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Clinical, Immunological, and Genetic Features of 11 Patients with Chronic Mucocutaneous Candidiasis

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Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare genetic disorder associated with an inability to remove fungal infections, notably candida albicans, leading to persistent and recurrent invasion of the skin, nail, and mucous membranes . Moreover, immune dysregulation in patients with CMC may cause various autoimmune diseases and affect growth and development. The advancements in next- generation sequencing techniques have provided valuable data to reveal the underlying reason for this disorder. Single transducer and activator of transcription-1 (STAT1), autoimmune regulator (AIRE), Caspase Recruitment Domain-containing protein 9 (CARD9), and Interleukin-17 Receptor A/C (IL-17RA/IL-17RC) are some of the most important involved gene.

The Aim of this study is to present the clinical manifestations and molecular findings of 11 CMC patients within 7 families who have been diagnosed with the disease.

Material and Methods

Patients who were clinically suspected to CMC were referred to Immunology, Asthma & Allergy Research Institute for immunological and molecular evaluation. Eleven patients met the criteria for entering this study. The diagnosis was based on their clinical history, physical examination, laboratory, and immunological evaluations including lymphocyte transformation test (LTT) to PHA and candida .

Genomic DNA of patients were extracted from whole blood and subjected to Whole Exomes Sequencing (WES). Further, WES results were confirmed in patients, and segregation analysis was performed for available parents' samples by Sanger Sequencing.

The Varsome tool and The American College of Medical Genetics and Genomics (ACMG) guideline were considered for the interpretation of sequence variants.

Results

The demographic data and clinical manifestations of the patients have summarized in table 1. Candida infections were present in all patients, the most clinical manifestation among them was recurrent oral candidiasis (thrush) (67%), skin and nail candidiasis (50%), and vaginal candidiasis (25%). Pneumonia was evident in one patient, and two more patients suffered from esophagitis and gastrointestinal infection, respectively. The LTT evaluations were normal against PHA while low T cell stimulations (<50% Stimulation index) were observed against candida in all patients.

Three novel mutations in STAT1 (c.1159 A>G), IL-17R (c.722-730 del), CARD9 (c.1032del-AGGC), and a previously reported 13 base pair deletion in the AIRE gene. These variants are considered likely pathogenic according to ACMG. The sequencing results and segregation study have been shown in Figure 1. No known variants were identified in 4 patients.

Table 1. Demographic and clinical features of the patients

Patient	Sex	Age of Onset (year)	Age of Diagnosis (year)	Family History/ Consanguinity	Current Status/Age (year)	Clinical Features
1	Male	7	56	Yes/No	Dead/61	Recurrent oral candidiasis (thrush)
2	Female	3	21	Yes/No	Alive/33	Recurrent oral candidiasis, vaginal candidiasis
3	Male	1	3	Yes/No	Alive/3	Recurrent oral candidiasis
4	Female	1	4	Yes/No	Alive/16	Recurrent oral candidiasis, vaginal candidiasis
5	Male	1	7	No/Yes	Alive/17	Recurrent oral candidiasis, pneumonia, fungal fingernails infection, diabetes type I
6	Male	1	2	No/Yes	Alive/10	Recurrent oral candidiasis, gastrointestinal infection
7	Female	<1	1	No/Yes	Alive/31	Recurrent oral candidiasis, fungal fingernails infection, Hypothyroidism
8	Female	6	29	Yes/Yes	Alive/31	Skin candidiasis
9	Male	3	4	Yes/Yes	Alive/5	Skin candidiasis
10	Female	7	8	No/Yes	Alive/16	Skin and nail candidiasis
11	Female	1	40	Yes/No	Alive/45	Seborrheic dermatitis, vaginal candidiasis, fungal infection on buttocks, candida esophagitis

