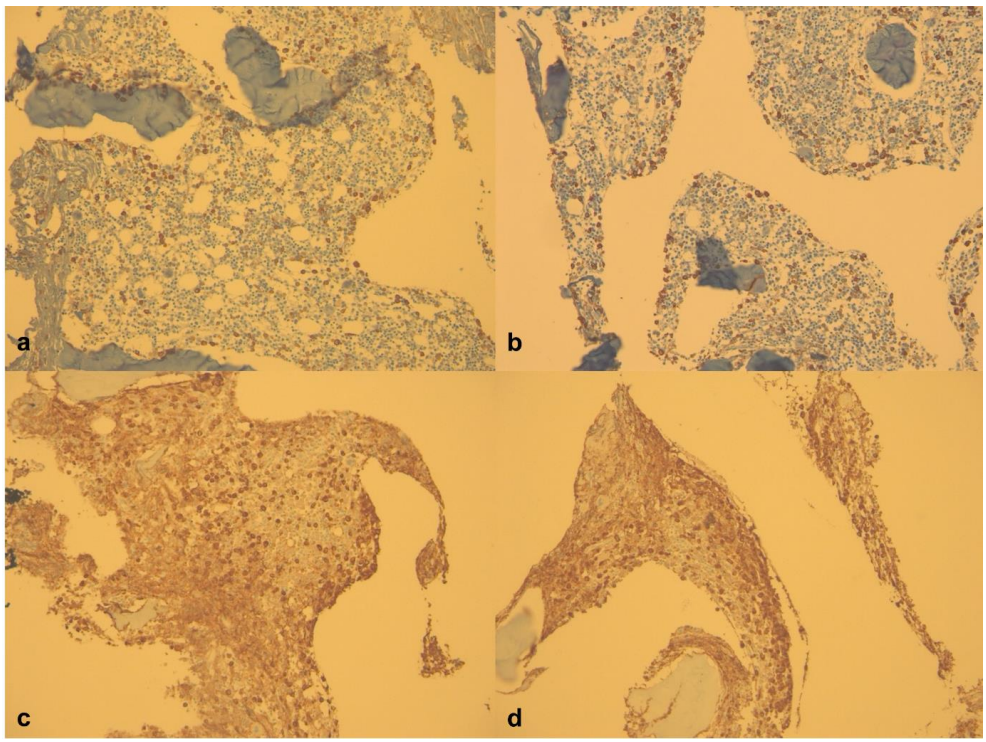
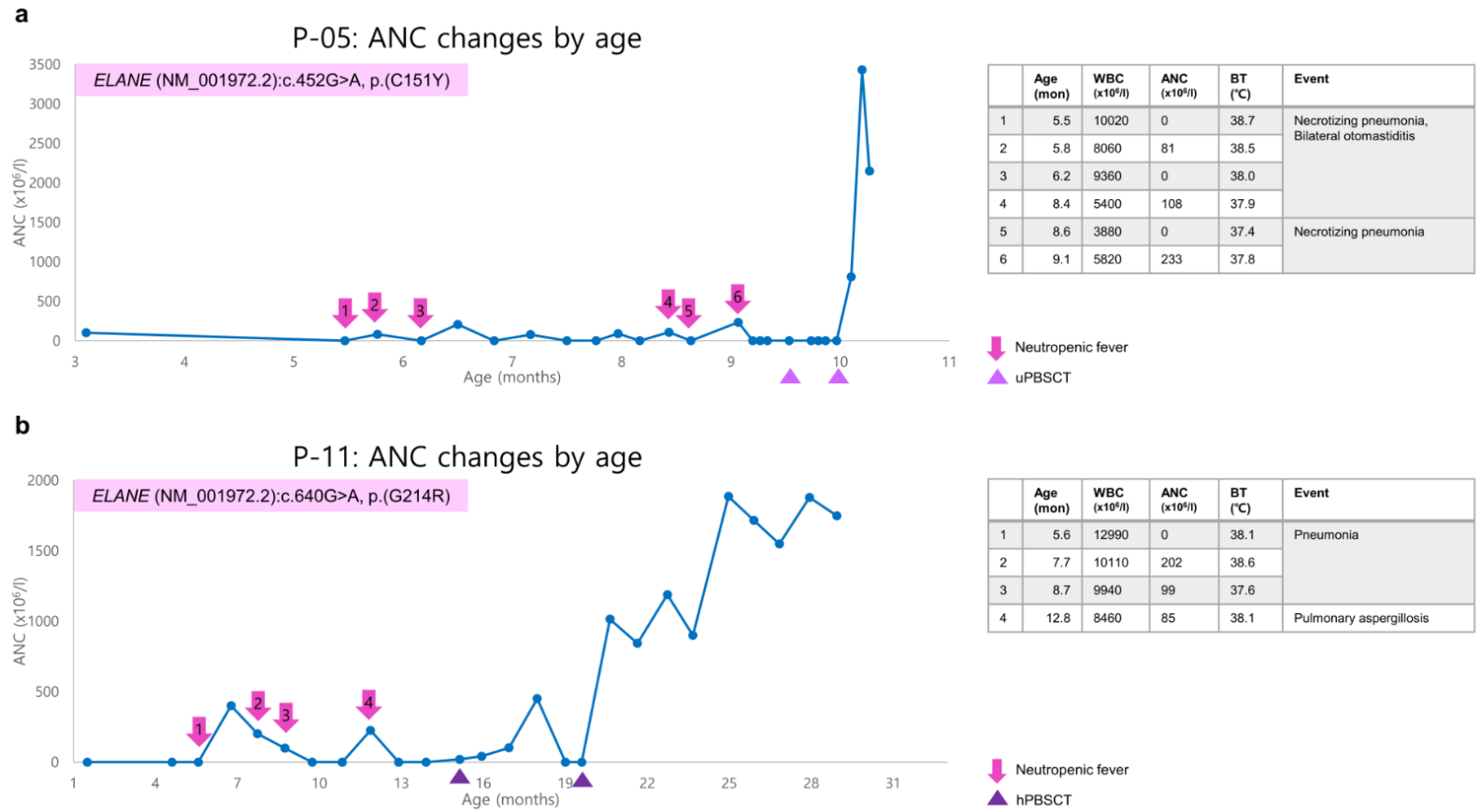



**Figure 9. The *ELANE* (NM_001972.2:c.640G>A, p.(G214R)) mutation in two patients showing different BM histologies.** (a-b) Patient P-05 had 12.6% of MPO-positive cells and MPO grade 0. (c-d) Patient P-11 had 45.5% of MPO-positive cells and MPO grade 3. MPO stain, ×200. MPO, myeloperoxidase




| | Age (mon) | WBC (x10⁶/l) | ANC (x10⁶/l) | BT (℃) | Event |
|---|---|---|---|---|---|
| 1 | 5.5 | 10020 | 0 | 38.7 | Necrotizing pneumonia, Bilateral otomastiditis |
| 2 | 5.8 | 8060 | 81 | 38.5 | |
| 3 | 6.2 | 9360 | 0 | 38.0 | |
| 4 | 8.4 | 5400 | 108 | 37.9 | |
| 5 | 8.6 | 3880 | 0 | 37.4 | Necrotizing pneumonia |
| 6 | 9.1 | 5820 | 233 | 37.8 | |

| | Age (mon) | WBC (x10⁶/l) | ANC (x10⁶/l) | BT (℃) | Event |
|---|---|---|---|---|---|
| 1 | 5.6 | 12990 | 0 | 38.1 | Pneumonia |
| 2 | 7.7 | 10110 | 202 | 38.6 | |
| 3 | 8.7 | 9940 | 99 | 37.6 | |
| 4 | 12.8 | 8460 | 85 | 38.1 | Pulmonary aspergillosis |

**Figure 10. Different clinical course of two patients (P-05 and P-11) who harbored the same pathogenic *ELANE* variant**

**(NM_001972.2):c.640G>A, p.(G214R)).** (a) P-05 underwent two uPBSCT, but he died of sepsis. (b) P-11 had successful second hPBSCT, which led to ANC level recovery. ANC, absolute neutrophil count; BT, body temperature; hPBSCT, haploidentical peripheral blood stem cell transplantation; uPBSCT, unrelated peripheral blood stem cell transplantation.

