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Psycho-cognitive assessment and quality of life in older adults with chronic obstructive pulmonary disease-carrying the *rs4713916* gene polymorphism (G/A) of gene *FKBP5* and response to pulmonary rehabilitation: a proof of concept study

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Purpose Chronic obstructive pulmonary disease (COPD) is characterized by pulmonary and extra-pulmonary multi-morbidity including depression, anxiety and cognitive disorders. Several studies investigated the association of the *FKBP5* gene polymorphisms with susceptibility to anxiety, depression, and behavioral disorders. The *FKBP5* gene codifies the FKBP51 protein which modulates the glucocorticoid receptor in the adaptive stress response. Genetic variants of the *FKBP5* gene have been associated to a higher risk of developing mental disorders. We analyzed the association of genetic variants and stress exposure investigating the susceptibility to psychological distress and the impact on cognitive balance and quality of life (QoL) of COPD patients carrying the rs4713916 polymorphism (G/A) and we examined its association, with COPD rehabilitative outcomes.

Materials and methods A pilot study evaluated cognitive, psychological, clinical alterations/disorders, QoL, and coping strategies in 70 older adults with COPD, undergoing pulmonary rehabilitation, stratified according to the FKBP5 rs4713916 genotype (GG or GA).

Results Carriers of rs4713916 polymorphisms (G/A) show better cognitive performances, a higher degree of independence in the daily living activities, better QoL, no presence of depressive mood and anxiety symptoms, no family history of psychiatric disorders, more ability to cope with stressors by avoiding emotions but demanding emotional support, and lesser use of anti-anxiety, anti-depressant, anti-psychotic, hypnotic-sedative drugs. No difference was found in the number of comorbidities.

Conclusion These results offer valuable insights into the role of FKBP5 in the complex network of mechanisms associated to clinical, psychological and behavioral features of COPD patients. *Psychiatr Genet* XXX: 000–000

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Keywords: anxiety, coping strategies, depression, pilot study, rehabilomics

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Introduction

Chronic obstructive pulmonary disease (COPD) is a multifactorial disease where different genes are associated to etiology and disease progression (Ragland *et al.*, 2019). Genetic polymorphisms (SNPs) are also associated with COPD susceptibility, severity, and therapeutic response (Li *et al.*, 2017; Russo et al., 2019a, 2019b; Ragland *et al.*, 2019).

Recently, a specific association between the polymorphism (rs4713916, GA) of the *FKBP5*gene (FK506 Binding Protein 5) and different endpoints of pulmonary rehabilitation (PR) response in COPD patients has been described (Russo et al., 2019a, 2019b).

Several studies demonstrated the role of genetic variants of FKBP5 (including the G/A), involved in negative feedback from the hypothalamic-pituitary-adrenal axis in the complex mechanism of responses and vulnerability to stress-related psychiatric problems (Binder, 2009; Roy *et al.*, 2010; Kang *et al.*, 2012). Interestingly, FKBP5 has also been proposed in a general population to modulate recovery from psychosocial stress in healthy controls (Ising *et al.*, 2008) as a risk factor for different psychiatric disorders, such as mood and anxiety disorders (Matosin *et al.*, 2018; Ferrer *et al.*, 2018).

FKBP5 is a heat shock protein 90-(Hsp90) associated to a co-chaperone encoded by the *FKBP5* gene. The human

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gene is located on the chromosome 6 at position p21.31 consisting of 13 exons and 12 introns spanning more than 150 kb of genomic DNA (Pelleymounter *et al.*, 2011). It is characterized by the presence of functional glucocorticoid responsive elements representing an intracellular short feedback loop (Hubler and Scammell, 2004). It has been highlighted that FKBP5 shall be considered as a scaffolding protein helping to organize protein complexes rather than as a (co)chaperone contributing to the folding of individual proteins (Fries *et al.*, 2017).

In COPD, GA carriers show better performances in the Six Minute Walking Test and display better lung functions when compared to GG patients. Patients carrying the rs4713916 GA polymorphism have a four-fold higher probability to respond to PR compared to GG patients (Russo *et al.*, 2019b).

