Clinical outcome of individuals carrying 5T;TG12 in trans with CFTR variants with varying clinical consequences

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Abstract

In conclusion, our data suggest that subjects with genotype 5T;TG12/VVCC likely have a very low risk of progressing to CF, as compared to those with F508del/5T;TG12. [4] This observation could lead to differentiate follow up in presence of at least one 5T;TG12. Knowing these data is crucial to offer a useful counseling for CRMS/CFSPID infants and for non-CF adults with CBAVD alone. Anyway further data are needed to evaluate the outcomes after a longer follow up.

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To the Editor,

according to the CFTR2 database (https://cftr2.org/), 5T;TG12 is a*Cystic Fibrosis* (CF) *transmembrane conductance regulator*(*CFTR*) variant with varying clinical consequences (VVCC), because when it is combined with a CF-causing variant on the other *CFTR*allele the whole clinical spectrum of CF phenotypes may appear including CF, CFTR-related disorders (CFTR-RD), or the absence of disease. It is very common in the Italian population, especially in infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID)[1-3] In a recent study we observed that 34.9% (45/129) of Italian subjects with F508del/5T;TG12 genotype were diagnosed as CF after a median follow-up of 6.7 years. Most of these patients had mild lung disease with pancreatic sufficiency and a low prevalence of CF-related complications.[4] To date few data are available on the long-term outcome of subjects with 5T;TG12*in trans* with another VVCC and here we report the clinical course of an Italian cohort.

We performed a retrospective analysis of the clinical records of all patients regularly monitored at six CF centres in Italy until 30 May 2021, who carried at least one 5T;TG12 *CFTR* variant *in trans* with another *CFTR* variant. We then focused on individuals carrying on the second allele a variant classified as VVCC according to CFTR2 database. The study was approved by the Ethical committee of the coordinator centre

(Florence, Ethics Clearance number 328/2021). Informed consent was obtained from all patients (or from their legal guardians) for the use of anonymous clinical data for research purposes.

During the follow-up, we reclassified patients as: i) CF, in the presence of pathological sweat chloride (SC) ([?] 60 mmol/L) value;[5] ii) CFTR-RD, in presence of clinical manifestations not meeting diagnostic criteria for CF.[6] We maintained the CRMS/CFSPID definition for asymptomatic infants identified by newborn screening (NBS) with a SC persistently in intermediate or normal range.[1] All enrolled individuals had *CFTR* exons sequenced (detection rate 98%) and multiplex ligation-dependent probe amplification.

We identified 27 subjects (median age as on 30 May: 10.74 ± 12.02 years), of which 12 homozygous for 5T;TG12 (median age 15.42 ± 15.55 years) and 15 carrying a VVCC on the second allele (median age 7.0 ± 6.77 years) (Table 1). Eighteen (66.7%) out of 27 were identified by NBS, while the remaining were diagnosed by symptoms. Four (14.8%) were adult patients. At the first evaluation, 18 (66.7%) were CRMS/CFSPID (15 in presence of a SC value < 30 mmol/L and 3 with SC 40–59 mmol/L), 8 (29.6%) CFTR-RD (4 identified for family history, 2 for respiratory symptoms and the other 2 for acute pancreatitis and congenital bilateral absence of the vas deferens (CBAVD), respectively) and one (3.7%) had a CF diagnosis at 21 years for pathological SC (62 mmol/L) performed in presence of CBAVD and bronchiectasis at computed tomography scan (Table 1).

After a mean follow up of 4 ± 3.22 years only one asymptomatic CRMS/CFSPID progressed to a CF diagnosis for pathological SC (112 mEq/l) at 4 years. Among CFTR-RD subjects (median age at 30 May: 22 ± 16.3 years), after a mean follow up of 7 ± 4.2 years, there were no diagnostic changes, so at study end 2 (7.4%) out of 27 individuals had a CF diagnosis. At study end all individuals had pancreatic sufficiency. Forced expiratory volume in the 1st second (FEV1) was evaluated in 8 subjects, resulting 105.8%±19.5 (range 88.2-141.0%). Only one patient, classified as CF had chronic *Pseudomonas aeruginosa* colonization. Interestingly, among the 8 cases diagnosed as CFTR-RD, there were four asymptomatic subjects identified for family history and with normal SC or in intermediate range. They had been classified as CFTR-RD on the basis of the genotype (three homozygous for 5T;TG12 and one double heterozygous for 5T;TG12 and D579G variant). At the end of the study, they had no alterations of the sweat test to support a CF diagnosis,[5] and in the same way they had no mono-organ involvement corresponding to the CFTR-RD classification.[6] Given the implications for the patients and management, give a correct and univocal label to these subjects is a very challenging area that remains to be resolved.