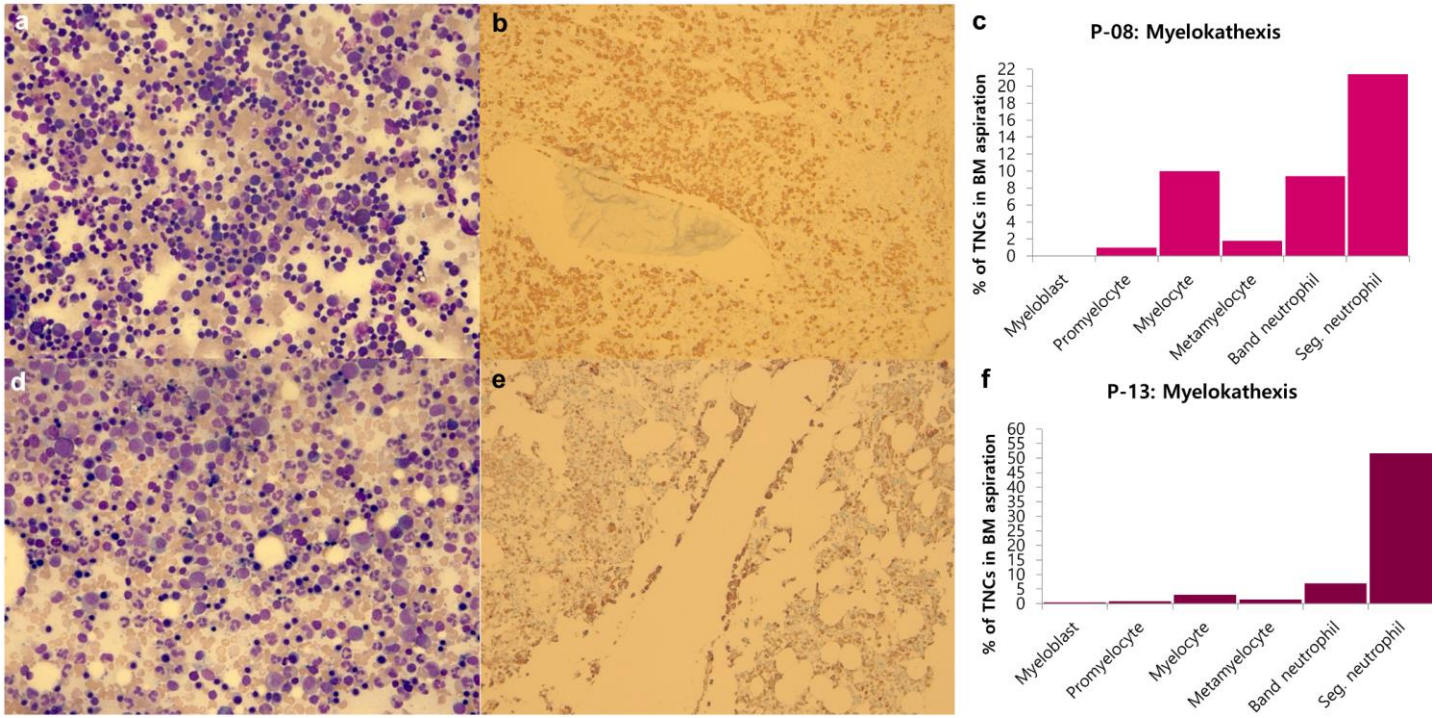
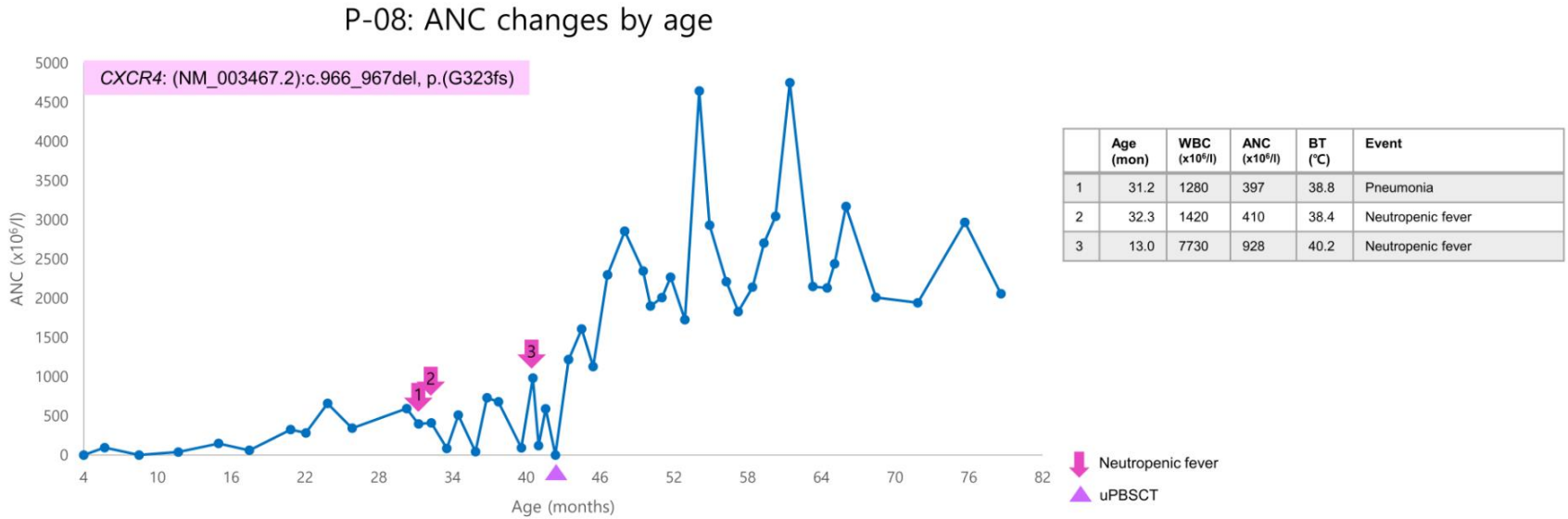
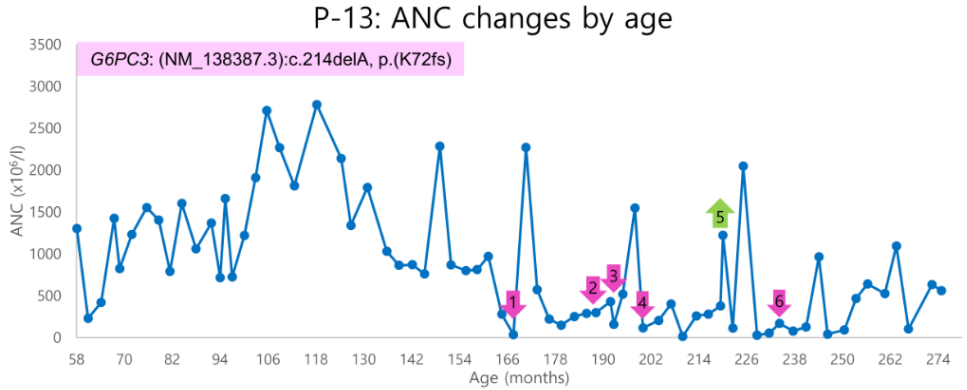



**Figure 11. Myelokathexis in patients with *CXCR4* and *G6PC3* mutations.** (a-c) Patient P-08 with *CXCR4* mutation. (d-f) Patient P-13 with *G6PC3* mutation. (a,d) Wright-Giemsa stain, ×200 (b,e) MPO stain, ×200. BM, bone marrow; MPO, myeloperoxidase; TNC, total nucleated cells.



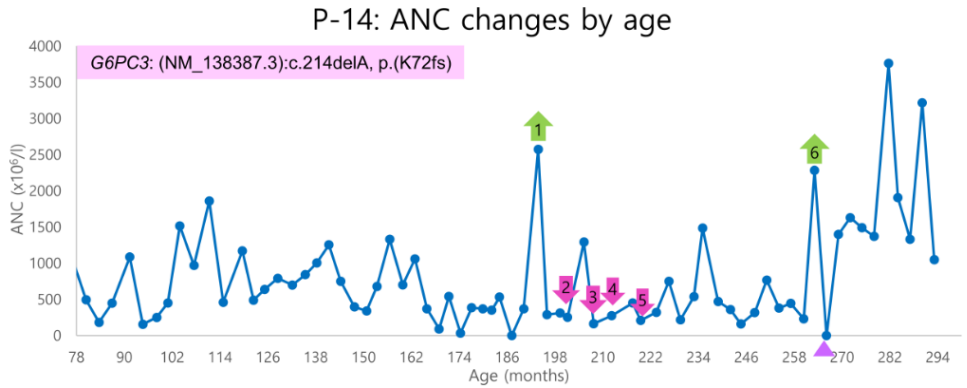

| | Age (mon) | WBC (x10⁶/l) | ANC (x10⁶/l) | BT (℃) | Event |
|---|---|---|---|---|---|
| 1 | 31.2 | 1280 | 397 | 38.8 | Pneumonia |
| 2 | 32.3 | 1420 | 410 | 38.4 | Neutropenic fever |
| 3 | 13.0 | 7730 | 928 | 40.2 | Neutropenic fever |

**Figure 12. ANC changes and clinical course of the patient (P-08) with a *CXCR4* mutation.** ANC, absolute neutrophil count; BT, body temperature; uPBSCT, unrelated peripheral blood stem cell transplantations; WBC, white blood cell.




| | Age (mon) | WBC (x10⁶/l) | ANC (x10⁶/l) | BT (℃) | Event |
|---|---|---|---|---|---|
| 1 | 167.5 | 1870 | 37 | 38.0 | Anke joint pain |
| 2 | 188.2 | 1500 | 298 | 37.8 | Cellulitis, otitis externa |
| 3 | 192.7 | 1590 | 159 | 38.4 | Pustular folliculitis |
| 4 | 200.0 | 1920 | 115 | 37.8 | Cellulitis, folliculitis |
| 5 | 220.0 | 2050 | 1223 | 38.1 | Inguinal abscess |
| 6 | 234.2 | 2410 | 169 | 37.8 | |

Neutropenic fever
Non-neutropenic fever




| | Age (mon) | WBC (x10⁶/l) | ANC (x10⁶/l) | BT (℃) | Event |
|---|---|---|---|---|---|
| 1 | 193.8 | 5360 | 2573 | 38.1 | Chest wall cellulitis |
| 2 | 201.2 | 2290 | 252 | 38.1 | Finger cellulitis |
| 3 | 207.7 | 2720 | 163 | 37.8 | Inguinal Cellulitis |
| 4 | 212.2 | 1950 | 273 | 38.9 | Pustular folliculitis |
| 5 | 219.5 | 2920 | 209 | 38.3 | Oral ulcer |
| 6 | 263.1 | 4960 | 2282 | 38.3 | Pneumonia |

Neutropenic fever
Non-neutropenic fever
uPBSCT

**Figure 13. ANC changes and clinical course of two brothers with the same *G6PC3* mutation.** ANC, absolute neutrophil count; BT, body temperature; uPBSCT, unrelated peripheral blood stem cell transplantations; WBC, white blood cell.

