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Review

The role of host genetics in susceptibility to severe viral infections in humans and insights into host genetics of severe COVID-19: A systematic review

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ABSTRACT

Background: Susceptibility to severe viral infections was reported to be associated with genetic variants in immune response genes using case reports and GWAS studies. SARS-CoV-2 is an emergent viral disease that caused millions of COVID-19 cases all over the world. Around 15 % of cases are severe and some of them are accompanied by dysregulated immune system and cytokine storm. There is increasing evidence that severe manifestations of COVID-19 might be attributed to human genetic variants in genes related to immune deficiency and or inflammasome activation (cytokine storm).
Objective: Identify the candidate genes that are likely to aid in explaining severe COVID-19 and provide insights to understand the pathogenesis of severe COVID-19.
Methods: In this article, we systematically reviewed genes related to viral susceptibility that were reported in human genetic studies (Case-reports and GWAS) to understand the role of host viral interactions and to provide insights into the pathogenesis of severe COVID-19.
Results: We found 40 genes associated with viral susceptibility and 21 of them were associated with severe SARS-CoV disease and severe COVID-19. Some of those genes were implicated in TLR pathways, others in C-lectin pathways, and others were related to inflammasome activation (cytokine storm).
Conclusion: This compilation represents a list of candidate genes that are likely to aid in explaining severe COVID-19 which are worthy of inclusion in gene panels and during meta-analysis of different variants in host genetics studies of COVID-19. In addition, we provide several hypotheses for severe COVID-19 and possible therapeutic targets.

1. Introduction

In late 2019, a novel respiratory disease caused by a novel coronavirus was identified in China now named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) (*Archived: WHO Timeline - COVID-19*, 2020). By August 2020, the COVID-19 (Coronavirus Disease-2019) pandemic caused more than 20 million confirmed infections and more than 700000 deaths (*Coronavirus disease (COVID-19) Situation Report – 205*, 2020). Most of COVID-19 cases are mild, while about 15 % develop severe disease that results in acute respiratory distress syndrome associated with dysregulated immune response, systemic inflammation and cytokine storm. Host genetic factors predisposing to severe viral infection include inborn errors of immunity which involve a single genetic mutation that predisposes to a certain type of infection, e.g., single viral infection as reported in the International Union of Immunological Societies (IUIS) list of human inborn errors of

Abbreviations: GWAS, genome wide association studies; SARS-CoV-2, SARS Coronavirus 2; SARS-CoV, SARS Coronavirus; IUIS, International Union of Immunological Societies; OMIM, Online Mendelian Inheritance in Man (OMIM); HSE, herpses simplex encephalitis; HSV-1, Herpes Simplex Virus 1; MeSH, medical subject heading; dsRNA, double-strand RNA; DC-SIGN, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; LDH, lactate dehydrogenase; IL-18BP, IL-18 binding protein; PBMCs, peripheral blood mononuclear cells; endoU, coronavirus endoribonuclease.

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immunity (Tangye et al., 2020). Additionally, viral susceptibility, like other polygenic diseases, can be determined by single nucleotide polymorphisms (SNPs) in genes that are involved in the immune response to viral infection with different allele frequencies and effect sizes. Those SNPs can be identified through Genome-Wide Association Studies (GWAS) (Cao et al., 2009; Hamano et al., 2005; He et al., 2006; Manolio et al., 2009). Our systematic review includes both types of studies (Case report studies for inborn errors of immunity and GWAS studies).

Immune response to SARS-CoV-2 can be divided into two phases. In the first phase, the body tries to eliminate the virus using regulated immune response in the early asymptomatic and non-severe disease stages, preventing progression to the severe stage. In the second phase, there is an inflammatory cytokine storm and hyper-activation of the immune system leading to severe disease and death in some cases (Shi et al., 2020). The high fatality rate of COVID-19 may be partly due to excessive production of cytokines and inflammatory mediators(cytokine storm) leading to a hyperactive non-productive immune state causing lung and other organs injury (Zhou et al., 2020). We found little published data about the role of first phase of immune response where the body tries to eliminate the virus. Accordingly, we shed light on both phases of immune response to viral infections during our review.

As of August 12, 2020, there are more than 200 host genetics studies – with different study designs – trying to identify possible associations between human genetic variants and the prognosis of COVID-19 patients. Most of these studies are Genome-Wide Association Studies (GWAS) and depend on the association of genetic variations with different phenotypes such as severe COVID-19 disease (*The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic*, 2020). It is essential for these investigators to have a list of candidate genes that are likely to be involved in COVID-19 pathogenesis. Genomics England used wide inclusion criteria to design a gene panel to investigate COVID-19. This panel includes nearly 500 genes associated with different immunological deficiencies in studies done on animals or humans (Martin et al., 2019). In our review, we refine this panel and create a gene list of the most likely genes that might be involved in severe COVID-19 disease based on a set of criteria discussed below in the methods section. These criteria dictate that our curated gene list contains only studies on humans and that genetic mutations predisposed to severe viral infections in otherwise healthy individuals (in case report studies) or predisposed to SARS-CoV or SARS-CoV-2 in GWAS studies providing the highest evidence for possible involvement in severe COVID-19 disease.

To our knowledge, there are no such systematic reviews dedicated to creating a catalog of host genes and genetic variants that confer susceptibility to severe viral infections in humans. Accordingly, we included different genes involved in both phases of the immune response to create a list of human genes and genetic variants that are highly likely to be associated with susceptibility to severe COVID-19 disease.

This gene list can benefit investigators in two ways: the first one is to make sure that those genes are present in gene panels used for host genetic studies as they are likely candidates of association with severe COVID-19 disease. The second one is to systematically evaluate evidence from different GWAS studies using meta-analysis for genetic variants on our gene list to increase the statistical power of evidence generated (Zeggini and Ioannidis, 2009). In addition, we provide new insights and different hypotheses for genes involved in severe COVID-19 disease based on our reviews of different viral susceptibility studies and briefly review the COVID-19 host genetics studies published up to this date.

2. Methods

We included two types of studies in our systematic review: case-report and case-control GWAS studies.

2.1. Search strategy for case-report studies

For case report studies of inborn errors of immunity, we used the International Union of Immunological Society (IUIS) list which is a highly validated list by immunology experts including only studies with compelling evidence of pathogenic variants predisposing to infections (Tangye et al., 2020). Next, we checked the OMIM database to find the related studies.