No studies are available in the literature to compare our results with. To date, CFTR2 database reports clinical data on 176 subjects with 5T;TG12, of which only 3 homozygous for this variant and all asymptomatic. Furthermore 439 patients carrying 5T;TG12 are reported in CFTR-France database (*https://cftr.iurc.montp.inserm.fr*): 19 (4.3%) have CF, 384 (87.5%) CFTR-RD (the most of them, 280, in presence of isolated CBAVD), 17 (3.9%) are asymptomatic subjects, one (0.2%) identified for fetal bowel anomalies and 18 (4.1%) with a pending diagnosis.

In our cohort we studied 10 individuals homozygous for 5T;TG12: one patient had CBAVD, another who suffered from recurrent pancreatitis and a third who had hypochloremic alkalosis. These patients were identified in CF centre that include 5T;TG12 in the first level *CFTR* genetic analysis.[3]

In conclusion, our data suggest that subjects with genotype 5T;TG12/VVCC likely have a very low risk of progressing to CF, as compared to those with F508del/5T;TG12.[4] This observation could lead to differentiate follow up in presence of at least one 5T;TG12.

Knowing these data is crucial to offer a useful counseling for CRMS/CFSPID infants and for non-CF adults with CBAVD alone. Anyway further data are needed to evaluate the outcomes after a longer follow up.

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Table 1: Age, genotypes, symptoms, sweat chloride values, and diagnosis on 30 May 2021 of enrolled subjects

Sex	**Age (years)**	**Second *CFTR* variant**	**Symptoms at study end**	**Last SC**	**Final Diagnosis**
M	27	F1052V	Bronchiectasis; CBAVD; Pa chronic detection	62	CF
F	5	S1455X	HA	112	CF
M	18	5T;TG12	Pancreatitis	55	CFTR-RD
F	16	5T;TG12		33	CFTR-RD
F	15	5T;TG12	HA	20	CFTR-RD
M	12	D1152H	HA	10	CFTR-RD
M	3	5T;TG12		46	CFTR-RD
M	14	D579G		50	CFTR-RD
F	47	5T;TG12		19	CFTR-RD
M	47	5T;TG12	CBAVD	31	CFTR-RD
F	11	5T;TG12		11	CRMS/CFSPID
M	8	R74W;D1270N		12	CRMS/CFSPID
F	7	5T;TG12		14	CRMS/CFSPID
F	6	R74W;D1270N		14	CRMS/CFSPID
F	6	5T;TG12		35	CRMS/CFSPID
F	6	5T;TG12		25	CRMS/CFSPID
F	5	5T;TG12		13	CRMS/CFSPID
M	4	5T;TG12		12	CRMS/CFSPID
M	3	D1152H		19	CRMS/CFSPID
M	3	L967S		10	CRMS/CFSPID
M	2	D1152H		42	CRMS/CFSPID
F	7	D1152H		58	CRMS/CFSPID
F	4	D1152H	HA	26	CRMS/CFSPID
M	1	D1152H		42	CRMS/CFSPID
F	3	Y1032C		35	CRMS/CFSPID
F	2	R117H;7T		32	CRMS/CFSPID

Sex	Age (years)	Second *CFTR* variant	Symptoms at study end	Last SC	Final Diagnosis
M	8	R117H;7T		27	CRMS/CFSPID

Abbreviations: CFTR: Cystic Fibrosis transmembrane conductance regulator; FEV_1: forced expiratory volume in the 1st second; SC: sweat chloride; HA: Hypochloremic Alkalosis; CBAVD: congenital bilateral absence of the vas deferens; Pa: *Pseudomonas aeruginosa* ; CRMS/CFSPID: cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis; CF: Cystic Fibrosis; CFTR-RD: CFTR-related disorder.

Conflict of Interest: The Auhtors declare no conflicts of interest

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