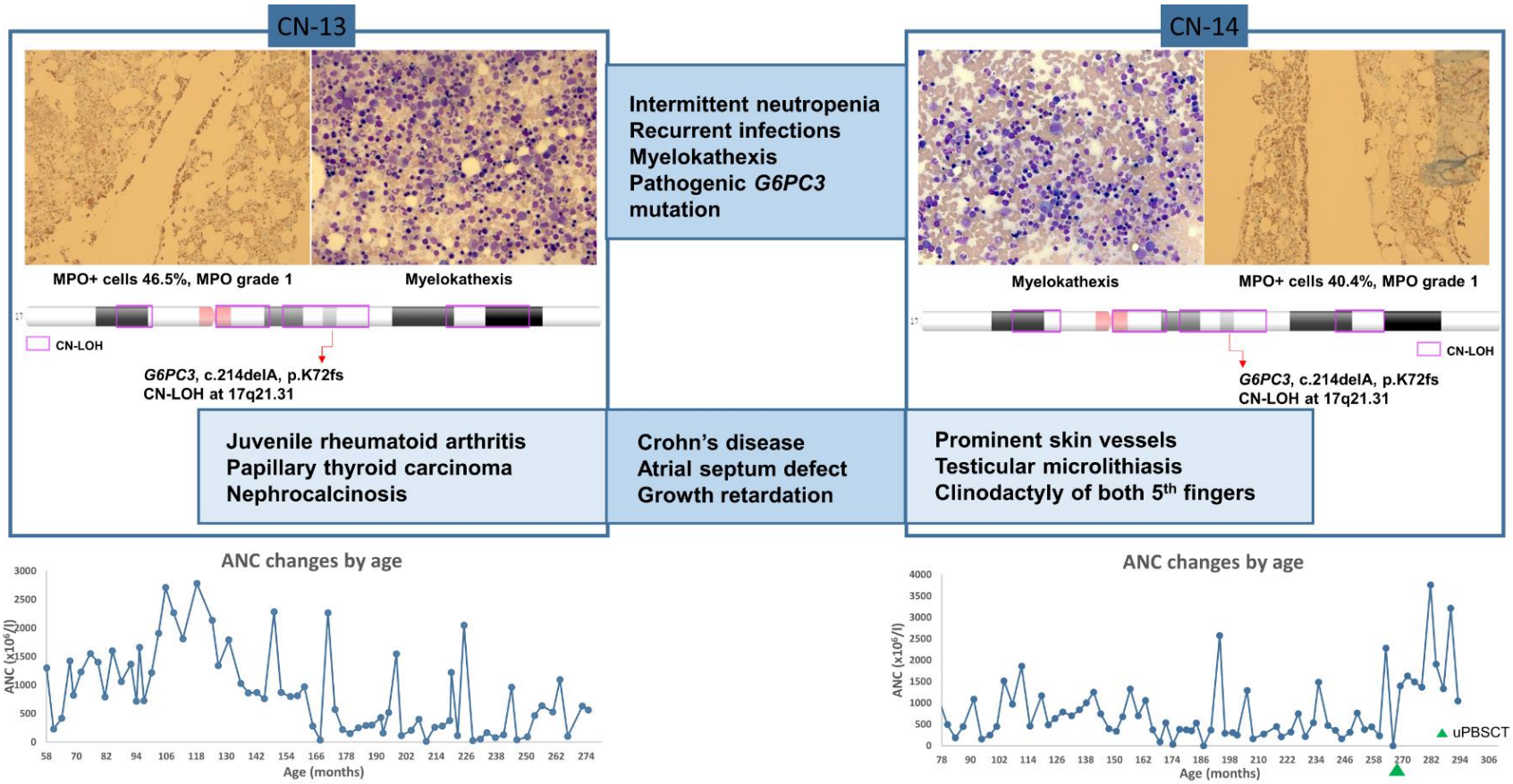
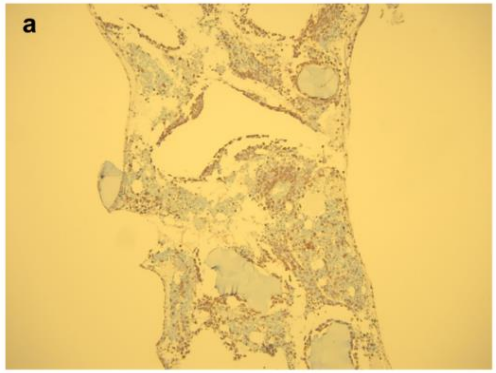
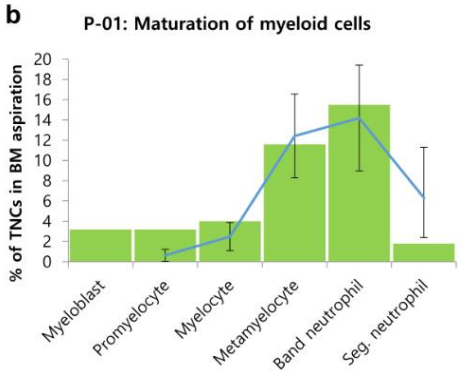


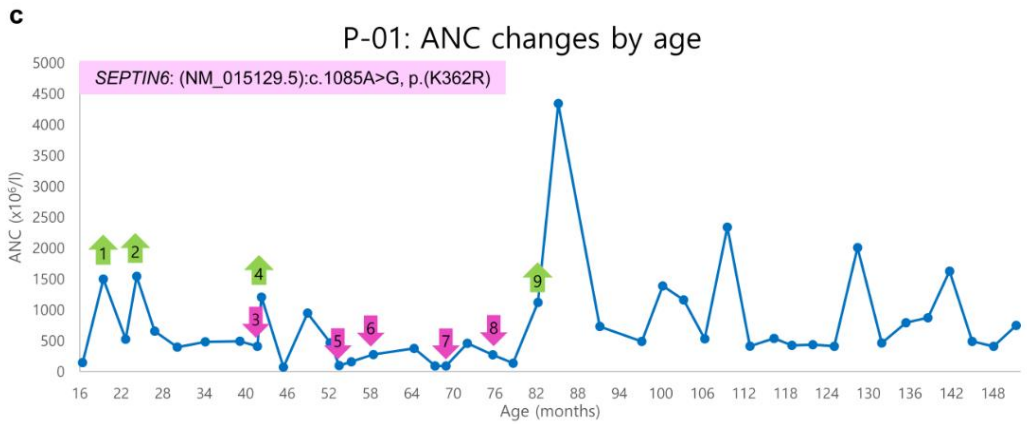

**Figure 14. Overlapping clinical, histological and genetic characteristics of the two brothers with the *G6PC3* mutation**

## 3.9. Chronic idiopathic neutropenia

One patient (P-01) with a variant of unknown significance in *SEPTIN6* (NM_015129.5:c.1085A>G, p.(K362R)) had intermittent neutropenia for more than 3 years. She experienced non-severe infections such as upper respiratory infection, acute pharyngotonsillitis and acute otitis media with neutropenic or non-neutropenic fever. She was a G-CSF non-responder. A BM exam revealed maturation arrest at the band stage, 30.1% of MPO-positive cells, MPO grade 1 and no dysplastic hematopoietic cells (**Figure 15**).




| | Age (mon) | WBC (x10⁶/l) | ANC (x10⁶/l) | BT (℃) | Event |
|---|---|---|---|---|---|
| 1 | 19.4 | 8820 | 1499 | 38.2 | Upper respiratory infection |
| 2 | 24.2 | 6170 | 1543 | 38.2 | Acute pharygotonsillitis |
| 3 | 41.7 | 2940 | 412 | 38.2 | Acute otitis media |
| 4 | 42.3 | 5120 | 1208 | 38.1 | Non-neutropenic ever |
| 5 | 53.5 | 2830 | 99 | 37.7 | Upper respiratory infection |
| 6 | 58.4 | 2580 | 279 | 38.4 | Upper respiratory infection |
| 7 | 68.9 | 1830 | 92 | 38.3 | Neutropenic fever |
| 8 | 75.7 | 1370 | 274 | 39.4 | Acute pharyngitis |
| 9 | 82.2 | 4000 | 1120 | 38.3 | Acute pharyngotonsillitis, acute otitis media |

Neutropenic fever

Non-neutropenic fever

**Figure 15. BM features and clinical course of the patient (P-01) who showed chronic idiopathic neutropenia with a *SEPTIN6* variant of**

**unknown significance.** (a) BM with 30.1% of MPO-positive cells and MPO grade 1. (b) Maturation arrest at the band stage. (c) Clinical course of the patient (P-01). (a) MPO stain, ×100. ANC, absolute neutrophil count; BM, bone marrow; BT, body temperature; MPO, myeloperoxidase WBC, white blood cell.