2.2. Inclusion criteria

1 Genes and genetic variants associated with susceptibility to single or multiple viral infections in otherwise healthy individuals
2 Genetic variants associated with a severe or life-threatening viral infection
3 Multiple unrelated cases from different families with in vitro validation of the effect of pathogenic variant
4 Few or a single case with rigorous validation of the genetic defect using in vitro studies

2.3. Exclusion criteria

1 Genetic variants associated with long term outcomes as malignancy
2 Genetic variants not rigorously validated using in vitro studies

2.4. Search strategy for case-control GWAS studies

For identification of Case-Control GWAS studies we queried PubMed Search Engine to identify studies that are within our scope using Medical Subject Headings (MeSH terms) and Boolean operators.

2.5. Search engine

PubMed, Google Scholar

2.6. MeSH terms and keywords

MeSH terms included: Genetic Predisposition to Disease (ID: D020022) and Virus Diseases (ID: D014777), while keywords included: SARS, Genetics, Corona, COVID-19

2.7. Search string in PubMed

("Genetic Predisposition to Disease"[Majr]) AND ("Virus Diseases"[Majr]) 998 articles
(("SARS Virus"[Mesh]) AND (Genetic [Title/Abstract]) 93 articles

2.8. Filtering strategy

Article type: Journal article
Species: Humans
Language: English

2.9. Inclusion criteria

1 Case-control studies
2 Single nucleotide polymorphism (SNP) associated with susceptibility to acute severe SARS-CoV or SARS-CoV-2 infection.
3 Authors report statistical significance of the results with a *P*-Value $<.05$ and odds ratio proving the effect of the variant on susceptibility to severe viral infections.

2.10. Exclusion criteria

1 Differential Gene expression studies

2 Association with other types of viruses other than SARS-CoV or SARS-CoV-2
3 Association of viral infection with variable number tandem repeats (VNTR)
4 Animal or in vitro studies

Two reviewers independently screened all the titles and abstracts to identify publications that are relevant. A third reviewer assessed the two independent lists of selected and rejected sources and made the final selection where there were discrepancies.

In each paper included in Tables 1 and 2, we included the following items whenever reported in the paper:

1) Genetics of severe manifestation:
- Official gene symbol
- Location of mutation in the genome
- Inheritance pattern
- Penetrance

2) Clinical manifestation of patients
3) Demographics
- Number of patients studied
- Their country of origin
- Whether patients are related or not

4) Statistical significance for GWAS studies (odds ratio, confidence interval and *P-value*)

3. Results and discussion

We reviewed case reports related to susceptibility to severe viral infections In general (Table 1) and GWAS studies related to susceptibility to severe infections of SARS-COV or SARS-COV2 (Table 2). We identified 40 genes that we expect to be highly involved in host genetic susceptibility to severe COVID-19, and hence deserve consideration during design and interpretation of case report and GWAS studies of COVID-19 and also during a meta-analysis of different GWAS studies. Table 3 below represents a brief version of our systematic review. However, it does not substitute Tables 1 and 2 (the complete version of our review), and we recommend that the reader refers to Tables 1 and 2 during reading.

3.1. Biological pathways involved

3.1.1. TLR Pathways and severe viral infections

Several studies reported genetic mutations involved in the TLR3 signaling pathway including TLR3, TRIF, TRAF3, and TBK1 genes. In a recent study done on 16 patients with adult-onset Herpes simplex encephalitis(HSE) using whole-exome sequencing (WES), 1 patient was discovered to have TLR3 deficiency, while the 8 other patients had mutations in other genes in the TLR3 signaling pathway(2 patients with a mutation in *IRF3*, 2 patients with mutations in *STAT1*, 2 patients with mutations in *TRIF*, 1 patient with a mutation in *TYK2*,1 patient with a mutation in *MAVS*, and finally 1 patient with a mutation in *TBK1*) (Mørk et al., 2015).

The most associated gene with severe viral infections is TLR3 which is a receptor for double-strand RNA, dsRNA (intermediate in the replication of many viruses which induces interferon(IFN)response to prevent the cytopathic effects of different viruses (Oshiumi et al., 2003)

In some cases, a single gene (e.g., *TLR3*) was involved in predisposition to several viruses (Lim et al., 2019; Zhang et al., 2007) and a single mutation (P 554S) predisposed to different viral infections (HSE and ARDS due to IAV) which support our hypothesis of the possible involvement of our reviewed genes in COVID-19 susceptibility, and hence the need for a candidate gene list (Lim et al., 2019; Zhang et al., 2007). Additionally, Other mutations were reported in *TLR7* or *TLR9* pathways leading to impaired interferon 1 production (Kawasaki and Kawai, 2014). Other mutations were reported in some interferon-stimulated genes (ISG) such as *MxA* which inhibits intracellular trafficking of invading viruses and *OAS-1* genes responsible for antiviral activity by inhibition of translation of viral proteins in addition to enhancing viral RNA degradation (Malterer et al., 2014).

3.1.2. Lectin Pathways and severe viral infections

Lectin pathway is an alternative pathway for pathogen detection through the carbohydrate moiety expressed on the surface of different pathogens (e.g. glycoproteins of viruses). Upon binding to lectin receptors, pathogens are internalized into the cell, degraded by lysosomes to be presented on the MHC II to T cells (Van Kooyk and Geijtenbeek, 2003). DC-SIGN (CD 209) (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) is a C-type lectin expressed on the surface of immature dendritic cells and macrophages in peripheral mucosal sites including alveolar macrophages (Tailleux et al., 2005). Several studies proved the binding affinity of DC-SIGN to different viruses including SARS-CoV Spike glycoprotein (Van Kooyk and Geijtenbeek, 2003; Marzi et al., 2004). Recently, SARS-CoV-2 binding to DC-SIGN and macrophage galactose lectin (MGL) was identified as ACE2 independent binding method to human cells and lung microbiota (Chiodo et al., 2020). Additionally, Polymorphisms of DC-SIGN were associated with a higher Lactate dehydrogenase (LDH) level in SARS-CoV patients– LDH is a systemic marker of inflammation (Chan et al., 2010). Moreover, Mannose-binding lectin was associated with SARS-CoV severity in patients (Zhang et al., 2005). Accordingly, polymorphisms in C-lectin genes might explain severe COVID-19 disease.

