A Novel STAT1 Mutation in an African American Male with Chronic Mucocutaneous Candidiasis

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ABSTRACT

Background: Chronic mucocutaneous candidiasis (CMC) is a disorder that manifests with frequent episodes of candidiasis of the skin and mucous membranes. The cause of CMC is frequently unknown but STAT1 mutations have recently been identified. We introduce a novel mutation in exon 9 of STAT1 in a patient with CMC.

Methods: A 19 year-old African American male with esophageal candidiasis, onycholysis, no endocrinopathy, and intact delayed type hypersensitivity responses was diagnosed with CMC in infancy. Two known generations of CMC suggested an autosomal dominant mode of inheritance of a monogenic defect. Genomic sequencing for known STAT1 mutations was normal. Whole exome sequencing was subsequently performed.

Results: Whole exome sequencing identified a novel mutation consisting of an amino acid substitution from glutamine to glutamic acid at position 243 of exon 9 of the STAT1 gene.

Conclusions: In past decades, patients with CMC were diagnosed on a clinical basis. Only recently have patients been able to be definitively identified with this disorder by genomic analysis. We report a novel STAT1 mutation presenting with a different CMC phenotype than previously reported with described STAT1 mutations.

INTRODUCTION

Chronic mucocutaneous candidiasis (CMC) was first reported in a child with chronic tetany and chronic mycelia stomatitis by Thorpe et al in 1929 (1). Since that time CMC has been a diagnosis of exclusion. Laboratory studies attempting to define the immunological defect assumed to be T cell in nature have been inconsistent and unrevealing (2). The most recent revelation indicating a STAT1 mutation in a caucasion population on exon ten may suggest a unifying molecular diagnosis for a complex immunological defect (3, 4, 5). The case presented below uniquely documents the clinical presentation of CMC in an African American male with a novel mutation of STAT1 at a different exon, exon nine, which may suggest an African founder.

MATERIALS & METHODS

The patient is a nineteen year old African American male who initially presented at 2 weeks of age with thrush which continued throughout his life. The family history suggested an autosomal dominant inheritance based on a paternal history of affected males, both father and paternal grandfather. The patient's father was diagnosed with CMC and eventually died at the age of 29 of an aspergillosis lung infection. The grandfather also died at the same age of unknown causes and was known to experience multiple fungal infections.

The patient was treated with multiple antifungals for chronic episodic thrush and was eventually placed on prophylactic fluconazole. At 12 years, he was diagnosed with migraines, depression, anxiety, and adjustment disorder. Perioral hypopigmentaion due to fungal involvement developed during this time period and remained to the present time of this description despite adequate treatment. Endocrine and metabolic studies were unrevealing. Throughout his adolescent and teenage years the patient was afflicted with multiple episodes of culture negative stomatatis and abdominal pain requiring hospitalization for pain control and parental nutrition. On one occasion an endoscopy noted severe candidal esophagitis with superficial bacterial overgrowth.

Immunological evaluation showed normal percentage and absolute numbers of T, B, and NK cells. Serum immunoglobulins were normal. Functional studies of T cells utilizing both antigen and mitogen stimulation were normal. Delayed type hypersensitivity for candida noted a robust reaction greater than 10mm after 48 hours. See Table 1 for pertinent labs. STAT1 evaluation showed a substitution of glutamic acid for glutamine at position 243 on chromosome 2. See Figure 1 for picture of chromosome 2.

Initial genomic sequencing for know STAT1 mutations was normal. Further analysis was then completed per the Radboud University Nijmegen Medical laboratory. To assess for the presence of mutations in signal transducer and activator of transcription 1 (*STAT1*) in the affected patient, we amplified the DNA, using a polymerase-chain-reaction (PCR) assay, and sequenced the amplified DNA fragments by Sanger's method. All coding exons of the coiled-coil (CC) domain of *STAT1*, ranging from exon 6 to 11, were amplified and analyzed. Primer sequences are provided in Table 2.

Figure 1: STAT1

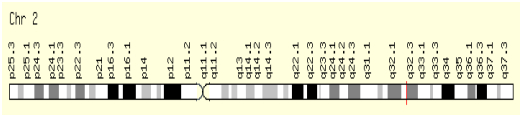

Table 1: Index Patient Pertinent Labs

Lab	Results
Delayed Type Hypersensitivty(48hour read)	Candida: 34 mm erythema, 15mm induration Trycophyton: 14mm erythema, 12mm induration
Immunoglobullins	IgG: 1488 (620-1400) IgM: 51 (33-232) IgA: 187 (75-375)
Mitogen Stimulations	Spontaneous: 35914 (0-280) Candida: 136588 (>15289) Tetanus: 90391 (>4761) Pytohemaglutinin 228893 (>135190)

Table 2: Primer Sequences

Fragment	Forward	Reverse
Exon 6	AACCAGCAAGTACACACCCTG	ACACCCCAAGCAATTGAAAC
Exon 7	TTCGTGTTTCTCTGGGTTCC	AAATACTCGGCAAATAGAAAGGAG
Exon 8-9	TGAATCTTGGCTTTTGTTGG	CAAAGGTACATTTATGTGTTTATGTGG
Exon 10	TTAATCCAGGCTGCTTCTGG	TGAATTAACGGTAAAATGTTCCTC
Exon 11	TCATTGTGATTGCCTCAACC	TTTCCTCAAAAGCACCCTATATAAC

RESULTS

The analysis noted a mutation in STAT1 which was not initially found by the original Sanger sequencing of the STAT1 gene since the mutated exon was not included in the initial Sanger analysis. The mutation of this index patient was located in exon 9 of the STAT1 gene. The mutation is Q243E which represents an amino acid substitution from glutamine to a glutamic acid on position 243 of exon 9. This mutation is unique to this patient as the previous study has shown a mutation in exon 10. The analysis suggests a similarity in the protein function effects from exons 9 and 10 of STAT1.

CONCLUSIONS

The diagnosis of chronic mucocutaneous candidiasis defines a group of patients suffering from a heterogeneous clinical spectrum. This spectrum involves infections often with Candida albicans of the nails, skin and oropharyngial mucosa (2). Endocrine and malignant disorders may also accompany this condition (2).
The laboratory evaluation of patients with CMC has been similarly heterogeneous. Standard blood immunological testing has failed to adequately define this group of patients and the diagnosis has often rested on the clinical and family history (2). Recently, investigators have discovered that a mutation in STAT1 may be the genotype for this clinical phenotype of CMC. The mutation was found in exon 10 in several caucasion Danish families affected with this disorder (3). We describe an African American family with autosomal dominant CMC. Despite normal laboratory immunological evaluation, the diagnosis in this family was primarily made on a clinical basis. STAT1 evaluation of one of the afflicted living family members showed a novel mutation in exon 9. The discovery of this STAT1 mutation suggests an African American founder effect.

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