## 3.11. Acquired neutropenia

No pathogenic mutations or candidate variants suspected as the cause of neutropenia were identified in 8 out of 16 (50.0%) patients. In these 8 patients, median neutropenia duration was 18.7 months. They showed intermittent neutropenia. Five out of 8 received G-CSF treatment and one of them was a G-CSF non-responder (P-06). Two out of the 8 (25.0%) patients (P-02 and P-16) experienced no infections or fever and both had hepatomegaly. Meanwhile, 2 (25.0%) patients suffered from neutropenic fever with non-severe infection, whereas 4 (50.0%) patients experienced neutropenic or non-neutropenic fever with non-severe infection. Four (50.0%) patients showed maturation block at the band stage, whereas 4 (50.0%) patients showed no maturation arrest. One of the 7 patients (P-02) had a history of immune thrombocytopenia and received intravenous immunoglobulin (IVIG) treatment. Fluorescent antinuclear antibody test revealed weak positivity. Another patient (P-07) had a history of Kawasaki disease and received IVIG treatment. She had an older brother who suffered from recurrent pneumonia in childhood but became healthy later. Meanwhile, there was a patient (P-16) who had the constitutional karyotype of 46,XX,add(14)(p13), the significance of which is not clear.

## 3.12. Re-diagnosis of 16 neutropenia patients based on genetic analysis

The causal pathogenic variants were detected in 7 patients and included 4 mutations in *ELANE*, 2 in *G6PC3* and 1 in *CXCR4*. They were re-diagnosed with CN with causal pathogenic variants. A patient with intermittent neutropenia for more than 3 years without identifiable causes was classified into chronic idiopathic

neutropenia. The 8 remaining patients were re-diagnosed as having acquired neutropenia (**Figure 16**).

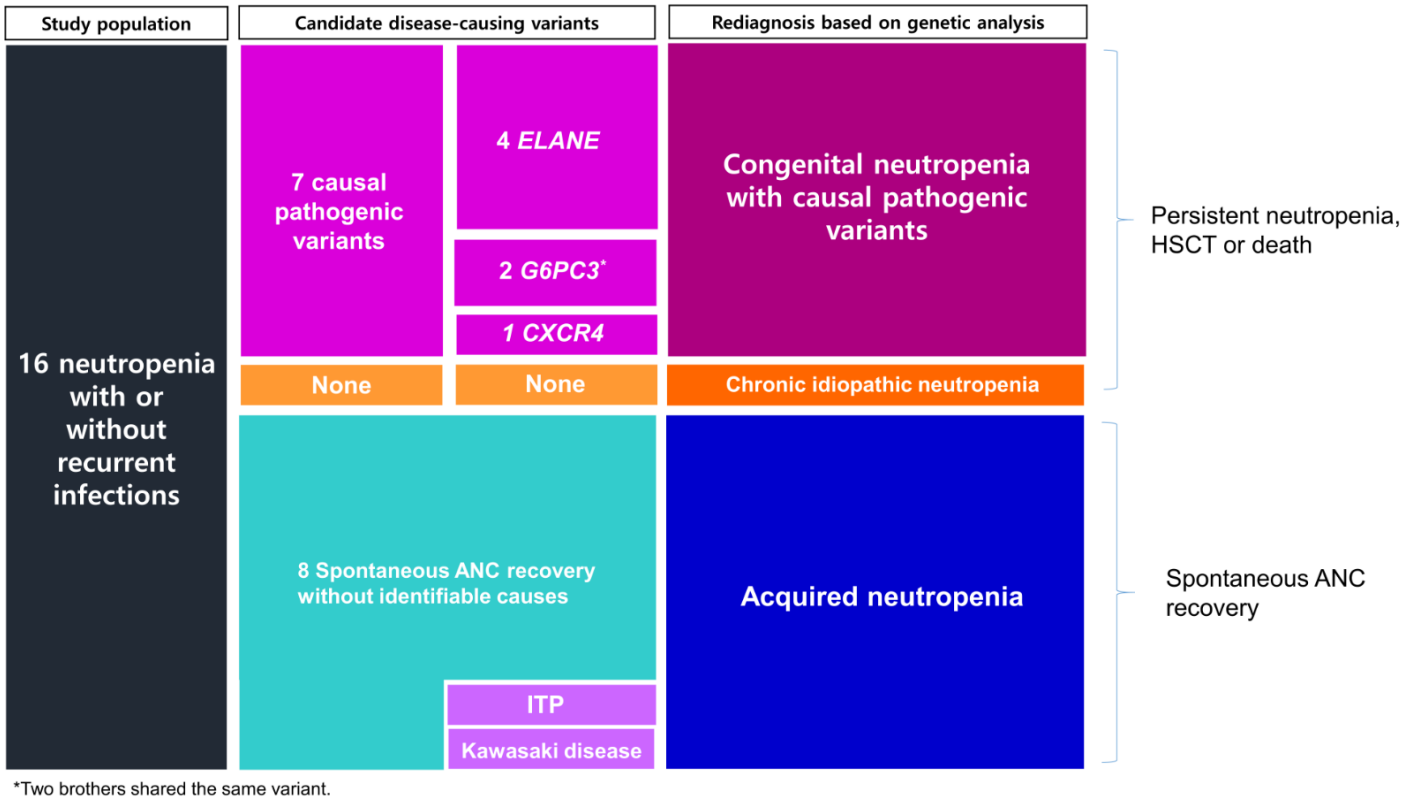



**Figure 16. Re-diagnosis of 16 neutropenia patients based on genetic analysis.** Seven patients with pathogenic variants in *ELANE*, *G6PC3* and *CXCR4* were diagnosed with CN with causal pathogenic variants. One patient harbored no pathogenic variant and was classified as chronic

idiopathic neutropenia. Other 8 patients who achieved spontaneous ANC recovery were re-diagnosed with acquired neutropenia. Two out of the 5 patients had a history of immune thrombocytopenia and Kawasaki disease, respectively, and both were treated with IVIG. ITP, immune thrombocytopenic purpura.ITP, immune thrombocytopenic purpura.

## 3.13. Genotype–BM histology correlations

Based on the genotyping results, we examined the relationship between genotype and BM histology, mainly focusing on maturation arrest and myelokathexis. Early maturation arrest at the promyelocyte or myelocyte stage was characteristic for *ELANE* mutations. The *CXCR4* mutation was associated with myelokathexis with MPO grade 2 and *G6PC3* mutations with BM retention with MPO grade 1. Maturation block at the band neutrophil stage was observed in the chronic idiopathic neutropenia patient (P-01) and 4 patients (P-02, P-04, P-07 and P-09) who were re-diagnosed with acquired neutropenia. The 4 patients with acquired neutropenia showed normal maturation with no myelokathexis (**Figure 17)**.

We analyzed the distribution of MPO-positive cells, MPO grade and M:E ratio in the context of genetic variants. MPO-positive cells ranged from 20% to 60% in the patients with acquired neutropenia. Among patients with pathogenic *ELANE* mutations 3 showed 10%−30% MPO-positive cells and 1 patient showed 40%–50%. Three patients whose BM displayed myelokathexis and who had pathogenic *G6PC3* and *CXCR4* mutations showed 40%–50% MPO-positive cells. Three patients with pathogenic *ELANE* mutations showed various distribution of MPO grades. BM of the patient with a pathogenic *CXCR4* mutation showed MPO grade 2, whereas BM of patients with *G6PC3* mutations showed MPO grade 1. The M:E ratio of patients with *ELANE* mutations ranged from 0.5 to 1.5, which was lower than normal. That of the patients with *G6PC3* mutations was 1.5–2.5, and that of the patient with a *CXCR4* mutation was increased to 7.5–8.5 (**Figure 18**).