Binding to DC-SING has been incriminated in the persistence of HIV infection in dendritic cells despite small viral loads. Instead of being degraded by lysosomes and presented to T-cells, HIV virus was able to survive inside dendritic cells under the cell membrane camouflaging the immune system (Kwon et al., 2002; Geijtenbeek et al., 2000). Consequently, we suggest dendritic cells might play the role of the safe house for SARS-CoV-2 explaining many cases of recurrent COVID-19 disease (Ravioli et al., 2020; Loconsole et al., 2020).

3.1.3. Inflammasome pathways and sever viral infections

Inflammasome activation occurs due to binding of pathogens or pathogen products and results in the release of IL-1β and IL-18 and finally cytokine storm. There are different platforms for Inflammasome activation including nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein (NLR) family members NLRP1, NLRP3, and NLRC4 (Broz and Dixit, 2016). Inflammasome activation is one of the main theories for explanation of the cytokine storm during COVID-19 causing severe manifestations in around 15 % of the infected population (van den Berg and te Velde, 2020; Rodrigues et al., 2020; Freeman and Swartz, 2020). NLRP3 activation in COVID-19 patients was proven in vitro in PBMCs and tissues of COVID-19 patients. Additionally, higher levels of IL-18 and Casp1p20(Inflammasome products) -in the sera of COVID-19 patients- were associated with COVID-19 severity and poor prognosis (Rodrigues et al., 2020). During our review, we identified a gain of function mutation causing inflammasome activation(NLRP1) and increased secretion of inflammasome induced cytokines (IL-18 and TNF-α) in the blood of patients who suffered from Juvenile-onset recurrent respiratory papillomatosis (JRRP) - Human Papillomavirus (Drutman et al., 2019). Hence, we invite researchers to study the possible involvement of NLRP1 in severe COVID-19 disease.

In line with these findings, the cytotoxic effect of IL-18 in viral infection was demonstrated in an 11-year- old patient who suffered from severe fulminant Hepatitis A virus (HAV). Over activation of IL-18 occurred due to loss of function mutation of IL-18 binding protein (IL-18BP) which buffers the effects of IL-18. IL-18 over activity leads to over activation of cytotoxic and Natural Killer cell (NK) leading to uncontrolled hepatocyte necrosis and liver failure (Belkaya et al., 2019). Recombinant IL-18BP was used as a treatment option for hereditary disorder of inflammasome activation and for Still's disease treatment

Table 1
Case-report studies of inborn errors of immunity related to virus susceptibility: overview of involved genes, genetic mutations, mode of inheritance, clinical manifestations and demographics of patients.

Official Gene Symbol	Genotype and inheritance pattern	Clinical manifestation	Demographics of affected patients	PMID
TLR3	Heterozygous dominant-negative mutation of TLR3(P 554S) c.1660C > T	Herpes simplex encephalitis(HSE) due to Herpes Simplex Virus-1 (HSV-1)	2 unrelated French children	17872438
	Autosomal recessive compound heterozygous c.1660C > T and c.2236 G > T		8-year-old Polish child	21911422
	Autosomal Dominant: G743D + R811I, D592 N, M374 T, and L360P Autosomal Recessive: R867Q		6 unrelated patients	25339207
	Heterozygous missense c.889C > G / p.Leu297Val		1 adult patient	26513235
	Autosomal Dominant P 554S (2 patients) and P680 L(1 patient)	Acute respiratory distress syndrome (ARDS) due to Influenza A virus (IAV) infection	3 unrelated children	31217193
UNC-93B	Autosomal Recessive 1034del4 of the gene 781G > A	Herpes simplex encephalitis after HSV-1	Two unrelated patients in two unrelated families whose parents are first cousins	16973841
TICAM1/ TRIF	Autosomal Recessive Nonsense mutation c.421C > T/R141X	Herpes simplex encephalitis after HSV-1	2-year-old Saudi Arabian boy born to consanguineous parents	22105173
	Autosomal Dominant c.557C > T/S186L		A 21-month-old girl with French, Portuguese, and Swiss descent	
	Autosomal Dominant c.1702 G > A/ pAla568Thr		73-year-old male	26513235
	Autosomal Dominant c.749C > T/Ser160Phe		69-year-old male	
IRF7	Compound heterozygous Autosomal Recessive p.Gln421X(Q421X) and p.Phe410Val (F410 V)	Acute respiratory distress syndrome (ARDS) following seasonal and pandemic influenza viruses	One child born to non-consanguineous parents of French descent	25814066
IRF3	Autosomal dominant R285Q Heterozygous mutation c.829G-A	Herpes simplex encephalitis after HSV-1	15-year-old Danish child. Father is carrier(incomplete penetrance) 34 years old patient	26513235
GATA2	Heterozygous Autosomal Dominant G > T substitution at nucleotide 16913 of exon 7 / R396L	Acute respiratory distress syndrome (ARDS) due to influenza A virus (IAV) disease(H1N1pdm)	Father (54 years)and his son(31 years) from a consanguineous family in Spain	29882021
	c.417dupT; p.V140CfsX44	Severe human Papillomavirus(HPV) infection		
	c.302delG p.G101AfsX16	Disseminated cytomegalovirus infection, cytocytomegalovirus gastroduodentis, severe HSV-2	N/A	23365458
IRF9	Homozygous Autosomal Recessive c.991 G > A	Life-threatening Influenza Pneumonitis infection due to Influenza A virus (IAV)	A 5-yr-old child born to first-cousin Algerian parents and living in France	30143481
	Homozygous autosomal recessive c.577 + 1G > T (NM_006084)	Death due to enterohemorrhagic fever subsequent to vaccination for yellow fever virus(sister) Repeated viral infections including Influenza B virus(brother)	2 children (siblings) of Portuguese origin and residents of Venezuela	30826365
IFNAR1	In P1, homozygous mutation in IFNAR1, c.674-2A > G In P2, compound heterozygous c.783 G > A;p.W261X and c.674-1G > A	life-threatening complications of vaccination with live attenuated measles(P1) and YF viruses(P2)	a 9-year-old boy in Iran at 1 year old (P1) a 14-year-old girl in Brazil at 12 year old(P2)	31270247
IFNAR2	Homozygous AR c.A311del	Fatal encephalitis following live attenuated MMR vaccine	13-month old infant	26424569
STAT2	Homozygous Autosomal Recessive c.381 + 5 G > C	Severe Measles virus infection after MMR vaccination	2 siblings from a parental consanguinity 5-y-old child His sibling later died of a 2-d febrile illness of viral cause	23391734
	homozygous , c.1836 C > A (p.Cys612Ter)	Neurological deterioration following viral infection	2 siblings P 1 and P2	26122121
	homozygous (c.381 + 5 G > C)	prolonged febrile illness with multisystem involvement following MMR vaccine	P3 from an unrelated family	
DBR1	Autosomal Recessive c.359 T > C (2) c.49 T > C (2)	Herpes Simplex virus-1 (HSV1), Influenza B virus, and norovirus (NV) viral encephalitis	2 Arab children 2 Portuguese children 1 Japanese child	29474921

