



**RAPID COMMUNICATION**

# Tuberous sclerosis complex (TSC), lymphangioleiomyomatosis, and COVID-19: The experience of a TSC clinic in Italy

Angela Peron<sup>1,2,3</sup>  | Francesca La Briola<sup>2</sup> | Fabio Bruschi<sup>2</sup> | Silvia Terraneo<sup>4</sup> |  
 Chiara Vannicola<sup>2</sup> | Roberto Previtali<sup>2</sup> | Sabrina Perazzoli<sup>5</sup> |  
 Emanuela Morengi<sup>6</sup> | Gaetano Bulfamante<sup>1</sup> | Aglaia Vignoli<sup>2</sup>  |  
 Maria Paola Canevini<sup>2</sup>

<sup>1</sup>Human Pathology and Medical Genetics, ASST Santi Paolo e Carlo, San Paolo Hospital, Milan, Italy

<sup>2</sup>Child Neuropsychiatry Unit – Epilepsy Center, ASST Santi Paolo e Carlo, San Paolo Hospital, Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

<sup>3</sup>Division of Medical Genetics, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah

<sup>4</sup>Respiratory Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Milan, Italy

<sup>5</sup>DAMA (Disabled Advanced Medical Assistance), Ospedale di Circolo e Fondazione Macchi, Varese, Italy

<sup>6</sup>Biostatistics Unit, Humanitas Clinical and Research Center, IRCCS, Milan, Italy

**Correspondence**

Angela Peron, San Paolo Hospital, Department of Health Sciences, Università degli Studi di Milano, Via di Rudini 8, 20142 Milano, Italy.  
 Email: angela.peron@unimi.it

**Abstract**

Individuals with comorbidities are at higher risk of coronavirus disease 2019 (COVID-19) and worse outcome, but little information has been available about patients with genetic diseases and COVID-19. This study aims at evaluating the presence and outcome of COVID-19 in a cohort of Italian patients with tuberous sclerosis complex (TSC) and/or lymphangioleiomyomatosis (LAM), and at reviewing the possible effects of mTOR inhibitors on SARS-CoV-2 infection. We included 102 unselected individuals with a diagnosis of TSC and/or LAM assessed between January 1, 2020 and April 24, 2020 (29% children, 71% adults). Twenty-six patients were on mTOR inhibitors. Demographic data, TSC manifestations, presence, and outcomes in individuals with confirmed or suspected SARS-CoV-2 infection were evaluated. Health status and outcomes of all patients on mTOR inhibitors were assessed. One patient with severe TSC had polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection, was admitted to ICU, and died. Nine additional patients either met the definition of suspect case or presented with at least two of the most common symptoms of SARS-CoV-2 infection. All recovered fully. None of the patients treated with mTOR inhibitors for their underlying comorbidities was diagnosed with COVID-19, and those who showed suspicious respiratory symptoms recovered fully. This cohort study provides preliminary information on COVID-19 in people with TSC in Italy and suggests feasibility to systematically evaluate the role of mTOR inhibitors in SARS-CoV-2 infection.

**1 | INTRODUCTION**

Coronavirus disease 2019 (COVID-19) has so far affected over 5 million people worldwide, and the Lombardy region in Italy was one of the first and most impacted areas after Wuhan, China (Zehender et al., 2020). Individuals with comorbidities are at higher risk of infection and worse outcome (Wu et al., 2020), but little information has been available about patients with rare genetic diseases and COVID-19.

Tuberous sclerosis complex (TSC) is one of the most common rare diseases, affecting 1 in 6,000 live births and causing multi-system morbidities in the brain, kidneys, heart, eyes, and skin (Northrup & Krueger, 2013). Adult women may have cystic pulmonary involvement (lymphangioleiomyomatosis [LAM]) that could lead to respiratory insufficiency (Northrup & Krueger, 2013). A sporadic form is also described in previously healthy women (S-LAM; Northrup & Krueger, 2013). The only approved treatment is the use of mTOR inhibitors (Everolimus

and Sirolimus), originally identified as immunosuppressants (Franz & Krueger, 2018).

Recommendations for patients with TSC during the COVID-19 pandemic are currently based on expert opinions (Tuberous Sclerosis Alliance, 2020; <https://www.tsalliance.org/wp-content/uploads/2020/03/COVID-19-Considerations-for-TSC-Medical-Professionals-WEB.pdf>). To provide evidence for these recommendations, we performed a study to investigate the presence and outcomes of SARS-CoV-2 infection in a cohort of Italian TSC patients.