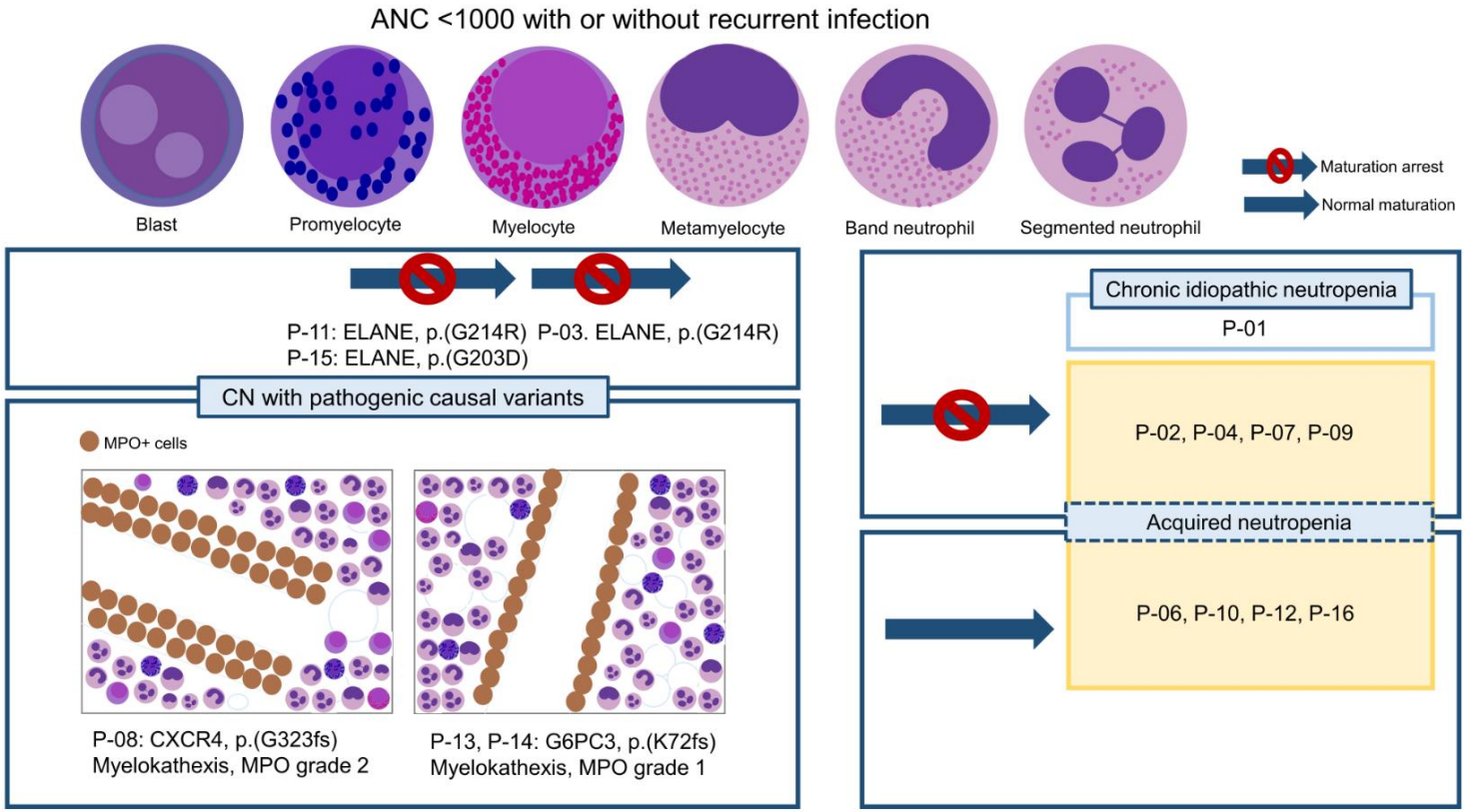



**Figure 17. Genotype–BM histology correlations in 16 neutropenia patients.** Early maturation arrest at the promyelocyte or myelocyte stage was characteristic for *ELANE* mutations. The *CXCR4* mutation was associated with myelokathexis with MPO grade 2, whereas the *G6PC3*

mutations were associated with bone marrow retention with MPO grade 1. Maturation block at the band neutrophil stage was observed in one patient with chronic idiopathic neutropenia and 4 acquired neutropenia patients. Other 4 patients showed normal maturation with no myelokathexis. BM, bone marrow.

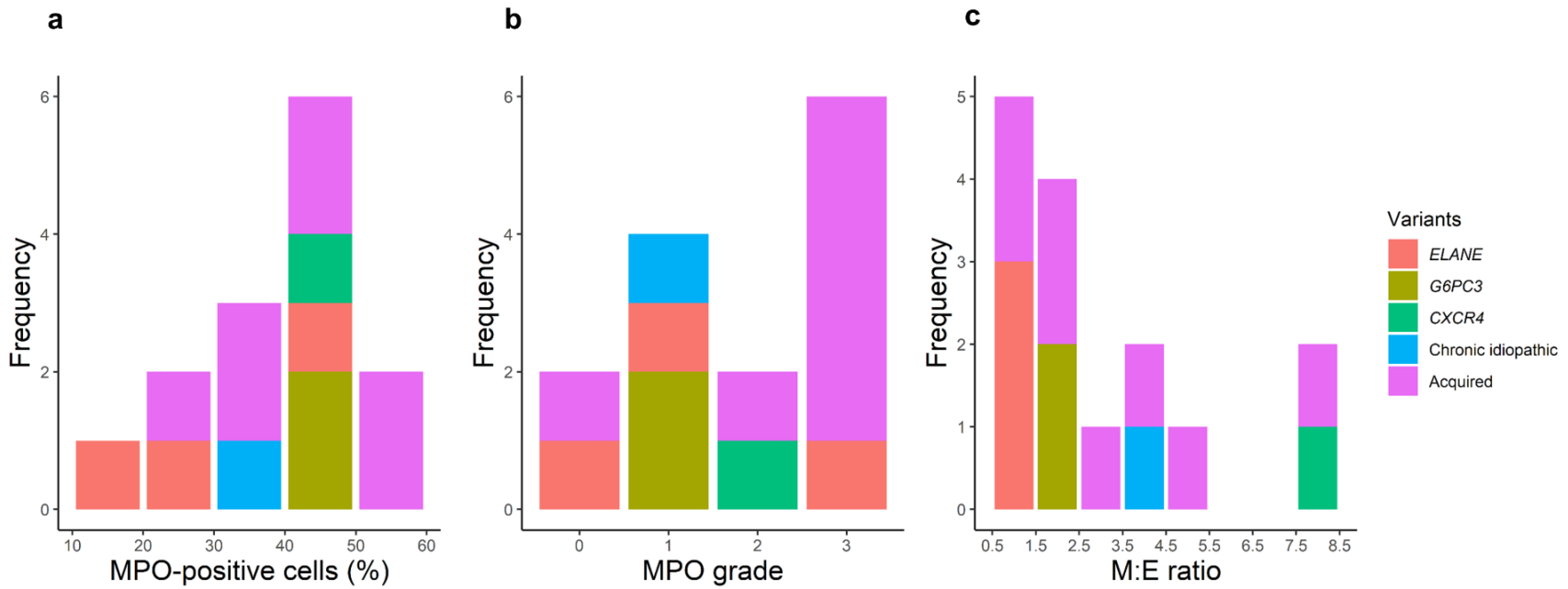



**Figure 18. Distributions of MPO-positive cells, MPO grade and M:E ratio in the context of genetic variants**

## 3.14. Congenital neutropenia: genetic and clinical aspects

Two comparisons were made in terms of genetic and clinical aspects. In comparison 1, the 16 patients were classified into 2 groups. Group 1-1 consisted of 7 patients with tier 1 variants and group 1-2 included the others. Permanent neutropenia (n = 5 in group 1-1 and n= 0 in group 1-2) and male patients (n = 7 in group 1-1 n = 1 in group 1-2) were more frequent in group 1-1 ($P$ <0.01 each). Severe infections were present at a higher percentage in group 1-1 (n = 6) than in group 1-2 (n = 1) ($P$ <0.01). ANC level at the latest follow-up was significantly lower in group 1-1 (median $0\times10^9$/l) than in group 1-2 (median $1.797\times10^9$/l) ($P$ <0.01). Early-stage maturation arrest was predominant in group 1-1 (n = 3 in group 1-1 and n = 0 in group 1-2), whereas late stage maturation arrest was predominant in group 1-2 (n = 0 in group 1-1 and n = 5 in group 1-2) ($P$ <0.05). Other clinical and histologic features such as the age when low ANC was discovered, family history of cancer or recurrent infections, fever pattern, G-CSF responsiveness, organomegaly, extra-hematopoietic features, initial ANC level, M:E ratio, BM cellularity, MPO-positive cells, MPO grade and myelokathexis were not significantly different. In comparison 2, 8 patients who did not achieve spontaneous recovery of ANC were categorized as group 2-1 and the other 8 patients who achieved spontaneous recovery of ANC were categorized as group 2-2. Like comparison 1, permanent neutropenia (n = 5 in group 2-1 and n = 0 in group 2-2), male patients (n = 7 in group 2-1 and n = 1 in group 2-2) and severe infections infections (n = 6 in group 2-1 and n = 1 in group 2-2) were more frequently observed in group 2-1 ($P$ <0.05, $P$ <0.01 and $P$ <0.01, respectively). The last ANC level was significantly higher in group 2-2 (median $2.246\times10^9$/l) than in group 2-1 (median $0.026\times10^9$/l) ($P$ <0.01). The number of G-CSF non-responders

was significantly higher in group 2-1 (n = 6) than in group 2-2 (n = 1) ($P$ <0.05).

Although this difference was not statistically significant, 6 of 7 patients (85.7%) in group 2-1 were G-CSF non-responders, whereas 4 out of 5 (80.0%) in group 2-2 were G-CSF responders ($P$ = 0.072). No patients in group 1-2 showed myelokathexis, whereas 3 of 7 (42.9%) patients in group 1-1 did ($P$ = 0.063). Most patients in group 1-1 (n = 5, 83.3%) and group 2-1 (n = 6, 85.7%) showed MPO grade of 2 or less ($P$ = 0.138), whereas most patients in group 1-2 (n = 5, 62.5%) and group 2-2 (n = 5, 71.4%) showed MPO grade 3 ($P$ = 0.103) (**Table 6**).

