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Patients with genetic disorders as risk group for COVID-19

Pacientes com distúrbios genéticos como grupo de risco para COVID-19

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ABSTRACT
The coronavirus disease (COVID-19) pandemic has seriously affected the global population and has raised concerns about the effect of this new disease on individuals with genetic disorders, many of which have a systemic effect, including impairment of the respiratory system. A lack of published literature about the consequences of SARS-CoV-2 infection in genetic disorders is observed, in this sense, the present review analyses the current knowledge about COVID-19 and its impacts on patients with genetic disorders, also genetic variants as factors of susceptibility and possible risks and preventive measures to those patients, highlighting the role of the restriction to social contact in prevention.

Keywords: COVID-19, SARS-CoV-2, genetic variations, respiratory impairment, genetic disorders, risk group, social distancing measures.

RESUMO
A pandemia da nova doença do coronavírus (COVID-19) afetou seriamente a população global e levantou preocupações sobre o efeito dessa doença em indivíduos com distúrbios genéticos, muitos dos quais com anomalias sistêmicas, incluindo comprometimento do sistema respiratório. Estudos científicos sobre as consequências da infecção por SARS-CoV-2 em pacientes com desordens genéticas ainda são escassos. Nesse sentido, a presente revisão analisa o conhecimento atual sobre COVID-19 e seus impactos em pacientes com desordens genéticas, bem como variantes genéticas como fatores de susceptibilidade, possíveis riscos e medidas preventivas a esses pacientes, destacando o papel da restrição ao contato social na prevenção.

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Palavras-chave: COVID-19, SARS-CoV-2, variações genéticas, comprometimento respiratório, distúrbios genéticos, grupo de risco, medidas de distanciamento social.

1 INTRODUCTION

The pandemic of the Coronavirus Disease 2019 (COVID-19) brought up the discussion about the health and pathogenic problems of this infectious agent on the general population, including individuals with genetic disorders. The new Coronavirus 2019 (SARS-CoV-2), is an RNA virus, of the order *Nidovirales*, *Coronaviridae* family and *Orthocoronavirinae* subfamily, highly pathogenic and capable of causing a respiratory syndrome [1]. All the clinical aspects of COVID-19 are not yet fully described [2], as far as the pattern of transmissibility, lethality and mortality. Lethality among hospitalized patients due to severe acute respiratory syndrome (SARS) is between 4.3 and 15%. The clinical spectrum of the infection is wide, ranging from a simple cold to severe pneumonia.

The mechanisms that act on the individuals' susceptibility, the resistance to infections and their pathological consequences, include: environmental factors, the nature of the infecting agent and also the genetic characteristics of the infected organism. To date, more than 5 million COVID-19 confirmed cases have been identified with about 350,000 confirmed deaths [3]. This disease appears to be more severe in patients over 60 years of age, male, with underlying respiratory or cardiac diseases, or chronic medical conditions, but, the available data regarding risk factor for poor outcomes is far from definitive [4,5,6].

The consequences of this viral infection for people with genetic disorders are still not fully known. This group of patients often has chronic and multisystemic conditions that make them even more vulnerable. This review analyses the current knowledge about the course of this new disease in some genetic disorders with respiratory impairment, including chromosomal syndromes and multisystemic mendelian disorders, also discuss preventive measures and the possible impacts caused by the infection of SARS-CoV-2 in these patients.

2 GENETIC INFLUENCES ON SARS-COV-2 ACTION MECHANISMS

The transmission of SARS-CoV-2 from human to human occurs mainly by direct contact with infected secretions and surfaces [7, 8]. The virus major target is the respiratory tract. Histological findings as multinucleated syncytial cells and interstitial mononuclear inflammatory infiltration have been identified in post-mortem analysis of infected lungs [9,

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10].

The susceptibility of the lungs tissue to the action of SARS-CoV-2 is associated to the high expression of the angiotensin-converting enzyme 2 (ACE2), which has been first identified by Hofmann et al. [11] as SARS-CoV-2 functional cell receptor and plays a crucial role in the disease pathogenesis [12, 10]. The infection begins with the attachment of the virus in the host cell, which is initiated by the binding of the spike (S) protein with its receptor, followed by the entry of the virus in the host cell through acid-dependent proteolytic cleavage of S protein by a cathepsin, mainly TMPRRS2 or another protease, and finally the fusion of the viral and cellular membranes [1].