## 2 | METHODS

This retrospective cohort study was conducted at the multidisciplinary TSC Clinic of San Paolo University Hospital in Milan and was approved by the Institution's Ethics Committee. The institution is currently operating as a COVID hospital, with an ICU and six COVID wards, and the remaining COVID-free wards ensuring essential services. Our TSC clinic is the largest in Italy, comprises a dedicated LAM clinic, and offers diagnosis and care to 388 affected children and adults from various parts of the country (Peron et al., 2018).

We included in the study all individuals affected with TSC and/or LAM who were seen in the outpatient clinics between January 1, 2020 and April 24, 2020 (corresponding to the surge of the epidemiological curve in Italy) during regular visits before the lockdown and for essential in-person clinical encounters thereafter. We included also the patients assessed through phone visits after the lockdown. Although the first confirmed community spread of COVID-19 in Italy was identified on February 21, we decided to extend the assessment period back to January as there is evidence that SARS-CoV-2 was present in the country since then (Zehender et al., 2020).

We reviewed all medical records to identify confirmed SARS-CoV-2 infections and/or suspect cases as defined by the European Center for Disease Prevention and Control (2020) or the World Health Organization (<https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov>). Changes in clinical status strictly related to TSC are not reported for the purpose of this article.

To investigate a possible effect of mTOR inhibitors, patients with LAM on Sirolimus and TSC patients on Everolimus were interviewed on April 17, 2020 and April 24, 2020, respectively. Patients and/or caregivers were asked to respond referring to the last 4 months.

Data collected included demographics, TSC manifestations, SARS-CoV-2 testing, history of signs/symptoms suggestive of COVID-19, hospital admissions, treatments, and outcomes. Patients were instructed to notify the TSC clinic of later changes in health status.

## 3 | RESULTS

A total of 102 individuals with TSC and/or LAM were included. Demographic characteristics are summarized in Table 1 and treatment with mTOR inhibitors in Table 2. Prevalence of TSC-related

**TABLE 1** Demographic characteristics of the cohort

<b>Total number of patients</b>	<b>102</b>
<i>Rare disease diagnosis</i>	
Definite diagnosis of TSC	93/102 (91%)
Sporadic LAM	9/102 (9%)
<i>Pre-existing pulmonary involvement (calculated on adults)</i>	
TSC-LAM	13/72 (18%)
Sporadic LAM	9/72 (13%)
Total	22/72 (31%)
<i>Sex</i>	
Females	64/102 (63%)
Males	38/102 (37%)
<i>Age</i>	
Whole cohort	102
Median age	25 years
Age range	2 m–72 years
Children	30/102 (29%)
Median age	8 years
Age range	2 m–17 years
Adults	72/102 (71%)
Median age	36 years
Age range	18–72 years
<i>Current residence</i>	
Northern Italy	83/102 (81%)
Lombardy	71
First endemic areas <sup>a</sup>	14
Central/southern Italy	15/102 (15%)
Outside Italy <sup>b</sup>	4/102 (4%)
Patients living in their homes	97/102 (95%)
Patients living in assisted living facilities	5/102 (5%)
<i>SARS-CoV-2 testing</i>	
Performed	6/102 (6%)
Not performed	77/102 (75%)
Information not available <sup>c</sup>	19/102 (19%)
Testing performed in the Italian population (as of April 24, 2020)	1,642,356/60,474,050 (3%)

Abbreviations: LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.

<sup>a</sup>The first endemic areas in northern Italy are identified as Codogno, Bergamo, and the Padua province.

<sup>b</sup>Italian patients who were living abroad at the time of the interview or were out of the country during the pandemic and could not go back to Italy.

<sup>c</sup>Assumed not to be tested, as only symptomatic individuals presenting to the emergency department or requiring hospitalization received nasopharyngeal swab in Italy as per government recommendations.

manifestations and molecular diagnosis were in line with those of the literature (Northrup & Krueger, 2013), and phenotypes were of variable severity (Peron et al., 2018), ensuring this is a representative sample of the general TSC population.