## Table 6. Comparisons between groups based on genetic evidence or spontaneous recovery of ANC

| | Comparison 1 | | | Comparison 2 | | |
|---|---|---|---|---|---|---|
| | Group 1-1 Congenital neutropenia with causal variants (n=7) | Group 1-2 Neutropenia without pathogenic genetic evidence (n=9) | Statistical significance | Group 2-1 No spontaneous recovery of ANC (n=8) | Group 2-2 Spontaneous recovery of ANC (n=8) | Statistical significance |
| Age at initial presentation* (month) | 3.0 (0.5-28.0) | 10.0 (6.0-17.0) | *P*=0.222 | 3.5 (0.6-25.0) | 10.0 (5.0-17.0) | *P*=0.399 |
| Sex, n (%) | | | *P* <.01 | | | *P* <.01 |
| Male | 7 (100.0) | 1 (11.1) | | 7 (87.5) | 1 (12.5) | |
| Female | 0 (0.0) | 8 (88.9) | | 1 (12.5) | 7 (87.5) | |
| Family history, n(%) | | | *P*=1.000 | | | *P*=1.000 |
| Yes | 3 (42.9) | 4 (44.4) | | 4 (50.0) | 3 (37.5) | |
| No | 4 (57.1) | 5 (55.5) | | 4 (50.0) | 5 (62.5) | |
| Organomegaly, n (%) | | | *P*=1.000 | | | *P*=1.000 |
| Yes | 3 (42.9) | 3 (33.3) | | 3 (37.5) | 3 (37.5) | |
| No | 4 (57.1) | 6 (66.7) | | 5 (62.5) | 5 (62.5) | |
| Extra-hematopoietic feature, n (%) | | | *P*=0.106 | | | *P*=0.282 |
| Yes | 4 (57.1) | 1 (11.1) | | 4 (50.0) | 1 (12.5) | |
| No | 3 (42.9) | 8 (88.9) | | 4 (50.0) | 7 (87.5) | |
| Severe infection, n(%) | | | *P* <.01 | | | *P* <.01 |
| Yes | 6 (85.7) | 1 (11.1) | | 6 (75.0) | 1 (12.5) | |
| No | 1 (14.3) | 8 (88.9) | | 2 (25.0) | 7 (87.5) | |
| Fever pattern, n (%)† | | | *P*=0.592 | | | *P*=1.000 |
| Neutropenic fever only | 5 (71.4) | 3 (33.3) | | 5 (62.5) | 3 (37.5) | |
| Neutropenic fever and non-neutropenic fever | 2 (28.6) | 4 (44.4) | | 3 (37.5) | 3 (37.5) | |
| Neutropenia pattern, n (%) | | | *P* <.01 | | | *P* <.05 |
| Permanent | 5 (71.4) | 0 (0.0) | | 5 (62.5) | 0 (0.0) | |
| Intermittent | 2 (28.6) | 9 (100.0) | | 3 (37.5) | 8 (100.0) | |
| G-CSF responder, n (%)‡ | | | *P*=0.242 | | | *P*=0.072 |
| Yes | 1 (14.3) | 4 (44.4) | | 1 (12.5) | 4 (50.0) | |
| No | 5 (71.4) | 2 (22.2) | | 6 (75.0) | 1 (12.5) | |
| Initial ANC* | 102 (0-958) | 146 (32-540) | *P*=0.872 | 124 (0-917) | 157 (16-682) | *P*=0.915 |
| Last ANC* | 0 (0-69) | 1797 (1366-3892) | *P* <.01 | 26 (0-567) | 2246 (1652-3946) | *P* <.01 |
| M:E ratio*§ | 1.6 (0.6-3.4) | 2.7 (1.3-4.1) | *P*=0.194 | 1.9 (0.8-3.2) | 2.4 (1.2-4.3) | *P*=0.354 |
| MPO-positive cell (%)*¶ | 42.38 (22.06-45.78) | 42.65 (32.21-50.64) | *P*=0.439 | 42.38 (26.45-46.05) | 42.7 (28.5-50.6) | *P*=0.259 |

| | | | | | | |
|---|---|---|---|---|---|---|
| MPO grade, n (%)*¶ | | | *P*=0.138 | | | *P*=0.103 |
| Grade 0, 1 or 2 | 5 (71.4) | 3 (33.3) | | 6 (0.75) | 2 (25.0) | |
| Grade 3 | 1 (14.3) | 5 (55.5) | | 1 (12.5) | 5 (62.5) | |
| Myelokathexis, n (%) | | | *P*=0.063 | | | *P*=0.200 |
| Yes | 3 (42.9) | 0 (0.0) | | 3 (37.5) | 0 (0.0) | |
| No | 4 (57.1) | 9 (100.0) | | 5 (62.5) | 8 (100.0) | |
| Maturation arrest, n (%) | | | *P* <.05 | | | *P*=0.143 |
| Early stage | 3 (42.9) | 0 (0.0) | | 3 (37.5) | 1 (12.5) | |
| Late stage | 0 (0.0) | 5 (55.5) | | 0 (0.0) | 4 (50.0) | |

*Values presented as medians (interquartile ranges).

†Two patients who did not suffer from infection or fever during the follow-up period were excluded.

‡Three (18.8%) patients in whom G-CSF was not administered were not included. Also, one patient who could not assess the response to G-CSF were excluded.

§One patient with diluted BM aspiration in which reliable differential count could not be made was excluded.

¶Two patients were not included due to inadequate BM section quality or retrospectively unavailable BM paraffin block for MPO stain.

Abbreviations: BM, bone marrow; G-CSF, granulocyte-colony stimulating factor; M:E, myeloid to erythroid; MPO, myeloperoxidase.

## 3.15. Comprehensive real-world data on neutropenia in Korean children

Including the 16 patients in this study, electronic medical records on a total of 345 neutropenia patients for the same period were reviewed. Two brothers with the same *G6PC3* variant were counted as one person. Identifiable causes of neutropenia were detected in 102 out of 345 patients (29.6%). Post-infectious neutropenia was the most common (n = 56, 54.9%) followed by neutropenia with disease-causing variants (n = 11, 10.8%), drug-induced neutropenia (n = 13, 12.7%), hemophagocytic lymphohistiocytosis (n = 8, 7.8%), neutropenia due to maturation arrest (n = 5, 4.9%), neutropenia due to depressed granulopoiesis (n = 3, 2.9%), neutropenia with trisomy 8 (n = 1, 1.0%), hyper IgM syndrome (n = 3, 2.9%) and autoimmune neutropenia (n = 1, 1.0%) (**Figure 19**).

Five patients who underwent genetic tests without BM exam harbored *ELANE* mutation (NM_001972.4:c.669C>A, p.(C223X) and c.455T>C, p.(L152P)) in 2 patients, hemizygous *TAZ* mutations (NM_001348362.1:c.227delC, p.(P76fs) and NM_000116:c.350A>C, p.(K117T) ) in 2 male patients and a homozygous *SLC37A4* mutation (NM_001467.6):c.1179G>A, p.(W393X)) in one patient.

Focusing on the 11 patients with pathogenic genetic variants including 8 patients without BM exam, variants in an *ELANE* gene were the most common (n=6, 42.9%), followed by *TAZ* (n = 2, 14.3%), *G6PC3* (n = 1, 7.1%), *CXCR4* (n = 1, 7.1%) and *SLC37A4* (n = 1, 7.1%) (**Figure 20**).

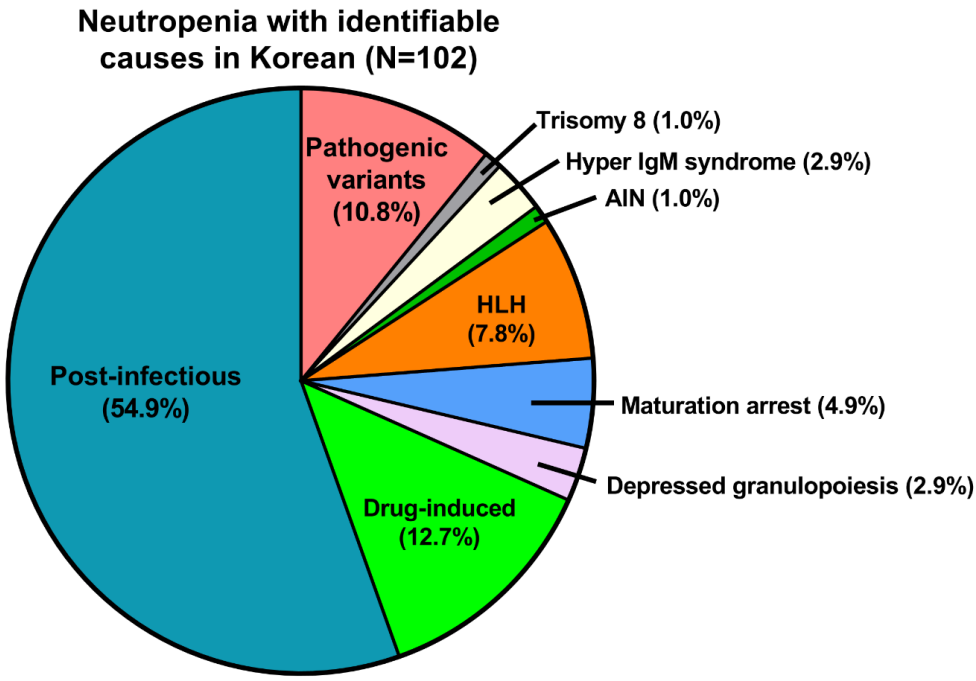



**Figure 19. Real-world data on identifiable causes of neutropenia in Seoul National University Children's Hospital from 2009 to 2018**