Patients with COPD often show psychiatric comorbidities, specifically: generalized anxiety, panic disorder, and depression (Su *et al.*, 2017; Montserrat-Capdevila *et al.*, 2018; Miravitlles *et al.*, 2018; Puteikis *et al.*, 2021; Strollo *et al.*, 2021). These conditions are associated with poorer quality of life (QoL) (Spruit and Wouters, 2019), physical impairments, lower compliance to treatment plans, more severe exacerbation rates with more frequent emergency admissions and, ultimately, higher 30-day mortality compared to their counterparts without anxiety or depression (Pollok *et al.*, 2019). It was reported that patients with COPD are two to five times more likely to meet the criteria for anxiety or depressive disorders compared to the general population (Pooler and Beech, 2014). However, there is a lack of evidence on the potential role of GA polymorphism on the cognition of people with COPD.

We know that comprehensive respiratory rehabilitation programs (i.e. PR) play a pivotal role in patients management and care (Augustin and Wouters, 2017). Furthermore, the National Institutes of Health (NIH) recent research plan on rehabilitation (O'Mara *et al.*, 2017) highlights the importance of identifying those precision medicine approaches which are relevant to rehabilitation, and to characterize those biomarkers that may be prognostic or guide prescription for rehabilitation interventions.

We therefore aimed at investigating the susceptibility to psychological distress and the impact on cognitive balance and QoL of COPD patients carrying the rs4713916 polymorphism (G/A) and at exploring its association with COPD rehabilitative outcomes in order to hypothesize individually tailored pulmonary rehabilitation strategies.

Materials and methods

Subjects

The study was approved by the Ethical Committee of the IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) San Raffaele Roma (Protocol number 15/2013). All participants gave separate consent to participate in clinical and genetic studies. The study had an interventional non-pharmacological design, and enrolled 70 patients, aged 70 or older, suffering from GOLD 3-4 COPD (GOLD 2019, global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019. Report and strategies), who were admitted to the Institute Pulmonary Rehabilitation Unit between July 2013 and December for a comprehensive 3 weeks' program.

All patients were part of a larger study on the application of Systems Medicine approaches in real-life evaluated with a multidisciplinary and multidimensional assessment protocol (Russo *et al.*, 2019b). All patients were of Italian origin, speaking Italian as their mother language.

We measured the following patient characteristics: demographics (age, sex, marital status, employment status, education); medical history and lifestyle (i.e. tobacco smoking habit; alcohol drinking habit, family history of COPD); comorbidities; BMI; cognitive performance, psychological status, QoL and coping strategies; pharmacologic therapy.

rs4713916 analysis

The methods for genotyping rs4713916 are described in detail in a previous publication (Russo *et al.*, 2019b). In summary, rs4713916 was genotyped using MBK_FKBP5 90 kits from Diatheva Srl (Italy) according to the company's instructions. A being the minor allele of the SNP, our sample did not include homozygous AA, but homozygous GG samples were present at 80.3% and GA at 18.3%.

Instruments for cognitive, psychologic and quality of life assessment

Upon patient admission in the PR Unit, we evaluated their cognitive performance.

The Mini-Mental State Examination (MMSE) is a brief 30-point questionnaire to evaluate cognitive performance. Scores are adjusted for age and education (Magni *et al.*, 1996). A score ranging between 18.3 and 23.8 defines the intermediate condition of Mild Cognitive Impairment (Pierobon *et al.*, 2018).

The Montreal Cognitive Assessment (MoCA) is a cognitive screening instrument (Nasreddine *et al.*, 2005). Raw scores are adjusted for age, education and sex (Conti *et al.*, 2015). Adjusted scores are classified into five equivalent scores (ES). According to Pierobon *et al.* (2018), cognitive impairment is present for ES = from 0 to 1 and absent for ES = from 2 to 4.

The Rey-Osterrieth complex figure test (ROCF) is a neuropsychological test to assess visuospatial constructional ability and visual memory. ROCF includes 18 units and the maximum score for each of the two tasks (direct and delayed copying) is 36. The scores are normalized to five ES (Caffarra *et al.*, 2002).

The change in functional independence for basic and instrumental activities of daily living (IADL) was evaluated both at admission and at discharge from the PR Unit.

Activities of daily living (ADL) refers to people's daily activities involving caring for one's self and body with questions aiming to assess the functional independence/dependence of subjects (Katz *et al.*, 1970). The score range for ADL is from 0 (total dependence) to six (independence). The degree of dependence is categorized as none, or dependence in one domain, 2–3 or >4 domains (Di Carlo *et al.*, 2016).

IADL refers to more complex tasks of everyday life, more demanding in terms of cognitive function such as using the telephone and managing money (Lawton and Brody, 1969). The degree of dependence is categorized as none, or dependence in one domain, 2–4 or >4 domains (Di Carlo *et al.*, 2016). Performances in ADL and IADL depend on cognitive (reasoning, planning), motor (e.g. balance, dexterity), and perceptual skills (Mlinac and Feng, 2016).

