

Clinical Communications

“FUT2” a potential genetic modifier in NCF1 deficiency

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Clinical Implications

- This study demonstrates that FUT2 secretor status may influence clinical severity and may be used as an additional prognostic marker in autosomal recessive chronic granulomatous disease.

TO THE EDITOR:

Chronic granulomatous disease (CGD) is a congenital defect of phagocytes that leads to early onset of severe and recurrent infections. This functional defect is caused by mutation in either of the *CYBB*, *NCF1*, *CYBA*, *NCF4*, *NCF2*, *RAC2* genes encoding for different components of nicotinamide adenine dinucleotide phosphate oxidase leading to defective reactive oxygen species (ROS) production.¹ The majority of the patients with CGD in an Indian cohort have *NCF1* defect and show varying clinical manifestations from severe to mild infections though having the same germline mutation.² Although residual ROS production is correlated with these varied clinical manifestations, the exact cause of this is not known.

Patients with CGD are prone to recurrent infection affecting natural mucosal barriers, leading to lower respiratory tract infection, multiple skin abscesses, inflammatory bowel disease, and other autoinflammatory phenotypes.³ FUT2 secretors have altered susceptibility to different bacterial and viral infections and diseases.⁴ *FUT2* encodes for an $\alpha(1,2)$ -fucosyl transferase that facilitates the attachment of a monosaccharide, L-fucose to specific O-linked glycan chains, producing $\alpha(1, 2)$ -fucosylated glycans expressed in mucosal tissues.^{5,6} After glycosylation, $\alpha(1, 2)$ -fucosylated proteins are secreted from mucosal epithelium into the lumen. *FUT2* controls the nature of various $\alpha(1,2)$ -fucosylated glycans secreted by mucosal surfaces; hence it was termed as “secretor” gene.⁵ Individuals with a functional *FUT2* allele are “secretors,” whereas those with mutations in this gene were termed “nonsecretors.” Single nucleotide polymorphisms (SNPs), c.428G>A and c.302C>T in *FUT2* leading to nonsecretory status in an Indian cohort, were most prevalent.⁷

We retrospectively incorporated 41 diagnosed *NCF1* defective patients with CGD. In all patients, ROS production was measured by the dihydroxyrhodamine assay and 0% cells were oxidized to rhodamine on neutrophils (99% cells were oxidized to rhodamine in controls). DNA samples of these cases were further processed to screen c.428G>A and c.302C>T polymorphisms in the *FUT2* gene by polymerase chain reaction and Sanger sequencing as determined previously.⁸

The proportion of secretors in patients with CGD was similar to normal subjects.⁷ A total of 78% (32/41) of patients with CGD were secretors and 22% (9/41) were nonsecretors. Of all the secretors, 84% were homozygous (SeSe) and 16% were heterozygous (Sese⁴²⁸) secretors. Eight of nonsecretory cases were homozygous for se⁴²⁸se⁴²⁸ and 1 patient was homozygous for se³⁰²se³⁰². There was no correlation between ROS production and *FUT2* genotype. The findings of our study should be tested in another cohort to exclude mere coincidence. Also, potential protein-protein interactions between wild-type and SNP versions of *FUT2* and *NCF1* should be studied.

The mean age of onset in CGD secretors was 1 year (median age: 1 year, range: 0.25–4 years) and 4.69 years in nonsecretors (range: 0.41–10 years). Age of presentation differed significantly as 59% secretors presented within first year of life compared with 22% of nonsecretors ($P < .05$) (Figure 1, A).

The clinical severity was correlated based on the number of infections requiring hospital stay, age at presentation, and outcome using Fisher’s exact test. A total of 66% of secretors were severe in comparison with 22% nonsecretors. Secretors have significantly increased susceptibility to infections ($P = .028$) in comparison with nonsecretors. Recurrent lower respiratory tract infection was the most predominant feature in both secretors and nonsecretors. Secretors have high rate of lower respiratory tract infections in comparison with nonsecretors (Figure 1, B). Susceptibility to pulmonary infections might be increased in secretors because of altered mucus characteristics such as sialic acid levels and the difference in the affinity of neutral antibodies to glycans.⁴ There was no significant difference in the proportion of patients with skin abscesses, pulmonary tuberculosis, and upper respiratory tract infections. A total of 22% of our secretors had chronic diarrhea; the nonsecretor cohort showed no diarrheal infections. This may be due to the influence of secretory status on composition of gut microbiota.⁴

Diverse susceptibility to microorganisms was observed in secretory and nonsecretory status, in our cases; *Staphylococcus aureus* was the most common organism isolated from both 9% secretors and 22% nonsecretors. Two of secretors had aspergillosis with none in nonsecretors. Secretors have increased susceptibility to viruses such as human influenza virus, rhinovirus, influenza A virus, respiratory syncytial virus, norovirus, rotavirus, and echovirus.⁴ However, as patients with CGD are not susceptible to viruses, they are not usually screened for viruses. Hence, screening patients for viruses may be helpful in these cases.

