DETECTION OF GATA2 MUTATIONS IN PATIENTS WITH NON-TUBERCULOUS MYCOBACTERIAL OR FUNGAL INFECTIONS WITHOUT KNOWN IMMUNODEFICIENCY IN RIO DE JANEIRO, BRAZIL

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INTRODUCTION

Infections caused by non-tuberculous mycobacteria (NTM) and disseminated or invasive fungal infections (IFI) are regarded as opportunists in immunocompromised patients. However, they are also observed in patients without an obvious cause of immunosuppression. In these situations, primary immunodeficiencies should be considered, especially disorders in the interleukin-12 (IL-12)- interferon-γ (IFN-γ) axis, which involves the GATA2 protein, a master hematopoietic regulatory factor. *GATA2* gene defects carriers can develop progressive loss of dendritic cells, monocytes, B lymphocytes, and natural killer cells during the lifespan. Sporadic or familial mutations are related to infection susceptibility, pulmonary dysfunction, lymphedema, warts, deafness, autoimmunity, aplastic anemia, and malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

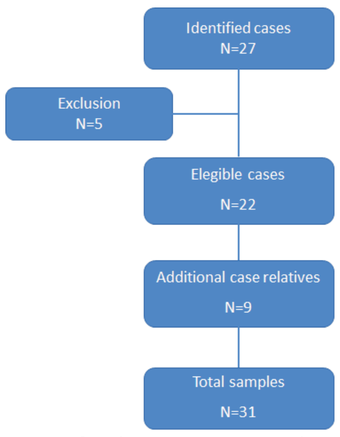
AIM

To identify *GATA2* mutations in patients with NTM and/or IFI without known causes of immunosuppression.

MATERIAL AND METHODS

DNA was extracted from peripheral blood and the six coding exons and intron 4 were amplified by PCR and sequenced by Sanger direct technique.

Figure 1. Study design of non-tuberculous mycobacteria or fungal infection patients with *GATA2* haplodefficiency, Brazil, 2015-2018

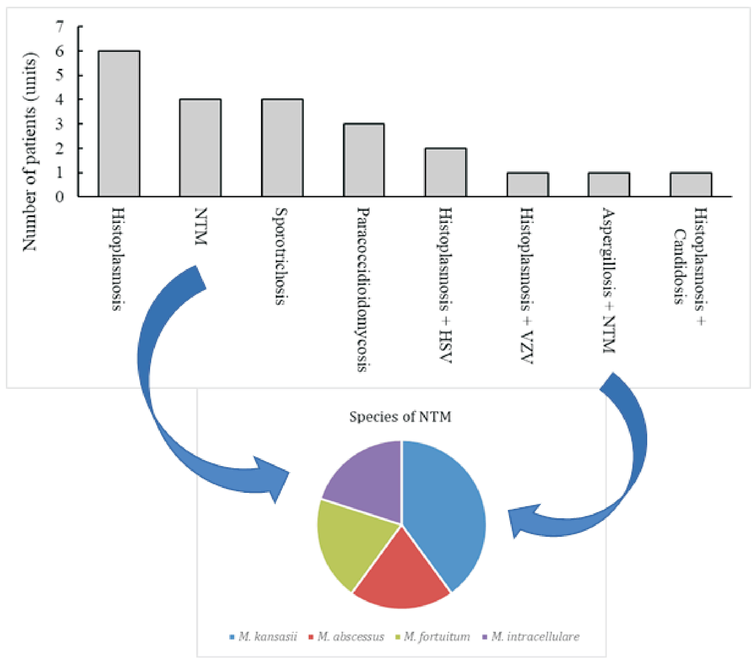


Demography	Cases (22)	Relatives (9)
Age (yrs)		
Median (min-max)	45,5 (19-75)	25 (10-74)
Sex		
Males	14 (63,6%)	6 (66,7%)
Females	8 (36,4%)	3 (33,3%)
Ethnicity		
Whites	13 (59%)	9 (100%)
Non-whites	9 (41%)	0 (0%)
Infections		
NTM	4 (18,2%)	-
IFI	17 (77,3%)	-
NTM + IFI	1 (4,5%)	-

Exclusion criteria: 5 patients refused to participate; n- number of individuals; NTM- non-tuberculous mycobacteria; IFI- invasive fungal infection

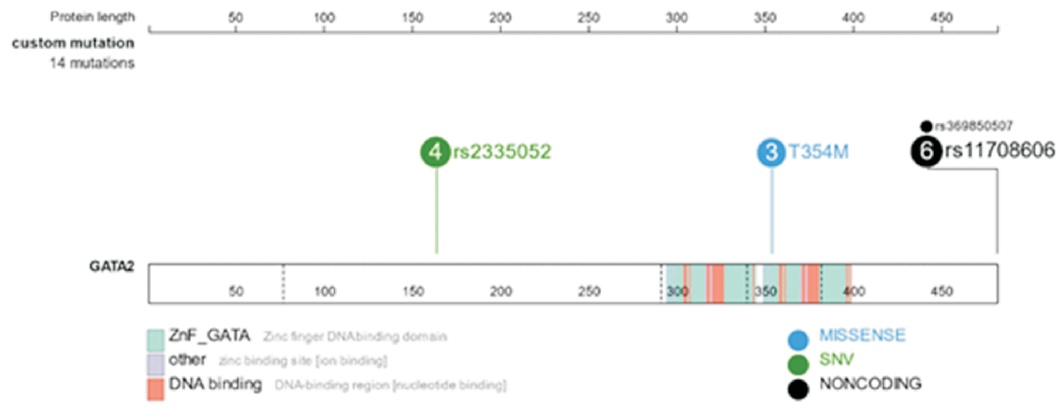
RESULTS

Figure 2. Frequency of mycobacterial and fungal infections in 22 ascertain patients



NTM – Nontuberculous mycobacteria; VZV- Varicella zoster virus; HSV - Herpes simplex virus.