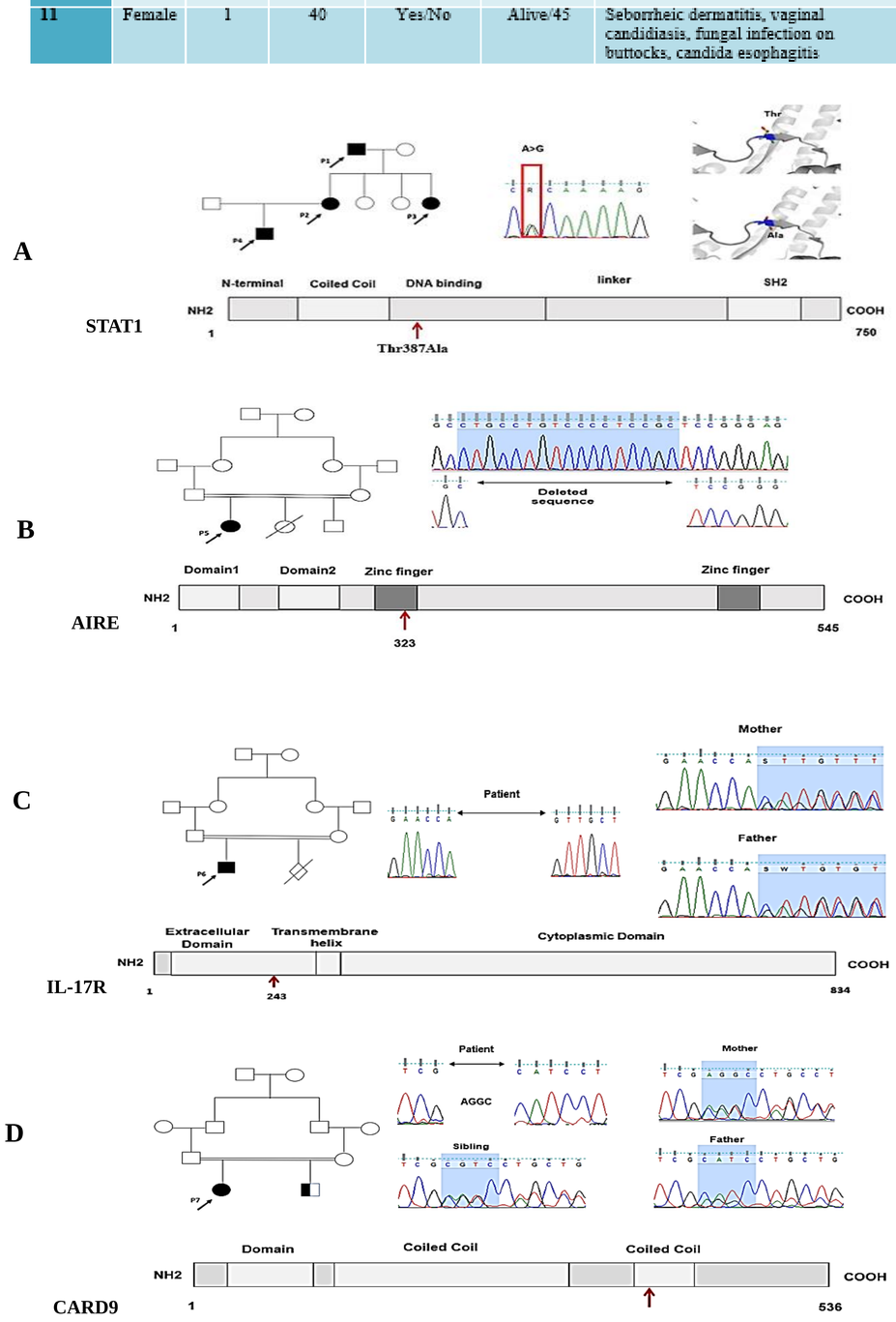

Figure 1. Schematic figures of the proteins, Sanger sequencing validation and pedigrees in four families (A-D). The proband has been shown with arrow.

Conclusion

This study provides versatile clinical and genetic implications for CMC patients. The results of this study can contribute to the provision of genetic counseling for these families to find affected members and early diagnosis. Moreover, the development of innovative therapeutic approaches for CMC would be applicable.

Conflict of Interest

In relation to this presentation, I declare that there are no conflicts of interest.

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