(*continued on next page*)

Table 1 (*continued*)

Official Gene Symbol	Genotype and inheritance pattern	Clinical manifestation	Demographics of affected patients	PMID
	Compound heterozygous c.37–38CT > GG; p.L13 G and c.589C > T; p. R197X(1)			
TBK1	AD c.619A > G = I207V	Herpes simplex encephalitis after HSV-1	50-year-old Danish woman	26513235
	AD c.149A > C = D50A "Incomplete penetrance"		11-month French patient	22851595
	c.476 G > G/C = G159A		7-year-old Polish patient (Incomplete penetrance)	
NLRP1	P1 and P2: AR homozygous missense mutation c.2819C > A for transcript variant 1 p.T755 N for isoform 1 -Gain of function mutation	Juvenile-onset recurrent respiratory papillomatosis (JRRP) - Human Papilloma virus	2 brothers of Belgian ancestry born to consanguineous (first-cousin) parents. They had the same mutation but not the same severity of manifestations	31484767
IL18BP	AR NG_029021.1: g.7854_7893del; NM_173042.2:c.508-19_528del	Fulminant viral hepatitis (FVH)	An 11-year-old girl born to consanguineous Algerian parents living in France	31213488
POLR3A POLR3C	Heterozygous mutations P1: L11 F in POLR3C P2: M307 V in POLR3A P3:Q707R in POLR3A and R438 G in POLR3C P4:R437Q in POLR3A and R84Q in POLR3C "Incomplete penetrance"	Acute severe Varicella-zoster virus(VZV) infections: P1 and P4: VZV encephalitis P2: VZV cerebellitis P3: VZV pneumonitis	4 unrelated children of European origins. P1 and P2 are 3 years old and 5 years old respectively Belgian boys. P3: 5 year old French boy P4: 11 year old German girl	28783042
TRAF3	Heterozygous Autosomal Dominant negative Missense (non-conservative) denovo mutation c.705C > T R118W	Herpes simplex encephalitis after HSV-1	French girl developed herpes simplex encephalitis at the age of 4	20832341
STAT1	Heterozygous missense c.796G4A, p.Val266Ile	Herpes simplex encephalitis after HSV-1	2 unrelated patients 68 and 65 years old males	26513235
IFIH1/ MDA5	Homozygous missense c.1093A > G, p.K365E	Recurrent life-threatening respiratory tract infections by human rhinovirus, respiratory syncytial virus, and influenza virus,	5-year old girl	28606988
	Homozygous c.2665A > T (p.Lys889*) Nonsense mutation	Susceptibility to Epstein Bar viral infection	5 years old girl born to consanguineous parents(Egypt)	29018476
	4 patients had rare splicing variant rs35732034 1 in homozygous and 3 others in heterozygous form 4 patients had a heterozygous mutation of rs35337543: splice variant (3 patients) and rs35744605 : stop gain (1 patient)	Severe respiratory infections due to human rhinovirus or respiratory syncytial virus	8 patients (children)	28716935

AD, Autosomal dominanat.

(Autoimmune disease) (Gabay et al., 2018) (Phase 3, ClinicalTrials.gov identifier: NCT03113760). Additionally, 3 small molecules were identified in silico as inhibitors of IL-18 (Krumm et al., 2017). We searched for IL-18 inhibition as a possible treatment option for severe COVID-19 using the keywords "COVID-19" and "IL-18" in clinicaltrials.gov and found no registered clinical trials. Accordingly, we think that IL-18 inhibition can provide a therapeutic option in patients with severe COVID-19 disease.

MDA5 gene encodes a protein responsible for sensing dsRNA (byproduct of viral replication) which activates interferon response. Several studies reported increased respiratory tract infections by several viruses caused by mutations in this gene (Asgari et al., 2017; Lamborn et al., 2017). Cornavirus is able to evade the MDA5 sensor using endoribonuclease designated EndoU which is highly conserved in different corona viruses (Hackbart et al., 2020; Deng and Baker, 2018). We suggest that Inhibition of EndoU in SARS-CoV-2 might represent a potential therapeutic target in COVID-19 patients.

3.2. Effect and site of genetic mutations

Mutations were identified in exons and introns of different genes as missense, nonsense, or frameshift mutations. The effect of mutations was mainly due to loss of function as illustrated in Table 1, while a single case of gain of function mutation was reported in NLRP1 gene (Drutman et al., 2019).

In some cases, we identified mutations in the promoter of some genes such as *MxA* and *DC-SIGN* associated with SARS-CoV susceptibility (Chan et al., 2010; Hamano et al., 2005; He et al., 2006). This reflects the importance of studying genomic regions involved in gene regulation as promoters and different regulatory RNA genes via WGS when investigating viral susceptibility in humans.

Surprisingly, we found that a mutation in the promoter of the *MxA* gene –casuing increased expression of the antiviral protein in the cell-led to increased susceptibility to subacute sclerosing panencephalitis (a complication of measles virus infection)! This can be explained by persistent infection by the measles virus due to MxA protein action which inhibits viral expression and prevent complete immunologic clearance (Torisu et al., 2004). This might be an alternative hypothesis

Table 2
GWAS studies for SARS-COV and SARS-COV-2 studies : overview of genes, genetic mutations, statistical significance, clinical manifestations and demographics involved in human viral immune response.

