Novel NCF2 Mutation Causing Chronic Granulomatous Disease

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INTRODUCTION

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder caused by defects in the NADPH oxidase complex, resulting in abnormal activity that leads to diminished reactive oxygen species production which act to kill pathogenic bacteria and fungi. Mutations in *NCF2* encoding the cytosolic factor p67^{phox} result in autosomal recessive CGD. Here we describe the clinical features and laboratory findings of three patients (two of them are siblings) carrying a novel c.855G>C *NCF2* mutation presenting with diverse clinical phenotype.

OBJECTIVES

To evaluate whether the novel c.855G>C *NCF2* mutation is pathogenic and cause the diverse clinical phenotype of CGD.

METHOD

Clinical Trio-Whole Exome or PIDD panel sequencing was done and indings were confirmed by Sanger sequencing. Neutrophil function was tested by DHR123 assay, superoxide production and their bactericidal activity. NADPH-oxidase components were assessed in cellular extracts of purified polymorphic nuclear cells by immunoblotting. This study has been approved by the ethical committee of "Meir" Medical Center, Kfar-Saba, Israel.

RESULTS

All 3 patients carry a novel missense *NCF2* variant (c.855G>C, p.Gln285His; Fig. 1). The two siblings were heterozygous for the novel mutation and for a previously described exon 8-9 duplication, one having history of severe pneumonia, lymphadenitis and recurrent skin abscesses and the other presenting in his 30s with discoid lupus erythematosus and without significant infectious history. The third unrelated patient was homozygous for the novel mutation and presented with suspected early onset interstitial lung disease.

Functional testing confirmed mutation pathogenicity with abnormal DHR123 assay (Fig. 2) and diminished superoxide production (not shown). The bactericidal activity of the two siblings was normal (1.18 and 0.44-log decrease) while the third homozygous patient had abnormal bactericidal activity of 0.06 log decrease (Fig. 3). Immunoblotting analysis (Fig. 4) showed absence of the p67^{phox} protein of the NADPH-oxidase components with normal gp91^{phox}, p47^{phox} and p22^{phox}.

Figure 1

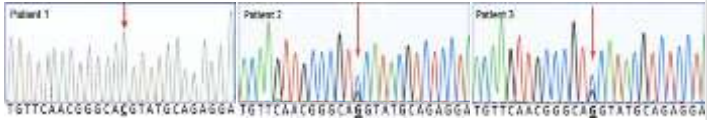


Figure 2

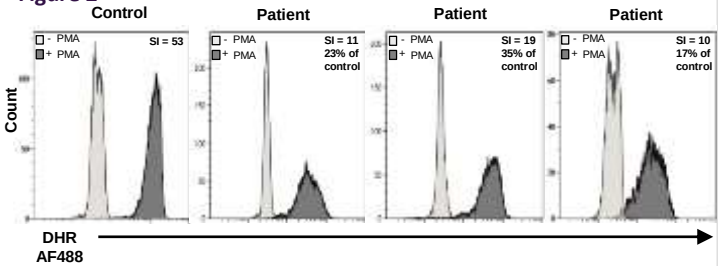


Figure 3

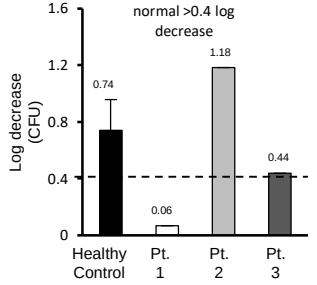
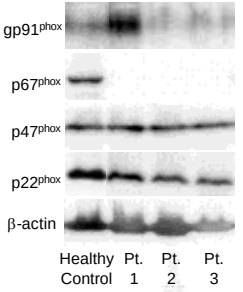


Figure 4



CONCLUSIONS

- **We describe a novel pathogenic c.855G>C *NCF2* mutation**
- **The patients present a diverse clinical spectrum ranging from early age ILD to adult onset DLE.**
- **These cases highlight the importance of suspecting CGD also in patients with unusual autoimmune diseases or recurrent mild infections**

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