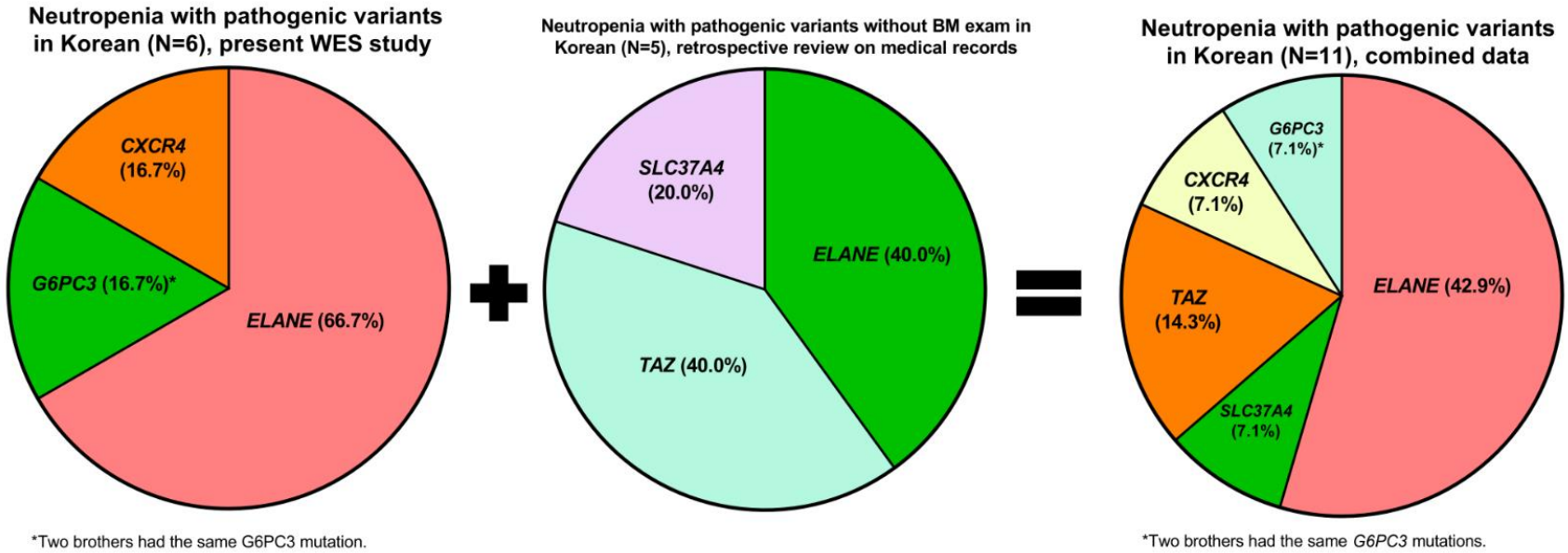



**Figure 20. Comprehensive data on disease-causing genetic variants in 11 neutropenia patients obtained by combining this WES study results of the 6 patients and medical records of another 5 patients for whom BM exam was not performed**

# 4. Discussion

We performed WES or TS on 16 neutropenia patients and re-diagnosed each of them on the basis of genetic study, BM histology and clinical features. A heterogeneous genetic landscape was noted in the 7 neutropenia patients with pathogenic variants, two of whom were brothers who shared the same variant: *ELANE* (n = 4, 66.7%), *G6PC3* (n = 1, 16.7%) and *CXCR4* (n = 1, 16.7%).

Combining real world data with our study results revealed ELANE mutations as the most common (42.9%) disease-causing variant of CN in Korean, which is similar to data in Caucasians. Mutations in other genes such as *HAX1*, *VPS13B*, *WAS* or *TCIRG1* were reported in Caucasians [2] and they were not detected in our cohort. This might be attributed to our small number of study population or ethnic difference. Genes such as *HAX1*, *VPS13B* or *TCIRG1* are inherted in autosomal recessive manner and mutations in these genes are thought to be uncommon in Korean due to rare consanguinity. Despite our effort to include as many CN patients as possible, some CN patients might have been missed due to follow-up loss or insufficent diagnostic work-up including BM exams or genetic tests.

The 4 patients with *ELANE* mutations showed permanent neutropenia with early-stage maturation arrest and no extra-hematopoietic manifestations. An *ELANE* mutation is associated with the most serious infectious complications [18], and one of the *ELANE*-mutated patients, who was the only non-survivor among the 16 neutropenia patients, died of sepsis. Two patients with the same *ELANE* mutation (G214R) showed totally different BM histology and clinical course, which suggests that the same mutation does not necessarily lead to the same or similar clinical phenotype or BM histology. *ELANE* mutations with the same codon

change are known to result in different clinical phenotypes. For example, *ELANE* p.(F43L), p.(A61V), p.(V101M), p.(S126L), p.(S126W), p.(P139L), p.(Q194X), IVS4+1G>A, IVS4+5G>A, p.(G214X), p.(R220Q) and p.(Y228X) can manifest as CN that can develop into MDS or AML, while they can also result in cyclic neutropenia with a relatively good prognosis [36]. In a case report on Korean patients with the same *ELANE* mutation (NM_001982.2:c.591+1G > A), different clinical phenotypes were found even within the same family [30]. In the present study, low MPO-positive cells and MPO grade might have affected poor prognosis due to decreased granulopoietic cell reservoir.

In the present study, a novel variant in *G6PC3* (NM_138387.3):c.214delA, p.(K72fs)) was discovered in two brothers. Of note, one of them showed an extra-hematopoietic feature of juvenile rheumatoid arthritis, which has not been reported as a consequence of *G6PC3* mutations. Furthermore, they showed myelokathexis, which has been reported as rare in patients with a *G6PC3* mutation [37]. Both brothers showed very similar clinical features and BM histology. The CNV analysis of these brothers detected the CN-LOH of the 17q21.31 region (chr17:45,287,005–48,276,944 in P-13 and chr17:44,771,405–48,276,944 in P-14), disclosing the mechanism of homozygous *G6PC3* mutations. Although we could not perform a trio study due to the unwillingness of their parents, we inferred the possible causes and mechanisms as follows. Among 22 autosomal chromosomes, homozygosity was observed only in chromosome 17 (data not shown), which tentatively rules out consanguinity. Chromosome 17 with CN-LOH at 17q21.31 might have been monosomy- or trisomy-rescued or a gamete carrying CN-LOH at 17q21.31 with non-disjunction might have been inherited [38]. On the basis of the same CN-LOH pattern of chromosome 17 in both brothers we may attribute the autosomal

recessive CN to either maternal or paternal whole uniparental isodisomy of chromosome 17 rather than to two carrier parents with the same mutation. (**Figure 21**).

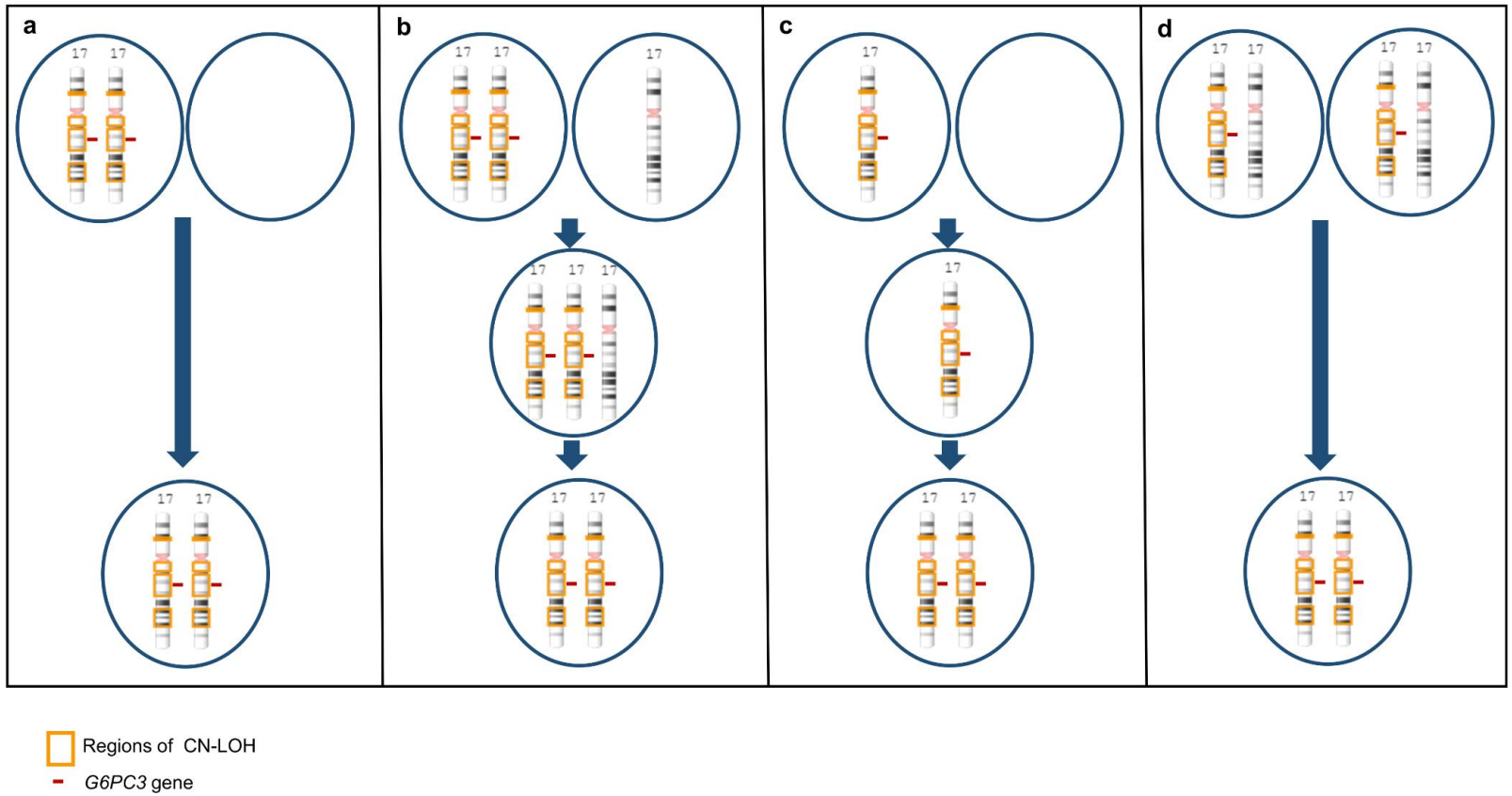



**Figure 21. Four hypotheses for the occurrence of homozygous *G6PC3* mutations by CN-LOH.** Four possible alternative scenarios are