Seventy-eight percent of *NCF1* defective patients with CGD were on follow-up. Forty-one percent secretors were on cotrimoxazole and fluconazole prophylaxis with minimal breakthrough infections, except 1 patient with aspergillosis who was started on voriconazole prophylaxis. Five patients showing secretory phenotype underwent hematopoietic stem cell transplantation (HSCT) and are doing well. Secretors are also prone to graft versus host disease (GVHD) after HSCT.⁹ Four patients who underwent HSCT also showed acute skin GVHD and 1 patient had skin, liver, and gastrointestinal tract GVHD. Five patients died awaiting HSCT (Figure 2). Eight nonsecretors were on cotrimoxazole and fluconazole prophylaxis with minimal

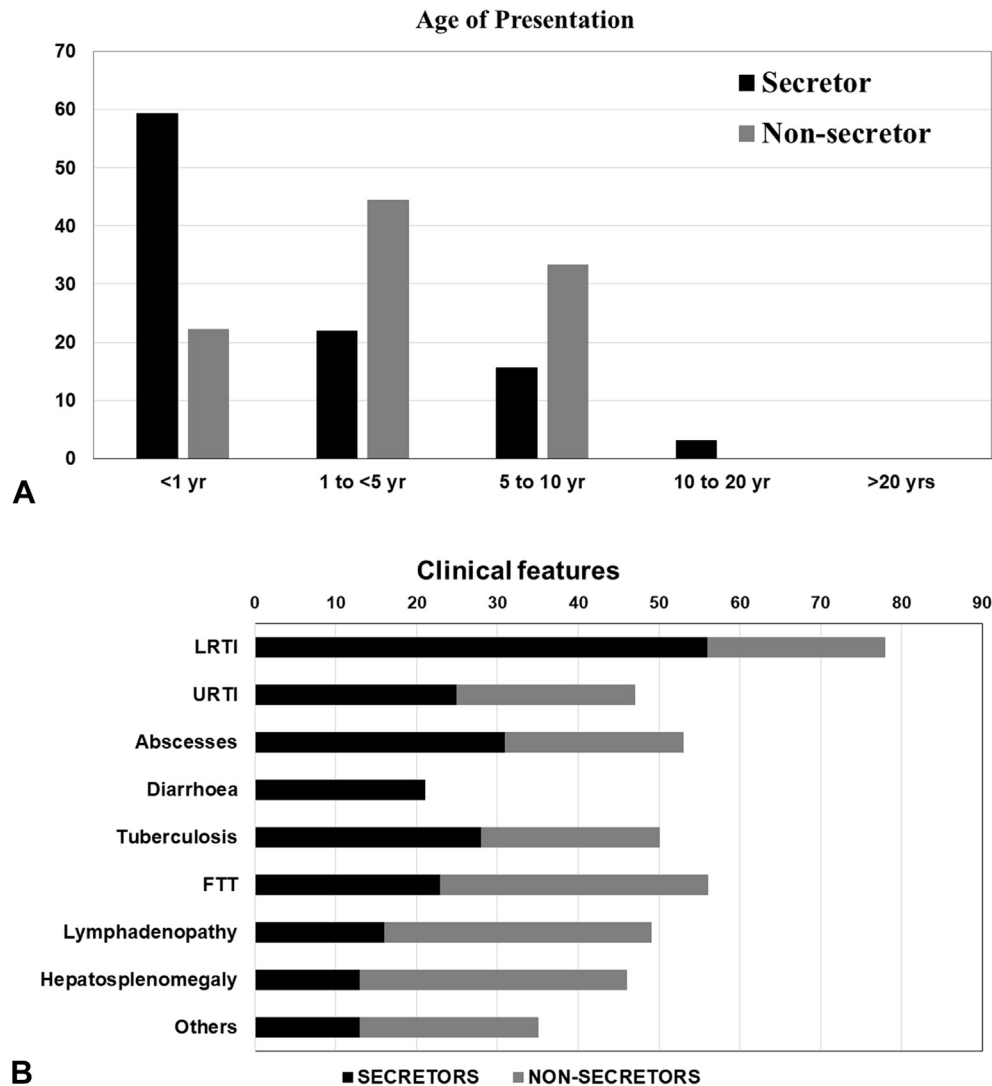


FIGURE 1. **A**, Age of presentation of NCF1 defective patients with chronic granulomatous disease (CGD). **B**, Clinical features of NCF1 defective patients with CGD. *FTT*, failure to thrive; *LRTI*, lower respiratory tract infection; *URTI*, upper respiratory tract infection.

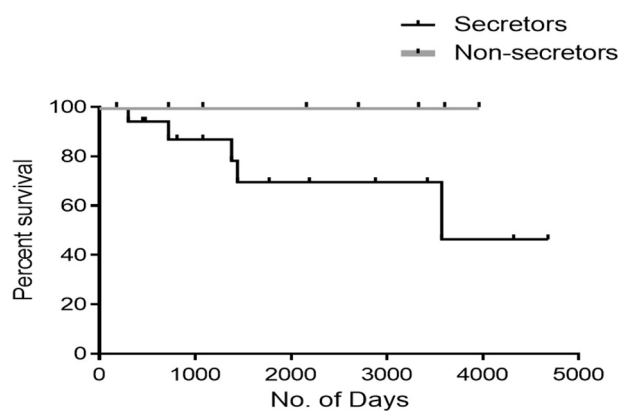


FIGURE 2. Kaplan-Meier curves for secretory status in a chronic granulomatous disease cohort.

breakthrough infections. None of the nonsecretors warranted HSCT.

It will be worthwhile to study these findings in patients with CGD other than NCF1 deficiency and other inborn errors of immunity. To conclude with, our study for the first time suggests that secretor status of FUT2 may serve as an additional marker that might make patients with CGD more susceptible to infections.

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