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P2RX7 GENE VARIANTS ASSOCIATE WITH ALTERED INFLAMMASOME ASSEMBLY AND REDUCED PYROPTOSIS IN CHRONIC NONBACTERIAL OSTEOMYELITIS (CNO)

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Introduction: Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disease primarily affecting children and adolescents. It can cause pain, hyperostosis and fractures, affecting quality-of-life and psychomotor development. The exact pathophysiology remains unknown, and no disease-specific biomarkers exist.

Objectives: This study aimed to investigate CNO-associated variants in *P2RX7*, encoding the ATP-dependent trans-membrane K^+ channel *P2RX7*, and their effects on NLRP3 inflammasome assembly, to explore potential for patient stratification and individualized care.

Methods: Whole exome sequencing in two CNO patients from the same family (mother and daughter), and target sequencing of *P2RX7* in a large CNO cohort (N=190) were conducted. Results were compared with publicly available datasets and regional controls (N=1873). Findings were integrated with demographic and clinical data. Patient-derived monocytes and genetically modified THP-1 cells were used to investigate potassium flux, inflammasome assembly, pyroptosis, and cytokine release.

Results: Rare damaging mutations in *P2RX7* were identified in two related CNO patients. Targeted *P2RX7* sequencing identified 11 additional CNO patients with rare damaging variants. Across the CNO cohort, rare variants unique to one (Median: 42 versus 3.7) or more (up to 11 CNO patients) participants were over-represented when compared to 190 randomly selected healthy controls. Patients with rare damaging variants were younger and more frequently required treatment with 2nd-line agents (DMARDs and/or bisphosphonates). Monocyte-derived macrophages from patients, and genetically modified THP-1-derived macrophages expressing variant P2X7 exhibited altered potassium flux, inflammasome assembly, IL-1β and IL-18 release, and pyroptosis.

Conclusion: Rare damaging *P2RX7* variants occur in a small subset of the here investigated CNO patients (5·7%). The genetically variable *P2RX7* gene may represent a CNO risk allele. Observations argue for inhibition of inflammasome activation and/or cytokine blocking strategies and may allow future patient stratification and individualized care.

Patient Consent: Yes, I received consent

Disclosure of Interest: None declared