Official Gene symbol	Genotype and inheritance pattern	Clinical manifestation	Demographics of affected patients	PMID
CD14	CD14-159CC	Severe acute respiratory syndrome (SARS) caused by SARS-CoVP = 0.04; odds ratio, 2.41; 95% confidence interval, 1.05 to 5.54	152 Hong Kong patientsand 198 controls	17913858
HLA-B	HLA-B*0703 >HLA-DRB1*0301	Severe acute respiratory syndrome (SARS) caused by SARS CoV OR[1], 4.08; 95% CI, 2.03–8.18; P = .00072 [Bonferroni-corrected P value, P(c) <.0022 OR, 0.06; 95%, 0.01–0.47; P = .00008 [after Bonferroni correction, P<.0042	90 Chinese unrelated patients of ages 22–85 yearscontrol is overall Hong Kong population of 18774	15243926
FCGR2A	HomozygousFcγRIIA-R/R131	Severe acute respiratory syndrome (SARS) caused by SARS CoV (P = 0.03; odds ratio: 3.2; 95% confidence interval: 1.1–9.1)	26 ICU[2] patients unrelated people from Hong Kong and200 controls	16185324
CCL2 ***CCL5***	CCL2 G-2518A	Severe acute respiratory syndrome (SARS) caused by SARS CoV$P = 1.6 \times 10(-4)$ OR 1.48 with 95% confidence interval (1.21 – 1.82)	932 Chinese descendants patients and 982 controls	25818534
		Susceptibility to developing SARSP < 0.0001, OR = 2.80, 95%CI:2.11–3.71)	495 SARS patients (Hong Kong) with 578 controls	
	RANTES (CCL5) -28 GAlleleRANTES-28 CG and GG	Related to ICU admission and death from SARS CoV infection.CG (P = 0.011OR = 4.27, 95%CI:1.64–11.1)GG (P = 0.011OR = 3.34, 95%CI:0.37–30.7)	356 Chinese SARS patients and 367 controls	17540042
***MxA* Promoter**	GG genotype (p = 0.0346) and G allele at -88 position(p = 0.0195)	increased risk of hypoxemia in SARS patients	22 SARS patient with hypoxemia and 22 SARS patients without hypoxemia	15766558
	GT genotype at position 88	Increased susceptibility SARS in comparison to GG genotypeOR = 3.06, 95% CI: 1.25–7.50	66 cases and 64 Close contact uninfected controls (Chinese Han population)	16824203
ABO	Blood Group A	Increased susceptibility to COVID19 infection (37.75% VS 32.16%) $P < 0.001$	1775 COVID19 cases compared to 3,694 controls of Chinese population	32750119
		Increased susceptibility to severe manifestation (odds ratio, 1.45; 95% CI, 1.20 to 1.75; P = 1.48×10^{-4})		32558485
		Blood Group A was higher in COVID-19 cases : 36.90% vs. 27.47%, P = 0.006	835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain 187 patients and 1991 controls from China	32562665
ABO	Blood Group O	Increased protection against COVID19 (25.80% VS 33.84%)$P < 0.001$	1775 COVID19 cases compared to 3,694 controls patients of Chinese population	32750119
		odds ratio, 0.65; 95% CI, 0.53 to 0.79; P = 1.06×10^{-5}		32558485
		Blood Group O was at lower risk of COVID-19 infection : 21.92% vs. 30.19%, P = 0.018	835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain 187 patients and 1991 controls from China	32562665
ApoE	e4e4 homozygotes	Increased probability of testing positive for COVID19OR = 2.31, 95% CI: 1.65 to 3.24, p = 1.19×10^{-6}	e4e4 homozygotes (n = 9,022) e3e3 (n = 223,457) from UK Biobank	32451547
SLC6A20LZTFL1CCR9FYCO1CXCR6XCR1	The peak association signal was at 3p21.31 region containing those 6 genes.$P<5 \times 10^{-8}$	The risk allele risk allele GA of rs1138594 was higher among patients who received mechanical ventilation than among those who received oxygen supplementation due to COVID-19 diseaseodds ratio, 1.77; 95% confidence interval [CI], 1.48 to 2.11; P = 1.15×10^{-10}	835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain	32558485
ERAP2	rs150892504allele T/C	Risk of death after COVID-19 disease8 fold increased risk	183 people who died from COVID-19 compared with 1324 COVID-19 cases who survived	(Lu et al., 2020)
BRF2	rs138763430allele T/C			

(*continued on next page*)

Table 2 (*continued*)

Official Gene symbol	Genotype and inheritance pattern	Clinical manifestation	Demographics of affected patients	PMID
		Risk of death after COVID-19 disease13 fold increased risk	183 people who died from COVID-19 compared with 1324 COVID-19 cases who survived	(Lu et al., 2020)
TMEM181	rs117665206allele T/C	Risk of death after COVID-19 disease5 fold increased risk	183 people who died from COVID-19 compared with 1324 COVID-19 cases who survived	(Lu et al., 2020)
ALOXE3	rs147149459allele A/ Grs151256885allele T/C	Risk of death after COVID-19 disease8 folds increased risk	183 people who died from COVID-19 compared with 1324 COVID-19 cases who survived	(Lu et al., 2020)
MBL2	Codon 54 variant B	Increased susceptibility to Severe acute respiratory syndrome (SARS) caused by SARS CoV severity of disease[OR], 1.73 [95% confidence interval {CI}, 1.25–2.39]; P=.00086	352 patients and 392 controls in Chinese population	16170752
OAS-1	GA and GG Genotypes in exon 3 of the gene	Increased susceptibility to Severe acute respiratory syndrome (SARS) caused by SARS CoVodds ratio 2.68; 95% CI; 1.17–6.15; p = 0.0178	44 SARS-CoV patients and 103 in Vietnam	15766558
	AG and GG genotypes in the 3'UTR of the OAS1	Protective effect against SARS CoV infectionORs (95% CI) of 0.42 (0.20-0.89) and 0.30 (0.09-0.97), respectively.	66 cases and 64 close contact uninfected controls from China	16824203
ICAM3	homozygousAsp143Gly	Increased susceptibility to Severe acute respiratory syndrome (SARS) caused by by SARS CoV evidenced by high LDH levels on admissionP = .0067; odds ratio [OR], 4.31 [95% confidence interval [CI], 1.37–13.56]	817 patients with (SARS) from Hong Kong	17570115
CD209 / DC-SIGN promoter	336 AA genotype	LDH level in SARS CoV patients was higher in AA genotype than GG/GA alleles60% chance of poor prognosis(mean + SD[3] = 1.14 ± 0.03 vs 1.03 ± 0.04, P = 0.019)	824 SARS patients divided into 2 groups : low and high LDH levels	20359516

[1] Odds ratio.
[2] Intensive Care Unit.
[3] Standard of error.