New researches have been focusing on investigating the interaction between the pathogen and the human host dynamics, including variable genetic factors, such as polymorphisms in signalling and interaction with other molecules. It has been shown that susceptibility to various infectious diseases is heritable and reflect the impact of a major gene [13]. As a consequence, understanding the genetic influence in susceptibility to SARS-CoV-2 infection is an important tool in order to prevent the manifestation of the disease and its lethal effects.

Kachuri et al. [14] argue that humans and viruses have a long co-evolution, which led to the emergence of polymorphisms that affect the immune response to infection. The authors examined immunological tests of 1028 individuals tested for SARS-CoV-2 for severe acute respiratory syndrome and identified 7 HLA class II susceptibility alleles (5 associated with other viruses) with possible implications for complex diseases and severity of COVID-19.

Pinto et al. [5] using bioinformatics' techniques and systems biology approach, analysed differences in the expression of the ACE2 gene in lung cells from patients with comorbidities associated with COVID-19 compared to individuals considered healthy. They found that *ACE2* was highly expressed in these patients, when compared to the control group, which supports the hypothesis that as more active *ACE2* is in the lung cells, it is greater the chance that the person will develop a severe condition of COVID-19. Some authors [15, 16] even point out that the increased expression of *ACE2* may explain the more severe outcome of the disease in diabetic patients.

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Besides *ACE2*, other authors as Asselta et al. [17] have identified the expression of *TMPRSS2* as another possible gene which modulates the susceptibility to SARS-CoV-2, because of its crucial role in the virus' entrance in the host cell and its relation with susceptibility to other infectious diseases as influenza [18]. In their study, Asselta et al. [17] found different haplotypes of *TMPRSS2* that could be related to SARS-Cov-2 susceptibility even among different populations. In a study with isolated VERO E6 cell lines expressing *TMPRSS2*, Matsuyama et al. [19] have demonstrated its high susceptibility to SARS-CoV-2 infection, suggesting that the infection is enhanced by the expression of this gene. In other way, the lack of gene expression may also influence the susceptibility of SARS-CoV-2 infection, as argued by Moraes et al. [20], who suggests that a decreased expression of the gene tribbles homolog 3 (*TRIB3*) with age in lung cells of male patients is associated with their vulnerability to develop severe COVID-19, since its protein predicted role of interaction with the nucleocapsid protein and the RNA-dependent RNA polymerase of the Human Coronavirus, would prevent the infection.

Other kinds of efforts have been made to study the COVID-19. The consortium "COVID Human Genetic Effort" has started a project by recruiting patients from many countries with different backgrounds, in order to analyse candidate genetic variations, in an attempt to clarify how those variations affect the action of the SARS-CoV-2 in different individuals [13]. The authors state that by investigating cases from a large number of patients, specially outliers, human genetic determinants of infection and disease can be revealed, for example, the pathogenesis of severe COVID-19 cases in young healthy individuals or the identification of naturally resistant individuals to SARS-Cov-2. These finding would provide insights into other type of cases, suggesting more specific treatment possibilities.

Attempts to identify the genetic variations that influence the susceptibility a to SARS-CoV-2 infection and its different outcomes have been widely recognized [21]. To date, a few genes, as *ACE2* and *TMPRSS2* have been recognized as possible therapeutic targets, but no specific treatment has been defined [22]. Therefore, understanding the underlying genetic mechanisms that modulate SARS-CoV-2 actions may be a tool to identify useful prognostic markers, to stratify patients and provide the best treatment possibilities.

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3 GENETIC DISORDERS AS POSSIBLE RISK FACTORS

The pathophysiology of acute respiratory syndrome (SARS), associated with COVID-19, present complex patterns, related to factors such as obesity and advanced age, along with the possibility of the enhanced risk of congenital disorders that include cardiac and respiratory abnormalities in its symptoms. Several genetics conditions present breathing difficulties due to anatomic or functional changes (Table 1).

