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ORAL ABSTRACTS

201.GRANULOCYTES, MONOCYTES, AND MACROPHAGES

Heterogeneous Genetic Landscape of Chronic Idiopathic Neutropenia Revealed By Whole Exome Sequencing

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Background: Adultpatients with persistent, unexplained neutropenia who do not fulfill the diagnostic criteria of any underlying disease are characterized as chronic idiopathic neutropenia (CIN) cases.It is an exclusion diagnosis that can be established after a thorough clinical/laboratory investigation for any underlying causes, including negative anti-neutrophil antibody testing, inconclusive bone marrow (BM) aspiration/biopsy and normal cytogenetics. CIN patients regardless of their absolute neutrophil counts (ANC) usually display a benign and uncomplicated clinical course. Although the pathogenesis of CIN remains largely unknown, we hypothesize that a constitutional/congenital background might exist, at least in some cases, that have potentially escaped diagnosis during childhood.
Aim of the study: To investigate the genetic landscape of neutropenia in CIN by conducting whole exome sequencing (WES) analysis in a number of adult CIN patients.
Methods: We have performed WES in 16 adult (median age 59 years, range 30-72 years) patients (11 females and 5 males) with CIN according to previously published criteria (Fioredda F, et al Hemasphere. 2023). The patients had median ANC 1.2 x 10^9/L (range 0.4-1.6 x 10^9/L) for prolonged period and unknown neutropenia onset in most cases. Genomic DNA was extracted from peripheral blood samples, coding fragment libraries were prepared, sequencing performed on Illumina NovaSeq 6000 System, and data subjected to an in-house pipeline for bioinformatic analysis for variant calling and annotations. Singleton analyses were performed focusing on genes associated with congenital defects of phagocytes, BM failure (BMF) and immune deficiency and dysregulation. Mean depth of coverage was 70x and the mean number of variants/sample was 22553.
Results: WES analysis identified 10 pathogenic/likely pathogenic (P/LP) variants in 10 patients. The variants consisted of 4 frameshift mutations, 3 nonsense mutations, 1 missense mutation, 1 splice-site mutation and 1 splice-region mutation. Pathogenic variants in congenital neutropenia (CN)-related genes included only a heterozygous mutation in *G6PC3*:c.511C>T,p.Gln171Ter (previously detected in one of our CN patients; Nikolouzakis TK et al, Ann Hematol. 2022). Pathogenic variants in genes associated with BMF were detected in two genes, namely *FANCM*:c.1492C>T, p.Gln498Ter and *CTC1*:c.3058C>T,p.Gln1020Ter, respectively. The majority of the pathogenic variants were found in genes associated with immune deficiency and dysregulation. These involved: (i) a heterozygous mutation in *DCLRE1C*:c.1784dup,p.Ile596fs (associated with immunodeficiencies affecting cellular and humoral immunity); (ii) a LP mutation in *ORAI1*:c.132_133del,p. Arg45fs and a pathogenic variant in *SPINK5*:c.1302+4A>T (related to combined immunodeficiencies with associated or syndromic features); (iii) a pathogenic variant in *MEFV*:c.2080A>G, p.Met694Val and a LP variant in *PSMG2*:c.703-2A>T (both genes associated with autoinflammatory disorders); (iv) a LP variant in *IRF7*:c.1089dup,p.Pro364Alafs (associated with defects in intrinsic and innate immunity); and (v) a LP variant in *PEPD*:c.738_739insGT,p.Ser247fs (associated with immune dysregulation). Regarding variants of undetermined significance (VUS) an average of 4.5 VUS variants per patient were detected in genes related to CN (*HAX1*, *VPS13B*, *LYST*), BMF (*GATA2*, *SAMD9*, *CXCR4*) or immunodeficiency (*TCF3*). However, none of these patients display clinical symptoms typical of these conditions. Specifically, the majority of the patients presented with mild/moderate neutropenia and rarely with severe neutropenia, they have relatively normal BM biopsies and do not display major symptoms or signs related to severe immunodeficiency or immune dysregulation syndromes.
Conclusions: This study is the first attempt of WES analysis in adult CIN patients and shows that there is a heterogeneous genetic landscape underlying the disease. More studies are required so that the detected P/LP variants and VUS can be associated with the clinical phenotypes to more accurately interpret their potential contribution to the neutropenia phenotype.

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