Figure 3. Schematic figure of GATA2 variants identified



ZnF- Zinc finger; SNV- single nucleotide variant.

Table 1. Summary of main clinical findings and *GATA2* aberrations, Brazil 2015-2018

	Age/Sex/ Ethnicity	Infectious and neoplastic diagnosis	Rheumatological manifestation	*GATA2* variant	Type of variant	MAF (%)	Follow-up
1.	75/M/W	*M. kansasii*, MDS/ AML	No	c.490 G>A; p. 164 A>T (rs2335052) in exon 3A	Polymorphism	23	Death
2.	50/M/W	*M. kansasii*, MDS	Arthritis, vasculitis, erythema nodosum	c.1061 C>T p.T354M in exon 5	Pathogenic Mutation	-	Death
3.	19/M/W	PCM	No	g.11199 G>A (rs369850507) and g.11223 C>T (rs11708606), both in exon 5	Polymorphism	04 and 12.3	Death
4.	55/F/N-w	*M. fortuitum*, Melanoma[1]	No	c.490 G>A; p. 164 A>T (rs2335052) in exon 3A and g.11223 C>T (rs11708606) in exon 5	Polymorphism	23 and 12.3	Death
5.	57/M/W	Histoplasmosis, NHL	No	-	-	-	Alive
6.	52/F/N-w	Sporotrichosis	Erythema nodosum	-	-	-	Alive
7.	37/M/N-w	Histoplasmosis + HSV	No	g.11223 C>T (rs11708606) in intronic region of Exon 5	Polymorphism	12.3	Alive
8.	42/F/N-w	Histoplasmosis, Ovary	No	-	-	-	Alive
9.	25/M/N-w	PCM	No	c.490 G>A; p. 164 A>T (rs2335052) in exon 3A	Polymorphism	23	Death
10.	40/F/W	*M. intracellulare*	No	-	-	-	Death
11.	74/F/N-w	Sporotrichosis	No	-	-	-	Alive
12.	58/M/W	Histoplasmosis + Candidosis	Arthralgia	c.999C>T (rs11708606) in intronic region of Exon 5	Polymorphism	12.3	Alive
13.	49/M/N-w	Sporotrichosis, MDS, Melanoma[2]	No	-	-	-	Alive
14.	36/F/N-w	Sporotrichosis	Arthralgia	c.999C>T (rs11708606) in intronic region of Exon 5	Polymorphism	12.3	Alive
15.	55/M/W	Histoplasmosis + HSV	No	-	-	-	Alive
16.	58/M/W	Histoplasmosis	No	-	-	-	Alive
17.	59/M/W	Aspergillosis + *M. abscessus*	Arthralgia	c.999C>T (rs11708606) in intronic region of Exon 5	Polymorphism	12.3	Alive
18.	24/M/W	Histoplasmosis	No	-	-	-	Alive
19.	29/M/N-w	PCM	No	-	-	-	Alive
20.	30/F/W	Histoplasmosis + VZV	Arthralgia	-	-	-	Alive
21.	30/M/W	Histoplasmosis	No	c.490 G>A; p. 164 A>T (rs2335052) at Exon 3A	Polymorphism	23	Alive
22.	39/F/W	Histoplasmosis	No	-	-	-	Alive

M- Male; F- Female; W- White; N-w- Non-white; FH – Familial history; PCM - Paracoccidioidomycosis; HSV- Herpes simplex virus; VZV- Varicella-zoster virus; NTM- Nontuberculous mycobacteria; MDS- Myelodysplastic syndrome; AML- Acute myeloid leukemia; NHL- Non-Hodgkin Lymphoma of skin; 1: Intestinal Melanoma; 2: Palmar Melanoma; MAF – Minor allele frequency in the population.

We found the pathogenic loss-of-function mutation c.1061 C> T; p.T354M in one patient, which resulted in a prevalence of 4.5% (1/22). This mutation was confirmed in his two sons. This patient underwent an allogeneic hematopoietic stem cell transplantation. We observed the polymorphism rs2335052 (c.490 G> A; p. 164 A>T) in 18.2% of cases (4/22), and two intronic polymorphisms, rs11708606 and rs369850507, in 27.3% (6/22) and 4.5% (1/22) of cases, respectively.

DISCUSSION

The missense mutation T354M was identified in one patient aged 30 years old at diagnosis who developed MDS with progression to refractory anemia with excess of blasts type 2 and was confirmed in their asymptomatic offspring. The mutation per si does not lead to symptoms, epigenetic modifications might be involved in development of the overt disease. In addition, we identified 3 polymorphisms in *GATA2* that are not considered pathogenic so far.

CONCLUSION

The identification of *GATA2* mutations is important in patients with NTM and/or IFI without known cause of immunosuppression because it can suggest germline background of a specific immunodeficiency associated with malignant neoplasms. *GATA2* mutation carriers require genetic counseling, prevention of related infection, hematologic surveillance and, in some cases, hematopoietic stem cell transplantation, the unique curative treatment available.

Projeto Gráfico: Área de Edição e Produção de Materiais Técnico-Científicos / INCA