Table 3
Brief summary of our review. It includes clinical manifestations and associated genes. For full details refer to Table 1 (case-reports) and Table 2 (GWAS studies).

Case-report studies of severe viral infections	
Clinical manifestation	**Genes involved**
Herpes Simplex Encephalitis (HSE) due to Herpes Simplex Virus-1(HSV-1)	*TLR3, UNC-93B, TICAM1,IRF3, DBR1,TBK1,TRAF3, STAT1*
Acute respiratory distress syndrome(ARDS) due to Influenza A virus(IAV) infection	*TLR3,IRF7,GATA2,IRF9,MDA5*
Severe respiratory infections after rhinovirus, respiratory syncytial virus or Epstein Bar virus	*MDA5*
Severe manifestation after vaccination with live attenuated viral vaccines(MMR, Yellow fever vaccine)	*IRF9,IFNAR1,IFNAR2,STAT2*
Acute severe Varicella-Zoster virus(VZV) infection	*POLR3A and POLR3C*
Fulminant viral hepatitis due to Hepatitis A virus (HAV)	*IL18BP*
Severe Human Papilloma virus infection	*NLRP1, GATA2*

GWAS Case-Control studies of SARS-CoV and SARS-CoV2	
Clinical manifestation	**Genes Associated**
Susceptibility to SARS-CoV infection	*CD14, HLA-B, FCGR2A,CCL2,CCL5,MxA,ABO,MBL, OAS-1, ICAM3, DC-SIGN*
Susceptibility to SARS-CoV2 infection	*ALOXE3, TMEM181, BRF2, ERAP2, LC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1, ABO, ApoE*

to explain the latency of Sars-CoV-2 and reemergence in some cases in addition to the DC-SIGN hypothesis described above. Additionally, higher expression of antiviral genes is not always a good prognostic factor as in the example of *MxA* which we should investigate and take into consideration during interpretation of differential gene expression studies of COVID-19.

Some genes such as *TLR3* were proven to have a role in susceptibility to certain viral infections such as HSV and Influenza virus (Case report studies) and a protective role against others such as HIV (GWAS studies) (Mørk et al., 2015; Sironi et al., 2012; Huik et al., 2013). Additionally, *FCGR2A gene* was associated with susceptibility to severe SARS-CoV (GWAS) and protection against severe Dengue hemorrhagic fever (GWAS) at the same time which adds to the complexity of pathogenesis and the need to characterization of the pathogenic effects of different mutations in vitro in animal models and cell cultures (Yuan et al., 2005; Loke et al., 2002).

3.3. Modes of inheritance

Mode of inheritance ranged from autosomal recessive in most cases-including some compound heterozygote occasionally (Ciancanelli et al., 2015; Guo et al., 2011; Zhang et al., 2018) to autosomal dominant in other cases- including dominant-negative mutations (Lim et al., 2014; Zhang et al., 2007; Pérez de Diego et al., 2010; Herman et al., 2012). The absence of manifestation of diseases in some parents or close family members carrying the same mutation of the index patient complicated interpretation of the results by investigators (Sancho-Shimizu et al., 2011; Herman et al., 2012; Ogunjimi et al., 2017). We did not find

sex-linked or mitochondrial inheritance in our review. In some instances, the same gene (*TLR3*) predisposing to the same disease (HSE), had different modes of inheritance according to the type of mutation being autosomal dominant in some children and autosomal recessive in others as demonstrated in Table 1 (Zhang et al., 2007; Lim et al., 2019; Mørk et al., 2015; Guo et al., 2011). Accordingly, studying close family members is essential to understand the penetrance of the suspected mutation and the inheritance pattern which can help us in prevention and prediction of severe COVID-19 disease in susceptible relatives of patients.

3.4. Patient demographics

On one hand, GWAS studies included patients from different age groups. On the other hand, almost all case report studies we reviewed were on children with a single study on old age population (Mørk et al., 2015),and this can be explained by the tendency to attribute unexpected severe manifestations in otherwise healthy young individuals to monogenic factors (single-gene disorders of inborn errors of immunity).

Surprisingly, we did not find any case report studies on healthy young population between the age of 18 and 50. Hence, we invite researchers to widen their inclusion criteria to include this age group in case report studies as most of them are healthy without preexisting conditions to confound the genetic theory of their susceptibility to severe COVID-19.

Countries of origin were diverse(as demonstrated in Tables 1 and 2) with most case report studies from European countries while GWAS studies included Japanese, Chinese, and Vietnamese among other eastern populations and this can be explained by the wide spread of SARS-CoV in China and Eastern countries (Zhong et al., 2003).

3.5. In vitro studies of different cells extracted from patients

Several studies tested different types of Interferon (IFN) responses or cytokine secretions in different cell lines from patients and compared them to healthy controls. Cell lines included fibroblasts, immortalized B-cells, or peripheral blood mononuclear cells (PBMCs). Some studies showed that genetic mutations had a negative effect on interferon or cytokine secretions, which decreased in vitro in all cell lines (Casrouge et al., 2006; Mørk et al., 2015; Ogunjimi et al., 2017; Pérez de Diego et al., 2010). Another study showed that interferon response was normal in certain cell lines (e.g. PBMCs) inferring the redundant role of the gene in those cells and the tendency of manifestation to be localized in a certain organ as encephalitis in the case of Herpes Simplex (Pérez de Diego et al., 2010). Accordingly, characterization of the effect of pathogenic mutations is essential in different cell lines and should not be restricted to PBMCs.