**TABLE 2** Patients on mTOR inhibitors during the study period

<b>Total number of patients on mTOR inhibitors</b>	<b>26</b>
Median age	26 years
Range	5–72 years
<i>Everolimus</i>	
Number of patients	17
Dose range	2.5–10 mg/day
<i>Indications to treatment</i>	
Subependymal giant cell astrocytoma (SEGA)	10
Renal angiomyolipomas	4
Drug-resistant seizures	3
<i>Sirolimus</i>	
Number of patients	9
Dose range	1–5 mg/day
<i>Indications to treatment</i>	
TSC–LAM	2
Sporadic LAM	7

Abbreviations: LAM, lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.

All patients/caregivers reported they were strictly abiding to national recommendations, namely lockdown. Those allowed to go for a walk because of underlying comorbidities such as intellectual disability and autism spectrum disorder were practicing social distancing when outside their homes. Twenty-four of 26 patients who were on mTOR inhibitors continued treatment (those who discontinued treatment are displayed in Table 3).

Complete information was available for all 102 patients until the end of February, and for 99/102 patients until the end of collection. As of April 24, one TSC patient had polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection. Nine additional patients either met the definition of suspect case (<https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov>) (5), or presented with at least two of the most common symptoms of SARS-CoV-2 infection (World Health Organization, 2020; [www.who.int/health-topics/coronavirus#tab=tab\\_3](http://www.who.int/health-topics/coronavirus#tab=tab_3)) (3), or were a close contact of a confirmed case (<https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov>) (1). Two of them required admission to the hospital, and seven were treated at home. Detailed phenotype, therapy with mTOR inhibitors, clinical course, and outcome are reported in Table 3. Nine additional patients described mild isolated respiratory symptoms that were judged non-suggestive of SARS-CoV-2 infection.

## 4 | DISCUSSION

To our knowledge, this is the first study of a rare genetic disease in a SARS-CoV-2-affected area. Although expert recommendations concerning COVID-19 and rare diseases are published (Orphanet, 2020;

<http://international.orphanews.org/summary/editorial/nl/id-200327.html>) and funding has been appropriated for studies expanding focus on this subject (National Institutes of Health, 2020), the prevalence and outcomes of COVID-19 in a rare disease cohort has not been reported.

At time of writing, the Lombardy region had a cumulative incidence of 739 confirmed cases of SARS-CoV-2 per 100,000 inhabitants (0.007) (Istituto Superiore di Sanità, 2020; [https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19\\_28-aprile-2020.pdf](https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_28-aprile-2020.pdf)). As a comparison, the identification of only one TSC patient with confirmed SARS-CoV-2 infection out of 71 living in Lombardy in our sample (0.014, 95% CI [ $<0.0001$ – $0.0829$ ]) would be in line with these numbers.

Since it is impossible to differentiate COVID-19 from community acquired respiratory infections based solely on signs and symptoms, we identified nine patients who reported symptoms suggestive of COVID-19, without confirmative reverse transcriptase polymerase chain reaction (RT-PCR) testing. One of these patients tested negative for SARS-CoV-2 on RT-PCR from nasopharyngeal swab. Despite being the gold standard for the diagnosis, RT-PCR has high rates of false negative results (Younes et al., 2020), and the Food and Drug Administration (2020) concluded that negative results do not preclude SARS-CoV-2 infection (<https://www.fda.gov/media/134922/download>). Therefore, we cannot rule out COVID-19 in this patient. Conversely, it is also possible that some of the suspect cases listed in Table 3 exhibited symptoms due to different causes, since testing was not performed in them. No data are available about suspected cases in the general population for comparison, and only future serological testing of IgG antibodies will be able to determine whether TSC patients are more susceptible (or less susceptible) to symptoms.

Our results suggest that TSC patients do not have an increased risk of developing COVID-19. Alternatively, these numbers could be explained by the excellent compliance to social distancing demonstrated by our patients and their families during this pandemic. On the other hand, the only patient with confirmed COVID-19 had unfavorable outcome. It must be noted that he was a male older than 60 years, who had severe TSC with several comorbidities and was living in an assisted living facility with the potential for high inoculum, which are known risk factors and might have influenced the severity of disease, and was not on Everolimus.