The following instruments were administered to all patients to assess psychologic status and QoL:

The Beck Depression Inventory (BDI-II) (Beck *et al.*, 1996) is a self-rating scale of 21 items, The range is from 0 to 63, a score of 13/14 or above is indicative of depressive symptoms). The Center for Epidemiologic Studies Depression Scale (CES-D) (Fava, 1983), the range is from 0 to 60. The CES-D contains 20 items measuring depressive signs experienced during the previous 7 days on a four-point Likert scale (from 0, never or rarely to three, most days or every day). The maximum total score is 60. A score ≥16 su GG samples signifies the presence of clinical depression. In the current study, the internal consistency was expressed by a Cronbach's alpha of 0.83 brief self-report scale designed to measure self-reported symptoms associated with depression experienced in the past week. The Zung Self-Rating Anxiety Scale (SAS) (Dunstan and Scott, 2018), focuses on the most common general anxiety disorders. It is a Likert scale, with raw scores that range from 20 to 80. A raw score >36 is considered clinically relevant

The Brief COPE is a short self-reported questionnaire developed to assess 14 coping strategies: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame (Carver, 1997). It represents a way to rapidly assess coping responses because it is a short 28-item self-report questionnaire with two items for each of the measured coping strategies. The range is from 2 to 8 with higher scores indicating increased use of that specific coping strategy.

The 36-Item Short Form Health Survey (SF-36, scores range from 0 to 100) provides a direct quantitative indication of an individual's health status and it has become the most widely used QoL evaluation tool in the world (Brazier, 1993).

The Maugeri Foundation Respiratory Failure Questionnaire (MRF-26, scores range from 0 to 5) is a brief questionnaire of 26 items validated to investigate QoL impairment in subjects with Chronic Respiratory Failure (CRF) irrespective of the causing disease (Carone *et al.*, 1999).

The Cumulative Illness Rating Scale (CIRS) is a measure of multi-morbidity (Miller *et al.*, 1992) providing the rating of 13 independent organ areas, a total pathology score, representing impairment of the whole person, is obtained by adding the sums for the 13 items together.

Statistical analysis

We managed and analyzed data using STATA12 and GraphPad Prism 8.1 (GraphPad Software Inc., La Jolla, California, USA). We transformed continuous variables logarithmically to normalize the distribution. We tested the differences in the distribution of studied endpoints according to genotype using the *t*-test or the Chi-square test. When we could not verify the assumption of normality, we used the Kruskal-Wallis test and the Jonckheere-Terpstra trend test. We used the Spearman correlation to compare the Brief COPE between different genotypes.

Continuous data were described as mean ± SD. We considered as statistically significant a *P*-value ≤0.05.

Results

A total of 70 patients, with severe stage 3–4 GOLD classification COPD, participated in the study. They were previously genotyped for rs4713916 (G/A) and thirteen patients displayed the GA phenotype (Russo *et al.*, 2019b). Table 1 shows the sociodemographic and the clinical characteristics of patients, stratified according to the rs4713916 genotype. T1

The mean age was 72.66 ± 8.6 for GG and 74.76 ± 6.4 for GA. All patients had been receiving an inhaled corticosteroid regimen in combination with bronchodilators, and were moderately overweight. No statistically significant difference was observed between the two groups with regard to sex, age, education, smoking habits, long-term oxygen therapy, BMI, CIRS score, number and type of comorbidity. The most represented comorbidities in both groups were cardiovascular diseases: 77.2 and 76.9% in GG and GA, respectively.

Interestingly, 36 out of 70 (51.64) % of GG carriers reported a medical or family history of psychiatric disorders versus no described cases among GA carriers (P = 0.0311).

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Table 1 Sociodemographic and clinical characteristics of the study population ($N = 70$), stratified according to FKBP5rs4713916 genotype (GG or GA).