Study of the effect of genetic mutation in vitro constitutes the cornerstone of case report studies as it is the proof of evidence of the causal relationship between this genetic mutation and the clinical manifestation. However, in vitro validation is not always the case in GWAS studies due to small cumulative effects of different variants and the reliance of GWAS on the statistical power for evidence.

3.6. Case report studies as a study design for COVID-19 host genetics studies

Table 1 in our results section includes Case report studies of inborn errors of immunity as extracted from the IUIS list (Tangye et al., 2020). Case report studies are used to investigate the genetic etiology of susceptibility to severe viral infections. Severe COVID-19 risk factors include old age, smoking and preexisting medical conditions such as diabetes mellitus, hypertension and cardiovascular disease (Ellinghaus et al., 2020). Nonetheless, there is increasing number of young healthy population with severe disease up to death (Liu et al., 2020). Unexpected clinical manifestations or complications from infection -e.g. COVID-19- in otherwise healthy individuals are a suggestion of the genetic origin of susceptibility. The presence of manifestation in otherwise healthy individuals is preliminary evidence that the preexisting medical conditions are not present to predispose the patient to severe manifestation. However, it is of paramount importance to consider whether these studies on a single patient or very few patients are sufficient to prove a causal relationship between the genetic mutation and severe manifestations. It has been reported in 2004 that 49 out of 232 disorders on the IUIS list were reported for the first time in single patients. In this paper, Casanova et al. report the importance of single patient case report studies for discovery of rare inborn errors of immunity and set guidelines for design and validation of such studies. In order to report an association based on a single patient, the investigator should confirm that the candidate genotype does not occur in the general population (very low minor allele frequency). Additionally, the variant reported must impair the gene function and lastly the patient specific phenotype should be confirmed in relevant cell culture or model organisms using Knock in or Knock out techniques– facilitated by the novel CRISPR technology among other suitable validation techniques (Casanova et al., 2014). In this model of case report study, we are investigating the direct causal relationship between a single genetic mutation and severe clinical manifestations. Statistical methods are essential to compare genetic variants in those patients with a matched control (e.g. general population or other family members who tested positive without severe manifestation or complication from COVID-19). On evaluation of potential genes suspected for causing clinical manifestation, investigators should start with previously implicated genes in the same phenotypes before investigating potential new genes and hence the importance of our candidate gene lists for viral susceptibility case report studies in humans. Case report studies of COVID-19 represents an opportunity for researchers to identify the largest number of genes associated with severe viral infections in humans and to confirm previous case-report studies of viral susceptibility. It did not escape our notice that case-report studies are essential for us to discover rare genetic variants (low minor allele frequency) which are difficult to discover using GWAS studies which depend on statistical significance (common genetic variants).Accordingly, we believe that case report studies should go hand in hand with GWAS studies.

3.7. GWAS as a study model for COVID-19 host genetics

In Table 2, we reviewed several GWAS case-control studies investigating the association of a specific gene locus with viral susceptibility to SARS-CoV and SARS-CoV-2. The philosophy of GWAS is that common diseases have common genetic variants in the general population that contribute partially to the pathogenesis of the disease in addition to different factors such as environmental factors or preexisting medical condition (Evangelou, 2018).Unlike case report studies, GWAS usually aim to identify different genetic variants with different effect sizes and are not limited to a single gene as in the case of case-report studies of monogenic inborn errors of immunity.

In our case, severe COVID-19 affects a significant number of the population and different factors have been associated with severe manifestation, and it is time for GWAS to discover the role of common and rare variants -with different effect sizes- in the pathogenesis of the disease. Accordingly, we invite GWAS investigators to widen their inclusion criteria to include all patients of different age groups to find common and rare variants associated with severe COVID-19. We predict that GWAS studies are more able to discover gene regulation elements involved in COVID-19 susceptibility more than case report studies because of the tendency to suspect genetic mutation with deleterious effect on proteins and neglect gene regulatory elements in case report studies as we can see on the IUIS list and also because of the wide use of WGS instead of WES in GWAS (Tangye et al., 2020).

Different populations and different ethnic groups in the same population need separate GWAS studies due to different genetic

backgrounds and SNPs frequencies variance (Huang et al., 2015).We also recommend correction for confounders during study design and statistical analysis including acquired causes of immune deficiency, age, preexisting medical conditions and the sequence of the virus itself as a virulence factor (Wu and McGoogan, 2020; Yoon et al., 2011). Statistical significance is the backbone of GWAS studies, and we suggest that meta-analysis of different GWAS should be done on our candidate gene lists to accumulate evidence and report the significance from larger cohorts of patients from different populations with more statistical significance.

3.8. Current status and implications of COVID-19 host genetics studies

As of August 21, 2020, we found 5 studies (one of them is a preprint) associating COVID-19 severity with different genes as in Table 2 (Ellinghaus et al., 2020; Kuo et al., 2020; Lu et al., 2020; Wu et al., 2020; Zhao et al., 2020).

Three studies reported that ABO genes are associated with severity of COVID-19 disease and that blood group A individuals are more susceptible to risk of infection and severe manifestation while blood group O has a protective effect (Wu et al., 2020; Zhao et al., 2020; Ellinghaus et al., 2020). Interestingly, ABO genes were previously reported to be associated with several viral infections. West Nile virus infection is mostly asymptomatic, and manifestation occurs in only 20 % of infected people. Symptomatic patients exhibited increased frequency of Blood group A (Kaidarova et al., 2016). Additionally, ABO genes were associated with Rota virus and SARS-CoV infections (Pérez-Ortín et al., 2019; Cheng et al., 2005). In vitro studies revealed that natural or monoclonal Anti-A antibodies (present naturally in blood group O individuals) provide protective effect against SARS-CoV infection by inhibition of binding of Spike protein of the virus to ACE2 receptors. This finding is in line with our reviewed GWAS studies indicating the protective effect of blood group O (Guillon et al., 2008). The largest COVID-19 GWAS published recently associates the locus 3p21.31 with severe manifestations of COVID-19(Mechanical ventilation). This locus contains six genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1). Notably, SLC6A20 interacts with ACE2 which is the cell surface receptor of SARS-CoV (Vuille-Dit-Bille et al., 2015). CXCR6 regulates the localization of CD8 T memory cells within the lung to combat airway pathogens, while CCR9 acts as a key regulator in the early phases of allergic inflammation of the airway (Wein et al., 2019; López-Pacheco et al., 2016). Noteworthy, CCR1 is a flanking gene that is associated with inflammatory cascade and airway hyperresponsiveness in mice after infection by the respiratory syncytial virus and pneumovirus of mice (Miller et al., 2006; Bonville et al., 2004). Functional antagonism of CCR1 results in improved survival of mice (Bonville et al., 2004). We suggest CCR1 and CCR9 as a potential therapeutic target in COVID-19 patients which needs further investigations. Other associated genes with severe COVID-19 are described in Table 2.