Table 1: Examples of genetic disorders with breathing impairment

	Disturbance	**CID-10**	**OMIM**
Chromosomal syndromes	Down syndrome (21 trisomy)	Q90.9	190685
	Prader Willi syndrome (deletion or imprinting 15q11-q13)	Q87.1	176270
Mendelian respiratory disturbances	Cystic Fibrosis	E84.9	219700
Lip and palate anomaly	Cleft lip and palate	Q.37	119530
	Pierre Robin sequence	Q87.0	261800
Growth disturbances	Achondroplasia	Q77.4	100800
	Jeune syndrome	Q77. 2.	208500
Innate errors of metabolism	Mucopolysaccharidosis type 1	E76.0	309900
	Mucopolysaccharidosis type2	E76.1	607014
Neuromuscular diseases	Spinal muscular atrophy	G12.0	253300
	Duchenne muscular dystrophy	G71.0	310200
Global developmental disorder	Rett syndrome	F84. 2	312750

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According to the Brazilian Federation of Associations of Rare Diseases (FEBRARARAS), [23] specific groups of these diseases may have an increased risk for infection: people with chronic lung or heart disease, common in mucopolysaccharidosis, patients with muscular dystrophies who usually have cardiac or pulmonary involvement, patients with diabetes, inherited metabolic diseases, patients with neuromuscular diseases that have impaired ventilation as in Duchenne Muscular Dystrophy, innate errors in metabolism, such as sickle cell anaemia, patients with immunosuppression, connective tissue diseases and genodermatoses. Veerapandiyan et al. [24, 25] have been discussing about the lack of information on how the COVID-19 public health emergency and resulting changes in health care delivery has impacted patients with spinal muscular atrophy and other muscular dystrophies. So, they assembled a group of specialists to provide recommendations on how to take care of these patients, taking in consideration the possibility of higher risks to SARS-CoV-2 infection, due to their susceptibility to major comorbidities, respiratory insufficiency, cardiac dysfunction and in muscular dystrophies patients, chronic immunosuppression from corticosteroids.

Patients with some forms of dwarfism such as Asphyxiant Thoracic Dystrophy or Jeune syndrome and Achondroplasia in children, could also be included at risk, due to alterations in the respiratory system, as narrowing of the rib cage in Jeune syndrome and obstructive sleep apnoea and / or muscular upper-airway obstruction in individuals with Achondroplasia [26, 27]. In a study published previously by one of the authors [28], it is reported a case of a child with Achondroplasia and Down's syndrome- 47, XY, +21, associated with a mutation in the type 3 receptor fibroblast growth factor gene (*FGFR3*) with heterozygous mutation *G1138A*, who had breathing problems with frequent hospitalizations that led to his death at the age of 6.

In mucopolysaccharidosis, lysosomal diseases due to failed degradation of glycosaminoglycans (GAG) and consequent cellular dysfunction, morbidity and mortality are frequently attributed to respiratory tract disorders, with airway obstruction, recurrent

infections and restrictive lung disease [29].

For these patients, FEBRARARAS [23] recommends special care in the COVID-19 pandemic, to avoid the risk of metabolic decompensation and viral infection, with continuity of necessary treatments, including respiratory physiotherapy to maintain unobstructed airways, with the use of protective measures.

Obesity has also been considered as another risk factor to COVID-19 [30]. This association puts in risk patients with Prader-Willi syndrome, a multisystemic congenital neurogenic anomaly, in which the gradual development of morbid obesity is common and patients are at risk of several potentially serious respiratory complications, as sleep disordered breathing, aspiration and respiratory failure associated with muscle hypotonia, which can cause constant clinical complications and may lead to death [31, 32, 33].

In cases of babies with cleft-lip and /or palate, congenital malformation that cause many health problems, who require constant therapeutic care, it is suggested the use of telemedicine or video based conversation for the continuity of treatments during COVID-19 pandemic also the protection of the patient/parents, as well as the health care team to maintain social distancing, according the current WHO recommendation [34]. Social distancing is especially important for those patients, because children with cleft palate often present upper airway obstruction and/or sleep disordered breathing [35]. Patients with syndromes that present this trait, as Pierre Robin sequence, should also consider those recommendations, due to common respiratory disturbances, like airway obstruction that is life threatening for neonates with this syndrome [36]. This attention could also be applied to Rett syndrome, cause of multiple deficiencies in girls, determining neuromuscular changes that can lead to important respiratory disorders, such as hypoventilation, central apnoea, episodic hyperventilation and air swallowing, the severity of those disturbances is variable and can be life threatening in many patients [37].