Characteristics	GG ($N = 57$)	GA ($N = 13$)	P-value
Sex			n.s.
Male	40.35%	53.85%	
Female	59.65%	46.15%	
Age	72.66 ± 8.6	74.76 ± 6.4	n.s.
Education (years)	9.21 ± 4.3	7.0 ± 2.3	n.s.
Marital status			n.s.
Married/with partner	50%	61.54%	
Widower	35.09%	15.38%	
Unmarried	3.51%	7.69%	
Separated/divorced	12.28%	15.38%	
Smoking habit			n.s.
Current smoker	16.33%	15.38%	
Exsmoker	73.47%	76.92%	
Nonsmoker	10.20%	7.69%	
Living situation			n.s.
Caregiver presence	73.69%	76.92%	
None	26.32%	23.08%	
Current occupation			n.s.
Employed	18.74%	0	
Housewife	10.42%	23.08%	
Retired	70.83%	76.92%	
LTOT	33.3%	30.77%	n.s.
ICS therapy	100%	100%	n.s.
BMI	27.95 ± 8.5	28.83 ± 9.5	n.s.
CIRS			n.s.
Severity	1.614 ± 0.242	1.531± 0.192	
Comorbidity	2.449 ± 1.444	2.889 ± 1.054	
Number × patients	3.593 ± 1.807	3.100 ± 1.595	n.s.
Comorbidity condition			
Circulatory system diseases (ICD-9-CM 390-459)	44 (77.2%)	10 (76.9%)	n.s.
Endocrine, nutritional, metabolic, and immunity disorders (240–279)	24 (42.1%)	6 (38.5%)	n.s.
Genitourinary system diseases (580-629)	7 (12.3%)	2 (15.4%)	n.s.
Neoplasms	3 (5.3%)	1 (7.7%)	n.s.
Drugs for neurological diseases			
Anti-anxiety, antidepressant, antipsychotic, hypnotic –sedative	19 (33.33 %)	4 (30.71%)	n.s.
Antiepileptic	4 (7.02%)	1 (7.69%)	n.s.
Anti-Parkinson	1 (1.75%)	0	n.s.
Analgesic	2 (3.51%)	0	n.s.
Anti-dizziness	1 (1.75%)	0	n.s.
No SNC drugs	30 (52.63%)	8 (61.54%)	n.s.

CIRS, Cumulative Illness Rating Scale; ICS, inhaled corticosteroid; LTOT, long-term oxygen therapy.
[a]Data are expressed as mean ± SD or percentage.

AQ5 this table

Thirty-two out of 70 COPD patients were receiving drugs active on the central nervous system (belonging to the following ATCC code N02-N07 classes: analgesics, antiepileptics, anti-Parkinson, psycoleptics, psychoanaleptics). GA carriers tended to receive less drugs for neurological disease (61.54% versus 52.63%) although this result was far from reaching statistical significance (Chi-square 0.0315; $P = 0.86$) (Table 1).

Finally, no association with smoking/alcohol consumption was observed.

According to the MMSE, the mean adjusted score was 25.81 ± 2.37 in the G/G patients and 26.32 ± 3.36 in the GA patients ($P = 0.0884$). However, according to the MoCA test, the mean adjusted score was 22.77 ± 4.45 in the GG patients and 26.34 ± 3.57 in the GA patients ($P = 0.0094$). When using the ES classification for the MoCA and ROCF tests (Caffarra *et al.*, 2002; Conti *et al.*, 2015), we observed a higher prevalence of patients with preserved cognitive functions in the GA group compared to the GG (MoCA and ROCF, direct copy). Table 2 shows COPD patients' cognitive performance, evaluated by the three different tools upon admission to the PR unit, stratified according to the FKBP5 rs4713916 genotype (GG, GA).

T2

When evaluating psychological status between the two groups of COPD patients, stratified according to the FKBP5 rs4713916 genotype (GG, GA), we found significant differences.

CES-D is popular for estimating prevalence rates in relatively large samples, as potential indicator of depression (Shafer, 2006; ASSOCIATION, A. P., 2013; Uher *et al.*, 2014). To strengthen the evidence provided by the CES-D, we used two other scales: the well-established BDI-II and the SAS (Shafer, 2006). Table 3 summarizes the results of the psychological and QoL assessment.

T3

According to the BDI-II and the CES-D, patients carrying GG showed higher levels of depressive symptoms in comparison with GA patients. Specifically, two domains evaluated by the CES-D, such as Depressive affect and Somatic problem and retarded activity, were not compromised in GA carriers.