We kept contact with all the patients on mTOR inhibitors and advised not to discontinue existing treatment, unless respiratory infections occurred. In such case, patients were advised to contact the TSC/LAM clinics, and adjustments in dosage or interruption of treatment were evaluated on a case-by-case basis after considering risks and benefits. None of the patients on Sirolimus or Everolimus had a confirmed SARS-CoV-2 infection, although 1/9 and 4/17, respectively, showed suspicious symptoms.

The PI3K/AKT/mTOR pathway plays a critical role in the response to infections (Keating & McGargill, 2016), and conflicting evidence exists about the possible protective or adverse effects of mTOR inhibitors on SARS-CoV-2 infection. On the one hand, there is concern about the immunosuppressant effect of mTOR inhibitors,

**TABLE 3** Characteristics of the TSC and LAM patients with confirmed SARS-CoV-2 infection, who met the definition of suspect cases, presented with at least two of the most common symptoms of SARS-CoV-2 infection, or were close contacts

Sex	Age	Ethnicity	Residence <sup>a</sup>	TSC manifestations	TSC mutational status	mTOR inhibitors	Timeline of symptoms	Hospital admission	Testing for SARS-CoV-2	ICU	Outcome
<i>Confirmed SARS-CoV-2 infection</i>											
M	61	Caucasian	Northern Italy—in a group setting (assisted living facility in Lombardy)	Severe ID, ASD, drug-resistant seizures, cortical tubers, subependymal nodules, retinal hamartomas, hypomelanotic macules, facial angiofibromas, fibrous cephalic plaque, shagreen patch, ungual fibromas, cardiac rhabdomyomas	TSC2	No	April 14, 2020: admitted to a COVID ward with fever and O <sub>2</sub> desaturation, bilateral interstitial pneumonia. Placed on helmet-based ventilation, unable to eat, fed and given antiepileptic drugs through NG tube April 17, 2020: clinically stable, was able to eat April 19, 2020: sudden worsening of symptoms, onset of renal failure. Moved to ICU, intubated and sedated. CRP: 327 mg/L; D-dimer: 2.921 ng/mL (nv: <500); creatinine: 2.33 mg/dL; azotemia: 121 mg/dL. Worsening bilateral interstitial pneumonia April 22, 2020: deceased	Yes	Positive	Yes	Deceased
<i>Suspect cases</i>											
F	16	Caucasian	Northern Italy—at home (Lombardy)	Severe ID, ADD, ASD, drug-resistant seizures, cortical tubers, subependymal nodules, SEGA, hypomelanotic macules, facial angiofibromas, cardiac rhabdomyomas, renal angiomyolipomas	TSC2	Everolimus (3 mg/day)	March 12, 2020: onset of fever, bronchitis, dry cough for a week, followed by asthenia Treated with cephalosporin Everolimus was not discontinued	No	No	No	Full recovery
F	8	Caucasian	Northern Italy—at home (endemic area in Lombardy)	Moderate ID, drug-resistant seizures, cortical tubers, subependymal nodules, SEGA, retinal hamartoma, hypomelanotic macules, facial angiofibromas, fibrous plaque, cardiac rhabdomyomas with infantile arrhythmia	TSC2	Everolimus (3 mg/day)	January 21, 2020: onset of fever (40°), rhinitis, followed by bilateral conjunctivitis on Day 1, diarrhea on Day 3, and anorexia and asthenia January 25–31, 2020: admitted and diagnosed with left pneumonia. Normal white blood cell count; CRP 12.1 mg/dL. Negative for pneumococcal infection Treated with paracetamol, cephalosporin, ampicillin/sulbactam Everolimus was not discontinued	Yes	No	No	Full recovery
M	22	Caucasian	Northern Italy—at home (Emilia Romagna)	Severe ID, ADHD, behavioral issues, drug-resistant seizures, hypomelanotic macules, facial angiofibromas, fibrous cephalic plaque, shagreen patch, ungual fibromas, cardiac rhabdomyomas with arrhythmia, renal and hepatic angiomyolipomas, renal cysts	Pending	No	March 10, 2020: onset of fever, anorexia, and asthenia (a few days later, the patient's father was admitted with bilateral interstitial pneumonia and RT-PCR-confirmed SARS-CoV-2 infection)	No	No	No	Full recovery