Regarding the well-known trisomy 21 (Down syndrome), Soares et al. [38] states that more than half of the causes of hospital admission are respiratory problems with obstruction in the upper airways, lower respiratory diseases, congenital heart diseases, pulmonary hypertension, pulmonary hypoplasia, obstructive sleep apnoea, immunodeficiencies, relative obesity and hypotonia and calls attention to the predisposition of these children to respiratory problems, sometimes presenting the need for ventilation. Although there are still no scientific reports of the new COVID-19 infection in patients with

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Down syndrome, characteristics such as mouth breathing, muscle hypotonia, immunological changes, heart diseases, sialorrhea, ineffective cough and obesity, can be considered at risk for the new disease.

Besides the common physical damage in this syndrome, immune components should also be taken into consideration when thinking about the susceptibility to COVID-19. Espinosa [39] emphasizes that individuals with Down syndrome frequently present chronic immune dysregulation, showing signs of autoinflammation, as elevated levels of cytokines and chemokines and consequently are more vulnerable to cytokine storms, a frequent event in several infectious diseases, including COVID-19 [40].

According to the social model of Down syndrome, that allowed several advances and prognostic modifications by the implementation of interventions, measures of social distancing, hygiene and protection are now recommended alongside a natural and balanced diet, adequate sleep routine, physical activities, care and affection. The same can be applied to another genetic disorders as Cystic Fibrosis (CF), characterized by dysfunction of the protein Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), with wide phenotypic manifestations, including progressive lung disease, in which the social distance actions have contributed to relatively low numbers of CF patients infected by SARS-CoV-2 in the European population [41], where the prevalence of this disease is high, with ten CF patients infected by SARS-CoV-2 in Italy, five in France, seven in the UK, five in Germany and three in Spain. Although, there is a suggestion of a possible modulation of the D allele of the ACE gene in the severity of cystic fibrosis as proposed by Marson et al. [42]. The authors also note that the few cases of CF may reflect the efforts of families to minimize social contact and hope that more robust data will be collected allowing the prediction of factors that may be associated with the severity of COVID-19 for these patients.

Retrospective analysis of critically ill COVID-19 patients shows that among those who die, 22% have cerebrovascular diseases, 22%, diabetes and 6%, chronic respiratory diseases [15]. It is important to highlight that the respiratory impairments common in genetic disorders, may place individuals with those conditions in the risk group for COVID-19, but many factors are involved in the outcome of the disease, such as environmental factors and genetic variations, such as polymorphisms (discussed in the first topic). In this way, it is not possible to define the development of the infection in those patients, especially because of the lack of peer-reviewed published literature about the effects of COVID-19 in individuals

with genetic disorders.

4 CONCLUSIONS

To date, there is a lack of data on the current knowledge of how individuals with genetic disorders are affected by COVID-19 and their susceptibility to SARS-CoV-2 infection. It can take months before enough epidemiological and clinical data are available to address this issue. Despite that, previous knowledge related to respiratory, cardiac and immune alterations frequent in patients with those disturbances can be helpful to predict the risks of COVID-19 to those individuals, taking in consideration that environmental factors and genetic variations may influence this disease outcome in each individual.

It is important that patients with genetic disorders and their families understand the severity of COVID-19, in this sense, private organizations of specific diseases as the Brazilian Federation of Rare Diseases (FEBRARAS), Down Syndrome International (DSI), Cystic Fibrosis Foundation (CFF) have been taking the role of spreading the relevant information relating COVID-19 and those genetic conditions. More studies are needed to clarify the effects of SARS-CoV-2 infection in patients with genetic disorders and provide scientific information to assist their families and health care systems in order to protect those individuals in a more specific way. For now, the current recommendations are that patients with genetic disorders and their families should follow the public orientation for people at risk for severe outcome of COVID-19, mainly the practice of social distancing and isolation.

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All authors have contributed equally to this review.

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