Table 2 Cognitive characteristics of the study population ($N = 70$), stratified according to FKBP5 rs4713916 genotype (GG, GA)

Characteristics	GG ($N = 57$)	GA ($N = 13$)	p
MMSE	25.81 ± 2.37	26.32 ± 3.36	0.1246[a]
Adjusted scores			
Score range	0	0	0.082[b]
30	48	10	
23.9–30	(84.2%)	(76.9%)	
≤23.8	9 (15.4%)	3 (23.1%)	
MoCA[c]			
Adjusted scores	22.77 ± 4.45	26.34 ± 3.57	0.0094[a]
ES = 0 (0 → 17.362)	9 (17.4%)	0	0.0361[b]
ES = 1 (17.363 → 19.500)	6 (11.5%)	1 (7.7%)	
Es = 2 (19.501 → 21.562)	4 (7.7%)	0	
Es = 3 (21.563 → 23.361)	14 (26.9%)	1 (7.7%)	
Es = 4 (>23.361)	19 (36.5%)	11 (84.6%)	
ROCF[c]			
Direct copy	26.97 ± 6.79	28.56 ± 10.58	0.124[a]
ES = 0 (≤28.87)	28 (53.8%)	3 (25%)	0.0055[b]
ES = 1 (28.88 → 30.04)	7 (13.5%)	0	
ES = 2 (30.05 → 31.21)	1 (1.9%)	3 (25%)	
ES = 3 (31.22 → 32.40)	0	0	
ES = 4 (≥32.41)	16 (30.8%)	6 (50%)	
Delayed copy	13.32 ± 5.77	12.75 ± 7.0	0.134[a]
ES = 0 (≤9.46)	11 (21.2%)	4 (33.3%)	0.092[b]
ES = 1 (9.47 → 11.22)	7 (13.5%)	0	
ES = 2 (11.23 → 12.98)	7 (13.5%)	4 (33.3%)	
ES = 3 (12.99 → 14.73)	7 (13.5%)	0	
ES = 4 (≥14.74)	20 (38.5%)	4 (33.3%)	

Data are expressed either as mean ± SD or in number of patients (percentage). Adjusted scores are classified into five equivalent scores (ES).
MMSE, Mini-Mental State Examination; ROCF, Rey-Osterrieth complex figure test.
[a]Unpaired T-Test.
[b]Analysis of contingency table: chi-square.
[c]5 GG carriers refused the MoCA and ROCF questionnaires; 1 GA carrier refused the ROCF questionnaire.

Table 3 Psychological and quality of life parameters of the study population ($N = 70$), stratified according to FKBP5 rs4713916 genotype (GG, GA)

Characteristics	GG ($N = 57$)	GA ($N = 13$)	P^a
BDI-II	15.12 ± 8.16	5.80 ± 2.17	0.0054
CES-D	12.50 ± 10.07	4.73 ± 6.65	0.0046
Depressive affect	3.10 ± 4.62	0.64 ± 1.57	0.0231
Well-being	4.21 ± 2.77	2.64 ± 2.80	0.0842
Somatic	5.00 ± 4.31	1.45 ± 2.77	0.0043
Inter-personal	0.19 ± 0.57	0.0 ± 0.0	0.0922
SAS	29.50 ± 8.46	22.55 ± 2.25	0.0017
Affective symptoms	7.27 ± 2.15	5.67 ± 1.12	0.0104
Well-being	9.77 ± 3.35	7.00 ± 1.94	0.0111
Somatic symptoms	22.50 ± 6.84	17.00 ± 1.77	0.0062
SF-36			
General health	73.21 ± 12.49	74.42 ± 7.42	0.084
Mental health	61.64 ± 8.79	67.67 ± 9.26	0.0455
Brief COPE[b]			
Denial	3.682 ± 1.567	4.877	0.018
Positive reframing	4.659 ± 1.916	5.750 ± 1.165	0.0798
Self-distraction	4.886 ± 1.660	6.625 ± 0.916	0.007
Use of emotional support	4.273 ± 1.453	5.250 ± 0.886	0.05

Data are expressed as mean ± SD.
[a]Non-parametric Mann–Whitney test.
[b]Kruskall-Wallis test.
Data are expressed as mean ± SD.

The SAS showed higher scores in GG carriers versus GA carriers, specifically in the domain of Affective symptoms (Table 3). In our sample 23.9% of GG carriers showed more clinically significant symptoms of anxiety (score >36 SAS rating scale) with respect to none in GA carriers. Looking at each different symptoms domain of SAS (affective symptoms, well-being, somatic symptoms) GA patients showed a significantly high level of perceived

healthiness (Table 3). Therefore, both the CES-D and the SAS suG/Gested that GA carriers have a healthier perceived well-being than GG.