**TABLE 3** (Continued)

Sex	Age	Ethnicity	Residence <sup>a</sup>	TSC manifestations	TSC mutational status	mTOR inhibitors	Timeline of symptoms	Hospital admission	Testing for SARS-CoV-2	ICU	Outcome
F	31	Caucasian	Northern Italy—at home (Lombardy)	Mild ID, personality disorder, seizures, cortical tubers, subependymal nodules, SEGA, white matter radial migration lines, retinal hamartomas, hypomelanotic macules, facial angiofibromas, fibrous plaques, unguinal fibromas, MMPH, renal angiomyolipomas (bilateral nephrectomy)	TSC2	No	April 24–30, 2020: admitted with fever and cough. Normal white blood count; CRP: 5.7 mg/L; pro-calcitonin: 0.74 ng/mL (nv < 0.15). Chest X-ray: diffuse bilateral interstitial markings Treated with azithromycin, piperacillin/tazobactam	Yes	Negative	No	Full recovery
F	50	Asian	Northern Italy - at home (endemic area in Lombardy)	Sporadic LAM, with impaired lung function	-	Sirolimus (1 mg/day)	March 2020: fever for 20 days and O <sub>2</sub> desaturation (to 80%) Treated with supplemental oxygen (already available to the patient because of LAM), paracetamol, amoxicillin/clavulanic acid (10 days), and levofloxacin (10 days). Refused admission to the hospital Sirolimus was discontinued, and resumed 10 days after fever resolved	No	No	No	Full recovery
<i>Patients presenting with ≥2 of the most common symptoms of SARS-CoV-2 infection</i>											
M	25	Caucasian	Northern Italy—at home (Lombardy)	Mild ID, seizures, cortical tubers, subependymal nodules, SEGA, hypomelanotic macules, facial angiofibromas, fibrous cephalic plaque, shagreen patch, unguinal fibromas, cardiac rhabdomyomas, renal angiomyolipomas	TSC2	Everolimus (5 mg/day)	February 11, 2020: Fever (40°), dry cough, severe asthenia, sore throat, and anorexia for 2 weeks Treated with paracetamol, steroid nebulizer, and azithromycin changed to amoxicillin because of drug interaction with Everolimus Everolimus was not discontinued	No	No	No	Full recovery
F	5	Caucasian	Central Italy—at home	Severe ID, drug-resistant seizures, cortical tubers, subependymal nodules, retinal hamartomas, hypomelanotic macules, cardiac rhabdomyomas, renal angiomyolipomas	TSC2	Everolimus (4 mg/day)	December 18–23, 2019: bronchopneumonia, treated with cephalosporin. Discontinued Everolimus December 30, 2019: resumed Everolimus January 12, 2020: onset of cough, rhinitis, and fever. Left pneumonia, treated with cephalosporin. Discontinued Everolimus January 30, 2020: resumed Everolimus February 3, 2020: cold, bronchitis, treated with cephalosporin. Discontinued Everolimus February 17, 2020: resumed Everolimus	No	No	No	Full recovery
M	51	Caucasian	Northern Italy—at home (Lombardy)	Normal cognitive functioning, anxiety, seizures, cortical tubers, white matter radial migration lines, one hypomelanotic macule, facial angiofibromas, hepatic angiomyolipomas	NMI	No	January 16, 2020: onset of cough, fever (2 days), and anosmia (10 days) Treated with paracetamol	No	No	No	Full recovery

(Continues)

TABLE 3 (Continued)

Sex	Age	Ethnicity	Residence <sup>a</sup>	TSC manifestations	TSC mutational status	mTOR inhibitors	Timeline of symptoms	Hospital admission	Testing for SARS-CoV-2	ICU	Outcome
<i>Close contact</i>											
M	41	Caucasian	Northern Italy—at home (endemic area in Lombardy)	Normal cognitive functioning, anxiety, seizures, cortical tubers, subependymal nodules, white matter radial migration lines, retinal hamartomas, hypomelanotic macules, facial angiofibromas, shagreen patch, ungual fibromas, cardiac rhabdomyoma, renal and hepatic angiomyolipomas	TSC2	No	April 2020: onset of rhinorrhea, otherwise asymptomatic. Patient's wife tested positive for SARS-CoV-2 during professional screening, asymptomatic	No	No	No	Asymptomatic

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CRP, C-reactive protein; ICU, intensive care unit; ID, intellectual disability; MM/PH, multifocal micronodular pneumocyte hyperplasia; NG, nasogastric; NMI, no mutation identified; RT-PCR, reverse transcriptase polymerase chain reaction; SEGA, subependymal giant cell astrocytoma.