shown. (A) One gamete has two copies of chromosome 17 with copy-neutral loss of heterozygosity (CN-LOH) in the 17q21.31 region, while the other gamete has no copies. A zygote with the two copies from one gamete (whole uniparental isodisomy of chromosome 17) is generated. (B) One gamete with two copies of chromosome 17 with CN-LOH at 17q21.31 and the other gamete with one copy of chromosome 17 without CN-LOH at 17q21.31 are fertilized and trisomy rescue occurs, leading to a zygote with two copies of chromosome 17 from one gamete (whole uniparental isodisomy of chromosome 17). (C) A gamete with one copy of chromosome 17 with CN-LOH at 17q21.31 fertilizes another gamete with no copies of chromosome 17. Following monosomy rescue, a zygote with two copies of chromosome 17 from one gamete (whole uniparental isodisomy of chromosome 17) is formed. (D) Two gametes can have the same chromosome 17 with CN-LOH at 17q21.31. With a probability of 25%, a zygote with two copies of chromosome 17 with CN-LOH at 17q21.31 is generated. We estimated that the chances of having chromosome 17 with the same CN-LOH regions in both parents are extremely low unless they are consanguineous, which was tentatively ruled out by homozygosity plots, which showed the same CN-LOH regions in chromosome 17 only. CN-LOH, copy-neutral loss of heterozygosity.

Regarding the BM histology, myelokathexis was a common feature in patients with *CXCR4* and *G6PC3* mutations. However, the former showed permanent neutropenia and dysplastic neutrophils, whereas the latter had intermittent neutropenia with no distinct dysplasia. The two brothers with *G6PC3* mutations showed very similar BM histology of myelokathexis with a strikingly increased proportion of old neutrophils in comparison with patients carrying *CXCR4* mutations, who showed relatively overall increase in the number of myeloid cells at each stage. The difference in myelokathexis features between patients with *CXCR4* and *G6PC3* mutations might have resulted from different mutated genes. Alternatively, it might be attributable to the different age when the BM exam was performed: the patient with the *CXCR4* mutation was 21 months old, whereas the *G6PC3* patients were 19 and 21 years old and therefore might have had a more advanced state of myelokathexis.

One of the 16 patients (P-01) was assessed as chronic idiopathic neutropenia because we could not find any related pathogenic candidate variants. She had intermittent neutropenia for more than 3 years; her BM exam revealed a low percentage of MPO-positive cells with MPO grade 1. We infer that considering the clinical course, there might be a veiled cause for her neutropenia, although it was not identified in this study by WES.

A total of 8 patients were re-diagnosed as acquired neutropenia. Pathogenic disease-causing variants were not detected in those patients who showed clinically benign course, which supported the likelihood of acquired or transient neutropenia. However, it would be possible that they have CN due to inherited variants in novel genes not yet associated with CN. So, they can be reassessed in the future when more genomic databases are available.

Meanwhile, for BM histologic assessment, we analyzed absolute count of MPO-positive cells in BM section using ImageJ and MPO grade. MPO-positive cell count in BM sections is not influenced by peripheral blood dilution or site variation in BM. For that reason, the amount of granulopoiesis is assessed more accurately in BM sections rather than in BM aspirates. Also, it might be useful to assess the absolute numbers of myeloid cells compared to the M:E ratio which is relative and is largely influenced by erythroid values and hemodilution. The MPO grade assessment on BM sections aids in evaluating the objective myelopoiesis status. Moreover, topological observation of myeloid cells near the trabecular bone helps us to determine whether neutropenia arises from defective production or BM retention.

We examined a relationship between genotype and BM histology based on the percentage of MPO-positive cells, MPO grade and M:E ratio. Patients with *ELANE* mutations showed variable ranges of MPO-positive cells and MPO grades, while their M:E ratios were consistently low (0.5–1.5), indicating that although the absolute numbers of MPO-positive cells are variable, myeloid cells tend to be relatively fewer than erythroid cells. We speculate that this might be attributable to apoptosis of myeloid precursors in patients with *ELANE* mutations. On the other hand, in the cases of myelokathexis caused by *CXCR4* and *G6PC3* mutations, MPO-positive cells constituted 40%–50% with MPO grade 1 or 2. The M:E ratio was increased in the patient with a *CXCR4* mutation (M:E ratio, 7.9), but it was not in patients with *G6PC3* mutations (M:E ratio, 1.5–2.5). These observations imply that the M:E ratio is not reliable for the assessment of myelokathexis. Instead, the combination of the percentage of MPO-positive cells and low MPO grade might be helpful for the evaluation of the BM retention status. Although information on

MPO-positive cells, MPO grade and M:E ratio provides clues to the BM granulopoiesis status, confirmation by genetic study is necessary for the accurate diagnosis of CN.

Clinically significant variants might have been missed in our study because of methodological limitations. Our CNV analysis detected no clinically significant gains or losses, contrary to the reported detection of 16.4% of pathogenic CNVs in IBMF patients [39]. WES-based CNV analysis by ExomeDepth has been reported to have sensitivity of approximately 40% for deletions and 30% for duplications compared to chromosomal microarray, which is the current gold-standard method for CNV analysis [40]. Pathogenic variants located in deep introns or variants with mosaicism might have been missed either.

Real-world data on neutropenia patients and their diagnostic work-up showed the pitfalls of the diagnostic algorithm for CN in our hospital, in which immunological work-up is not performed routinely. Meanwhile, a retrospective review on medical records revealed pathogenic variants in *ELANE*, *TAZ* and *SLC37A4* in 5 patients. Patients with *TAZ* or *SLC37A4* mutations showed cardiomyopathy or glycogen storage disease as their main clinical phenotype, respectively. Close association between immunodeficiency and CN warrants immunological studies including immunoglbulin quantification and lymphocyte subset analysis for diagnosis of CN. Physiologically low immunoglobulin levels should be considered for neonates. Considering the heterogeneity of CN in terms of genotypes and phenotypes, WES or expanded next generation sequencing panel which covers genes related to immunodeficiency and IBMF as well as CN would be necessary.

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# 국문 초록

**서론:** 선천성 호중구 감소증은 유전학적, 형태학적, 조직학적인 측면에서 다양한 양상을 가지는 혈액학적 질환이다. 본 연구를 통해 한국인 선천성 호중구 감소증 환자의 원인이 되는 유전자 돌연변이를 찾고 유전자 돌연변이, 골수 조직 소견 및 임상적 표현형 간의 관계를 분석하고자 하였다.

**방법:** 2009년부터 2018년까지 골수 검사를 통해 선천성 호중구 감소증 진단을 받은 16명 환자의 골수 또는 말초 혈액 검체를 대상으로 전체엑솜염기서열 분석 또는 표적염기서열분석을 시행하였다. ImageJ 소프트웨어를 사용하여 골수 조직의 절대적 골수세포형과산화효소 양성 세포 계수를 시행하고, 골수세포형과산화효소 등급을 0부터 3까지 4단계로 나누어 반정량하였다. 동일 기간 동안 호중구 감소증이 있었던 345명의 소아 환자 데이터를 검토하여 포괄적인 호중구 감소증 원인에 대해서도 분석하였다.

**결과:** 7명의 환자에서 선천성 호중구 감소증의 원인이 되는 병적 돌연변이가 *ELANE*, *G6PC3*, *CXCR4* 유전자에서 발견되었다. 그 중 *G6PC3* 유전자의 동형 돌연변이는 복제수 중립 이형접합성 소실이 기전이 되어 발생한 기보고 없는 돌연변이였다. *ELANE* 유전자 돌연변이를 가진 환자들은 골수구계 세포와 적혈구계 세포 비율이 0.5–1.5로 낮았으며, *G6PC3*와 *CXCR4* 유전자 돌연변이를 가진 환자들은 골수카텍시스를 보이면서, 골수세포형과산화효소 양성 세포가 40%–

50% 이고, 골수세포형과산화효소 등급은 1 또는 2 였다. 후향적 의무기록 검토 결과, 5명의 환자에서 *ELANE*, *TAZ*, *SLC37A4* 유전자의 병적 돌연변이가 있었다.

**결론:** 본 연구의 결과를 토대로, 호중구 감소증 환자에서 면역학적 검사, 골수 검사, 전체엑솜염기서열 분석 또는 면역결핍증과 다른 선천성 골수부전 관련 유전자를 포함하는 확장된 차세대 염기서열 분석 패널을 이용한 유전자 분석을 권장한다.

**주요어:** 선천성 호중구 감소증, 전체엑솜염기서열 분석, 호중구 감소증, 차세대 염기서열 분석

**학번:** 2020-35277