Moreover, according to the SF-36, GA carriers showed a M*ental Health* score higher than GG carriers. No differences were observed about *General Health* between the two groups.

The perceptions of illness and coping strategies are important determinants among factors influencing outcomes in COPD treatment and management, and patients 'quality of life (Lee *et al.*, 2013; Stoilkova-Hartmann *et al.*, 2015; Russo *et al.*, 2017; Vaske *et al.*, 2017). Looking at the coping strategies, GA carriers showed higher levels of association with self-distraction and denial, avoidance strategies, moderate level with use of emotional support, a tendency to use positive reframing, than GG carriers (Table 3). All significant data associations were confirmed using both the Kruskal-Wallis test and the Jonckheere-Terpstra trend test.

After 3 weeks of PR, all COPD patients showed a better perception of their state of disability related to respiratory disease and an increase in their personal autonomy levels (Table 4). Specifically, patients carrying GA showed a degree of functional independence, in basic and IADL (ADL and IADL) higher than GG patients: their level of independence increased moderately after the 3-week PR program.

T4

Discussion

This is the first study showing that the FKBP5 rs4713916 gene polymorphism (G/A) may be related to better cognitive performance and mood disorders in an elderly population suffering from COPD. Furthermore, we demonstrated the association between FKBP5 polymorphism and cognition in this cohort and we found a different response to respiratory rehabilitation in subjects carrying the GA allele versus those with the GG genotype.

FKBP5 is considered as a candidate gene for investigating the impact of genetic susceptibility to stress-related psychiatric symptoms. This evidence is supported by a meta-analysis involving 12 491 patients and 14 091 healthy controls which showed that rs4713916 is associated with major depressive disorder (MDD) susceptibility (Rao *et al.*, 2016), and thus the major allele (G) is more common among patients than controls. Different meta-analyses showed a bidirectional association between COPD and depressive disorders with the latter being associated with worse clinical outcomes in COPD (Atlantis *et al.*, 2013; Blakemore *et al.*, 2014). However, the pathobiology of COPD-depression relationship is far from being clarified. Previous data reported that the level and number of inflammatory biomarkers [interleukins (IL) such as IL-6, IL-1β, IL-18 and tumor necrosis factor-α)] may play a role in triggering the lung and systemic inflammatory response, including neuro-inflammation. Moreover, high levels of IL-6 are related to MDD (Rybka *et al.*, 2016). In previous studies (Russo et al., 2019a, 2019b), we evaluated the serum levels of IL-6 in the same patients included in this study. When stratifying the data of serum levels of IL-6 for FKBP5 rs4713916 we found that the levels are lower in GA carriers than in GG (50.96 ± 43.78 versus 220.7 ± 202.6 pg/ml; $P = 0.0022$ according to the Mann–Whitney test). Thus, in our study GG patients showed more depressive symptoms than GA, according to the CES-D and the BDI-II tests, suggesting a correlation between IL-6 levels and depressive mood.

We have found that the FKBP5 rs4713916 variant is related to better cognitive performance. Previous work reported that FKBP5 rs1360780 (C/T) is associated with cognitive function in a non-clinical population aged over 50. Specifically, individuals carrying the T allele showed poorer attention/concentration (working memory) compared with individuals carrying the G allele (Fujii *et al.*, 2014). In Caucasian populations, rs1360780 and rs4713916 are in strong linkage disequilibrium (LD). The LD is the nonrandom association of alleles at different loci in a given population. The loci are in LD when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and randomly associated (Lekman *et al.*, 2008).

The results we obtained at the MoCA and ROCF tests indicate that GA carriers probably present a better performance in terms of non-amnesic abilities such as executive and praxis functions. This peculiar pattern of cognitive dysfunction has been extensively described in patients with COPD (Scarlata and Antonelli-Incalzi, 2011) and it is remarkable that a genetically determined feature can exert a protective effect.

FKBP5 is responsive to stress exposure and elevated glucocorticoid levels, which affect its subsequent transcription (Vermeer *et al.*, 2003; Zhang *et al.*, 2008; Lekman *et al.*, 2008; Zimmermann *et al.*, 2011; Zannas and Binder, 2014).

All of these observations suggest a genotype-dependent risk of chronically elevated plasma cortisol levels in the context of chronic or recurrent stress, which also may increase the risk of stress-related disorders, such as depression (Graydon and Ross, 1995).