<sup>a</sup>This column indicates the geographical residence and whether the patient was living in a group setting or at home.

which could expose TSC patients to increased risk of SARS-CoV-2 infection. Although the doses initially used in TSC individuals were not much lower than those used in oncology, lower effective doses have been used in clinical practice (i.e., for subependymal giant cell astrocytomas; Franz & Krueger, 2018), which could therefore have limited immunosuppressive effect. On the other hand, mTOR inhibitors showed paradoxical immunostimulatory effects by boosting T-cell response (Keating et al., 2013), and the use of low-dose Everolimus was found to decrease the infection rate in elderly volunteers enrolled in a randomized, double-blinded, placebo-controlled trial (Mannick et al., 2018). In mice studies, Keating et al. (2013) showed that rapamycin enhanced protection against H5N1 infection, and data from the 2012 Middle East respiratory syndrome (MERS) outbreak suggest that treatment of cells with mTOR inhibitors decreased MERS-CoV replication in vitro (Kindrachik et al., 2015). The hypothesis that mTOR inhibitors may be beneficial in SARS-CoV-2 infection is therefore intriguing, but additional studies are required to obtain a definitive answer. A prospective assessment of COVID-19 in TSC patients who take mTOR inhibitors for their underlying condition may shed light into this interesting question.

#### 4.1 | Limitations

Although this preliminary study represents the first assessment of COVID-19 in patients with a rare genetic disease, it has several limitations. First, SARS-CoV-2 testing was limited in our cohort, and we cannot estimate the confirmed infection rate in TSC patients. Second, some asymptomatic patients could have been infected with SARS-CoV-2 but would have been missed due to limited testing. Finally, this study relies on patients' reports and is restricted to a small sample size.

## 5 | CONCLUSIONS

This rare disease cohort provides a screenshot of the presence and outcomes of SARS-CoV-2 infection among patients with TSC in Italy. Although our observations seem reassuring, physicians and patients should keep in mind that TSC patients remain at risk of contracting SARS-CoV-2. A prospective analysis is warranted to estimate the real infection rate in TSC patients and to evaluate the effects of mTOR inhibitors on COVID-19.

#### ACKNOWLEDGEMENTS

The authors would like to thank all the colleagues of the TSC Clinic of the San Paolo University Hospital in Milan, especially Dr Rosangela Arancio, and the families for kindly participating in this study. Angela Peron wishes to thank Prof. Dave Viskochil for assisting with English proofreading and Prof. Darcy Krueger for the fruitful discussion on the subject. This article is dedicated to the memory of our patient affected with TSC who untimely passed during the COVID-19 pandemic.



## CONFLICT OF INTEREST

Angela Peron, Francesca La Briola, Aglaia Vignoli, and Maria Paola Canevini received consulting fees from Italfarmaco outside the submitted work. The other authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

**Angela Peron:** Designed the study and wrote the manuscript; evaluated the patients and acquired the data; performed statistical analyses; critically revised the manuscript for important intellectual content. **Francesca La Briola:** Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. **Fabio Bruschi:** Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. **Silvia Terraneo:** Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. **Chiara Vannicola:** Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. **Roberto Previtali:** Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. **Sabrina Perazzoli:** Evaluated the patients and acquired the data; critically revised the manuscript for important intellectual content. **Emanuela Morengi:** Performed statistical analyses. **Gaetano Bulfamante:** Critically revised the manuscript for important intellectual content. **Aglaia Vignoli:** Critically revised the manuscript for important intellectual content. **Maria Paola Canevini:** Critically revised the manuscript for important intellectual content.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Supplementary Table S1.