Elucidation of host genetic factors contributing to susceptibility to severe viral infection will help us understand the pathogenesis of severe viral infections in humans and facilitate genetic counseling conversation with index patients and their families (Patch and Middleton, 2018). Possible treatment options for severely affected patients include treating them with the recombinant deficient factor (protein) as in case of Interferon-gamma treatment in deficient patients (Holland, 2001). Vaccination of only genetically predisposed individuals during vaccine clinical trials with different treatments can remove a major confounding factor (inherent genetic susceptibility and resistance) (Glass et al., 2012). Additionally, Vaccination can be reserved to those who are genetically predisposed to severe infections especially during early phases of production.

3.9. Limitations

One case report study reported that 2 mutations in TLR3 (D592 N and M374 T) were not deleterious in vitro) (Lim et al., 2014), while another study reported the redundant effect of the mutations in 2 out of 12 patients' PBMCs (Zhang et al., 2007), and hence adherence to strict guidelines for reporting a single gene to cause in inborn errors of immunity is essential (Casanova et al., 2014).

GWAS studies are used to associate specific variants, e.g., SNPs, with a specific phenotype (e.g., viral host susceptibility) using statistical power. However, GWAS studies do not provide an understanding of disease mechanisms and pathogenesis (van der Sijde et al., 2014). Follow-up investigations need to be conducted in lab to understand the molecular function of genes and variants and their role in causing clinical manifestations.

During our review of genes potentially involved in the COVID-19 response, we excluded genes differentially expressed in patients such as ACE2 and TMPRSS2 genes whose polymorphisms were not proven to be associated with severe COVID-19 (Wen et al., 2020; Sungnak et al., 2020; Bilinska et al., 2020; Hoffmann et al., 2020) because we wanted our study to be restricted to genes with mutations involved directly in association with the severe disease.

We did not include animal models or cell culture studies that were not replicated in human patients due to lower evidence compared to case reports and GWAS studies. We also excluded studies of genes involved in conventional primary immunodeficiency and limited our focus to genes involved mainly in viral susceptibility to create a list of likely candidate genes responsible mainly for viral susceptibility in otherwise healthy individuals. Immune function is affected by acquired factors that play a major role in the immune response to different infections (Brodin et al., 2015). We wanted, however, to focus on the role of the genetic origin of infection susceptibility. Hence, this review of host genetic susceptibility to viral infection is not the only factor to consider in understanding the pathogenesis of severe viral infections in humans including SARS-CoV-2.

4. Conclusion and future perspectives

In conclusion, our systematic review provides a detailed analysis of human genetic studies of susceptibility to severe viral infections in humans including case-report and case-control GWAS. Our gene list represents a list of candidate genes that are likely to aid in explaining severe COVID-19 pathogenesis which are worthy of inclusion in gene panels during early implementation and late interpretation by meta-analysis of different variants from different GWAS.

Those genes are involved in multiple immunological pathways including TLR, C-lectin, and Inflammasome pathways (NLRP1). We propose case report study method for discovering novel monogenic causes of severe viral disease in young healthy individuals without preexisting medical conditions (very low minor allele frequency that would prevent statistical significance in large population) and propose GWAS for the general population to discover common and rare genetic variants with different effects size associated with severe disease. We did not find case-report studies on healthy young population between the age of 18 and 50. Hence, we invite researchers to widen their inclusion criteria to include this age group in case report studies as much of them are healthy without preexisting conditions to confound the genetic theory of susceptibility to severe COVID-19. ACE2 independent method of viral entry into human cells using DC-SIGN (lectin pathways) has been proven in vitro for SARS-CoV-2. We hypothesize that this might explain the recurrence of COVID-19 in some cases as HIV was proven to use the same DC-SIGN binding mechanism to remain latent in Dendritic cells for long periods. Moreover, *MxA* gene promoter polymorphism was also associated with increased expression of the antiviral gene leading to decreased expression of viral proteins at the same time preventing complete immunological clearance of measles virus and predisposition to severe complication to subacute sclerosing panencephalitis. This also might explain latency and reactivation of COVID-19 in some cases. Whole-genome sequencing is essential for studying the polymorphisms

in gene promoters and other regulatory genes such as regulatory RNA as these elements were underrepresented in our findings (only 2 promoters of genes MxA and OAS-1 out of 40 genes). Some genetic mutations did not affect peripheral blood mononuclear cells production of interferon while it affected other cell lines inferring the redundant role of some genes in some cell lines and indicating the importance of studying different cell lines in vitro to characterize the mutation effect.

Up till now, 3 studies elucidated the effect of the ABO system on COVID-19 susceptibility to infection. The largest GWAS of COVID-19 host genetics revealed a significant signal at region 3p21.21 which contains SLC6A20 gene (interacts with ACE2), CXCR6 (regulates localization of CD8 T memory cell within the lung to combat airway pathogens) and CCR9 (a key regulator of early phases of allergic inflammation of the airway). Finally, CCR1 is a flanking gene to this region associated with inflammatory cascade and airway hyperresponsiveness in mice after infection with respiratory syncytial virus and pneumovirus of mice. We suggest CCR1, CCR9, IL-18 and EndoU(SARS-CoV-2 protein) inhibition as a potential therapeutic targets in COVID-19 patients that need further investigations.

CRediT authorship contribution statement

Abdelazeem Elhabyan: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Saja Elyaacoub:** Investigation, Writing - review & editing. **Ehab Sanad:** Investigation, Writing - review & editing. **Abdelwahab Abukhadra:** Investigation, Writing - review & editing. **Asmaa Elhabyan:** Investigation, Writing - review & editing. **Valentin Dinu:** Supervision, Writing - review & editing, Visualizaion, Validation.

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