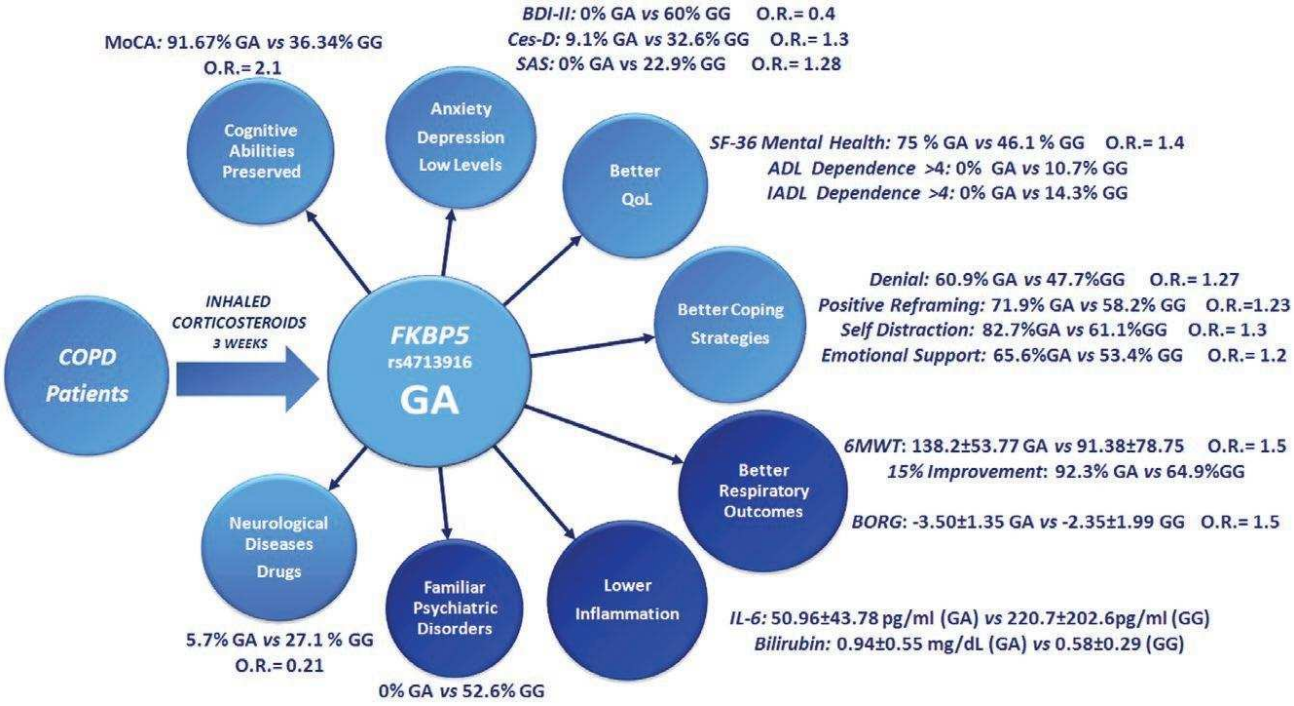
Several studies have shown that psychological distress influences the QoL and predicts exercise capacity better than pulmonary functioning (Zimmermann *et al.*, 2011). Psychological distress increases a physical and social malfunctioning, inadequate adherence to therapy, more medical visits and hospital re-admissions, and mortality risk (Graydon and Ross, 1995). Moreover, many studies suggest that there is a high prevalence of anxiety and depression disorders in COPD (Vögele and von Leupoldt,

Table 4 Quality of life characteristics and degree of dependence of the study population ($N = 70$), stratified according to *FKBP5* rs4713916 genotype (GG, GA), before and after the respiratory rehabilitation

	GG ($N = 57$)			GA ($N = 13$)		
Characteristics	Before PR	After PR		Before PR	After PR	
MRF-26	71.84 ± 1	52.23 ± 18.9	−19.60 ± 22.3	71.79 ± 13.6	45.73 ± 18.6	−26.07 ± 13.01
Total score	6.43	4	2	0	8	−32.48 ± 14.28
Daily activities	76.05 ± 20.63	56.33 ± 20.68	−19.73 ± 25.72	78.63 ± 18.75	46.15 ± 19.23	−19.66 ± 15.44
Disability perceived			−20.47 ± 24.52		45.30 ± 20.51	
	67.87 ± 15.78	47.39 ± 21.12		64.96 ± 16.95		
ADL	5.15 ± 1.72	5.21 ± 1.45	0.06 ± 2.0	5.15 ± 1.72	5.61 ± 0.96	−0.46 ± 0.88
Degree of dependence**						
None	65.95%	75%		75%	77.78%	
1	2.13%	0		0	0	
2–3	10.64%	14.28%		8.33%	22.22%	
>3	21.28%	10.72%		16.67%	0	
IADL	5.04 ± 2.64	5.97 ± 2.54	0.93 ± 1.02	5.82 ± 1.47	5.88 ± 1.96	0.06 ± 0.18
Degree of dependence ***	36.17%	57.14%		45.45%	50.%	
None						
1	17.02%	17.87%		18.18%	12.5%	
2–4	29.79%	10.71%		36.37%	37.5%	
>4	17.02%	14.28%		0	0	