## ORCID

Angela Peron  <https://orcid.org/0000-0002-1769-6548>

Aglaia Vignoli  <https://orcid.org/0000-0003-4638-4663>

## REFERENCES

- European Center for Disease Prevention and Control. (2020). *Case definition and European surveillance for COVID-19*. Retrieved from <https://www.ecdc.europa.eu/en/case-definition-and-european-surveillance-human-infection-novel-coronavirus-2019-ncov>
- Food and Drug Administration. (2020). *New York SARS-CoV-2 real-time RT-PCR diagnostic panel*. Rockville, MD: Author. Retrieved from <https://www.fda.gov/media/134922/download>
- Franz, D. N., & Krueger, D. A. (2018). mTOR inhibitor therapy as a disease modifying therapy for tuberous sclerosis complex. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, 178(3), 365–373. <https://doi.org/10.1002/ajmg.c.31655>
- Istituto Superiore di Sanità. (2020). *Aggiornamento nazionale 28 aprile 2020 - ore 16:00*. Retrieved from [https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19\\_28-aprile-2020.pdf](https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_28-aprile-2020.pdf)
- Keating, R., Hertz, T., Wehenkel, M., Harris, T. L., Edwards, B. A., McClaren, J. L., ... McGargill, M. A. (2013). The kinase mTOR modulates the antibody response to provide cross-protective immunity to lethal infection with influenza virus. *Nature Immunology*, 14(12), 1266–1276. <https://doi.org/10.1038/ni.2741>

- Keating, R., & McGargill, M. A. (2016). mTOR regulation of lymphoid cells in immunity to pathogens. *Frontiers in Immunology*, 7, 180. <https://doi.org/10.3389/fimmu.2016.00180>
- Kindrachuk, J., Ork, B., Hart, B. J., Mazur, M., Holbrook, M. R., Frieman, M. B., ... Jahrling, P. B. (2015). Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrobial Agents and Chemotherapy*, 59(2), 1088–1099. <https://doi.org/10.1128/AAC.03659-14>
- Mannick, J. B., Morris, M., Hockey, H. P., Roma, G., Beibel, M., Kulmatycki, K., ... Klickstein, L. B. (2018). TORC1 inhibition enhances immune function and reduces infections in the elderly. *Science Translational Medicine*, 10(449), eaaq1564. <https://doi.org/10.1126/scitranslmed.aaq1564>
- National Institutes of Health. (2020). *News releases*. Retrieved from <https://www.nih.gov/news-events/news-releases/nih-supported-research-survey-examine-impact-covid-19-rare-diseases-community>
- Northrup, H., Krueger, D. A., & International Tuberous Sclerosis Complex Consensus Group. (2013). Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology*, 49(4), 243–254. <https://doi.org/10.1016/j.pediatrneurol.2013.08.001>
- Orphanet. (2020). *COVID-19 and rare diseases*. Retrieved from <http://international.orphanews.org/summary/editorial/nl/id-200327.html>
- Peron, A., Vignoli, A., La Briola, F., Morengi, E., Tansini, L., Alfano, R. M., ... Canevini, M. P. (2018). Deep phenotyping of patients with tuberous sclerosis complex and no mutation identified in TSC1 and TSC2. *European Journal of Medical Genetics*, 61(7), 403–410. <https://doi.org/10.1016/j.ejmg.2018.02.005>
- Tuberous Sclerosis Alliance. (2020). *COVID-19 considerations for TSC medical professionals*. Retrieved from <https://www.tsalliance.org/wp-content/uploads/2020/03/COVID-19-Considerations-for-TSC-Medical-Professionals-WEB.pdf>
- World Health Organization. (2020). *Coronavirus overview*. Retrieved from [www.who.int/health-topics/coronavirus#tab=tab\\_3](http://www.who.int/health-topics/coronavirus#tab=tab_3)
- Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., ... Song, Y. (2020). Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Internal Medicine*, 13, e200994. <https://doi.org/10.1001/jamainternmed.2020.0994>
- Younes, N., Al-Sadeq, D. W., Al-Jighefee, H., Younes, S., Al-Jamal, O., Daas, H. I., ... Nasrallah, J. K. (2020). Challenges in laboratory diagnosis of the novel coronavirus SARS-CoV-2. *Viruses*, 12(6), E582. <https://doi.org/10.3390/v12060582>
- Zehender, G., Lai, A., Bergna, A., Meroni, L., Riva, A., Balotta, C., ... Galli, M. (2020). Genomic characterization and phylogenetic analysis of SARS-CoV-2 in Italy. *Journal of Medical Virology*. <https://doi.org/10.1002/jmv.25794>

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Peron A, La Briola F, Bruschi F, et al. Tuberous sclerosis complex (TSC), lymphangioleiomyomatosis, and COVID-19: The experience of a TSC clinic in Italy. *Am J Med Genet Part A*. 2020;182A:2479–2485. <https://doi.org/10.1002/ajmg.a.61810>