Data are expressed as mean ± SD or in percentage.
ADL, activities of daily living; IADL, instrumental activities of daily living; PR, pulmonary rehabilitation.
*$P = 0.0455$.
**$P < 0.001$ between 'before PR' and 'after PR' in GA patients.
***$P = 0.0025$ between 'before PR' and 'after PR' in G/G patients; $P = 0.003$ at basal level between GG and GA patients; $P < 0.001$ after rehabilitation between GG and GA.

Fig. 1



Schematic representation of the influence of the GA genotype on clinical, cognitive, and psychological features of COPD patients undergoing pulmonary rehabilitation. Previously published data (Russo *et al.*, 2019b) are reported in darker color. COPD, chronic obstructive pulmonary disease.

2008). These symptoms reduce health outcomes in terms of exercise tolerance, QoL and exacerbations. It was suggested that coping strategies may play an important role in mediating the relationship between personal resources such as knowledge of the disease, self-efficacy and social support and psychological responses such as

depression and anxiety in COPD patients (Mewes *et al.*, 2016). We reported, recently, that the change in distance (Δ six minutes walking distance: 6MWD) between final and baseline value in meters is positively associated with Self-distraction, Active Coping, and Planning strategies (Russo *et al.*, 2017).

We can speculate that GA carriers have more cognitive and psychological resources to better adapt and manage their chronic health conditions (i.e. COPD and multi-morbidity). Figure 1 summarizes the phenotype of subjects carrying rs4713916 evaluated in our study.

Recently, a new study describes the presence of a specific 'psychologic' comorbidity cluster related to COPD not present in a matching age control population (Triest *et al.*, 2019). In respect to the clinical characterization, this cluster is distinguished by the worst QoL. The smaller occurrence of mood disorders in the matching age control population may be the cause of the absence of a 'psychologic' cluster in this population. Remarkably, the frequency of exacerbations, the severity of the dyspnea, and functional exercise performance were similar among all COPD comorbidity clusters. These observations highlight the need for detailed phenotyping beyond the above-mentioned clinical outcomes.

Most likely, patients carrying the FKBP5 rs4713916 GA do not fall into the 'psychologic' comorbidity cluster. On the other hand, COPD patients carrying FKBP5 rs4713916 G/G may fall in the 'psychologic' comorbidity cluster with psychological conditions representing an important subgroup for targeted mechanistic and intervention studies. Thus, it is possible that GA carriers benefit more from the PR compared to GG carriers.

These findings could represent a potential tool for clinical practice. First, they could provide a reliable biomarker able to predict the response to PR following acute exacerbation of COPD and allow for better resource allocation and therapeutic planning. It could provide clinicians with a tool to screen and stratify elderly COPD patients according to their psycho-cognitive profile. Further research would be needed in order to ascertain whether the FKBP5 polymorphism, and specifically rs4713916 GA carriers may act as a proxy in predicting clinical outcomes such as frailty, hospital admission and mortality in elderly COPD patients. The promising results of this explorative study deserve validation with a larger *ad hoc* study, currently under consideration.

This study has several limitations: the sample size is quite small and requires to be confirmed by larger populations; we were not able to identify any subject with a AA genotype, making it impossible to verify whether a haplotypic gradient occurs; finally, we were not able to investigate the association between FKBP5 rs4713916 alleles, the psycho-cognitive profile and the clinical and biologic markers of glucocorticoid resistance such as, for instance, adrenocorticotropic hormone and cortisol circulating levels.

In conclusion, our study shows that rs4713916 is associated with better outcome in older adults with COPD. These results offer valuable insights into the role of FKBP5 in the complex network of mechanisms associated with clinical and behavioral features of COPD patients and may be used as a proof of concept benchmark for future clinical studies.

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Conflicts of interest

There are no conflicts of interest.

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