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About the Author

Ms. Staadegaard is an epidemiologist working at the Netherlands Institute for Health Services Research in the Netherlands. Her main research interests include the epidemiology of infectious diseases, with a current focus on respiratory infections.

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Address for correspondence: Lisa Staadegaard, Nivel, Otterstraat 118, 3513 CR Utrecht, the Netherlands; email: l.staadegaard@nivel.nl

Novel SARS-CoV-2 Variant Derived from Clade 19B, France

Slim Fourati, Jean-Winoc Decousser, Souraya Khouider, Melissa N'Debi, Vanessa Demontant, Elisabeth Trawinski, Aurélie Gourgeon, Christine Gangloff, Grégory Destras, Antonin Bal, Laurence Josset, Alexandre Soulier, Yannick Costa, Guillaume Gricourt, Bruno Lina, Raphaël Lepeule, Jean-Michel Pawlotsky, Christophe Rodriguez

Author affiliations: Institut Mondor de Recherche Biomédicale, Université Paris-Est, Créteil, France; (S. Fourati, S. Khouider, A. Gourgeon, A. Soulier, J.-M. Pawlotsky, C. Rodriguez); Hôpital Henri Mondor, Créteil (J.-W. Decousser, M. N'Debi, V. Demontant, E. Trawinski, G. Gricourt, R. Lepeule, C. Rodriguez); Hôpital Albert Chenevier, Créteil (C. Gangloff); Université de Lyon, France (G. Destras, A. Bal, L. Josset, B. Lina); Grand Hôpital de l'Est Francilien, Jossigny, France (Y. Costa)

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We report a novel severe acute respiratory syndrome coronavirus 2 variant derived from clade 19B (HMN.19B variant or Henri Mondor variant). This variant is characterized by the presence of 18 amino acid substitutions, including 7–8 substitutions in the spike protein and 2 deletions. These variants actively circulate in different regions of France.

During fall 2020, new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, some of which have become variants of concern, progressively replaced the original strains in regions

Table. Amino acid changes within the spike protein sequence of the HMN.19B variant in France compared with the reference sequence of the international GISAID database (GenBank accession no. NC_045512.2), in comparison with other recently identified SARS-CoV-2 variants*

Spike protein sequence				
HMN.19B (Henri Mondor variant)	20I/501Y.V1 (UK variant)	20H/501Y.V2 (South African variant)	P1 20J/501Y.V3 (Brazilian variant)	CAL.20C (Californian variant)
				S13I
L18F		L18F	L18F	
			T20N	
			P26S	
	Del69/70			
		D80A		
			D138Y	
	Del144			
				W152C
			R190S	
		D215G		
		Del 242–244		
		R246I		
		K417N	K417T	
L452R				L452R
		E484K	E484K	
N501Y	N501Y	N501Y	N501Y	
	A570D			
A653V				
H655Y			H655Y	
Q677H†				
	P681H			
		A701V		
	T716I			
D796Y				
	S982A			
			T1027I	
	D1118H			
G1219V				

*Bold type indicates amino acid changes observed in ≥1 of the recent variants.
†Inconstantly detected, recently found in the genome of the "Midwest" variant (Q677H variant) observed in Ohio (USA) in December 2020 and January 2021.

where they were first identified. We report a new SARS-CoV-2 variant of interest derived from clade 19B (tentatively named HMN.19B variant, or Henri Mondor variant) that is actively circulating in France.

On January 21, 2021, a hospital administrative assistant receiving long-term treatment with anti–tumor necrosis factor-α (adalimumab) for ankylosing spondylitis sought treatment for headache, fatigue, and rhinitis suggestive of coronavirus disease (COVID-19). SARS-CoV-2 RNA was confirmed by reverse transcription PCR (RT-PCR). Her partner (household contact), along with 2 nurses from the same occupational health unit sharing their locker room with the administrative assistant, sought treatment for symptoms suggestive of COVID-19 during January 21–23. Virus was confirmed in all instances by RT-PCR.

The slightly immunocompromised administrative assistant and her immunocompetent partner reported a history of symptomatic COVID-19 infection in early October 2020, confirmed in both cases by a positive RT-PCR result. However, both patients tested negative for SARS-CoV-2 protein N antibodies in January 2021. One of the 2 infected nurses had received a first dose of COVID-19 vaccine (Pfizer-BioNTech, https://www.pfizer.com) 11 days before her positive RT-PCR result. All 4 patients experienced mild COVID-19 and did not require hospitalization.

Full-length genome sequencing revealed that the 4 cluster members were infected with a new phylogenetic variant stemming from clade 19B, tentatively called HMN.19B variant or Henri Mondor variant (Appendix, https://wwwnc.cdc.gov/EID/article/27/5/21-0324-App1.pdf). Compared with the reference sequence (GenBank accession no. NC_045512.2) from the international GISAID database (https://www.gisaid.org), variant HMN.19B carries 25 nt substitutions, with a high ratio of nonsynonymous (n = 18) to synonymous (n = 7) mutations, 2 deletions, and a high number of amino acid substitutions within the spike protein (n = 8) at key positions: spike substitutions in comparison with other recently emerged variants (Table) and all mutations (Figure).

In the 4 weeks after its first detection, our laboratory, which maintains 1 of the 4 national SARS CoV-2

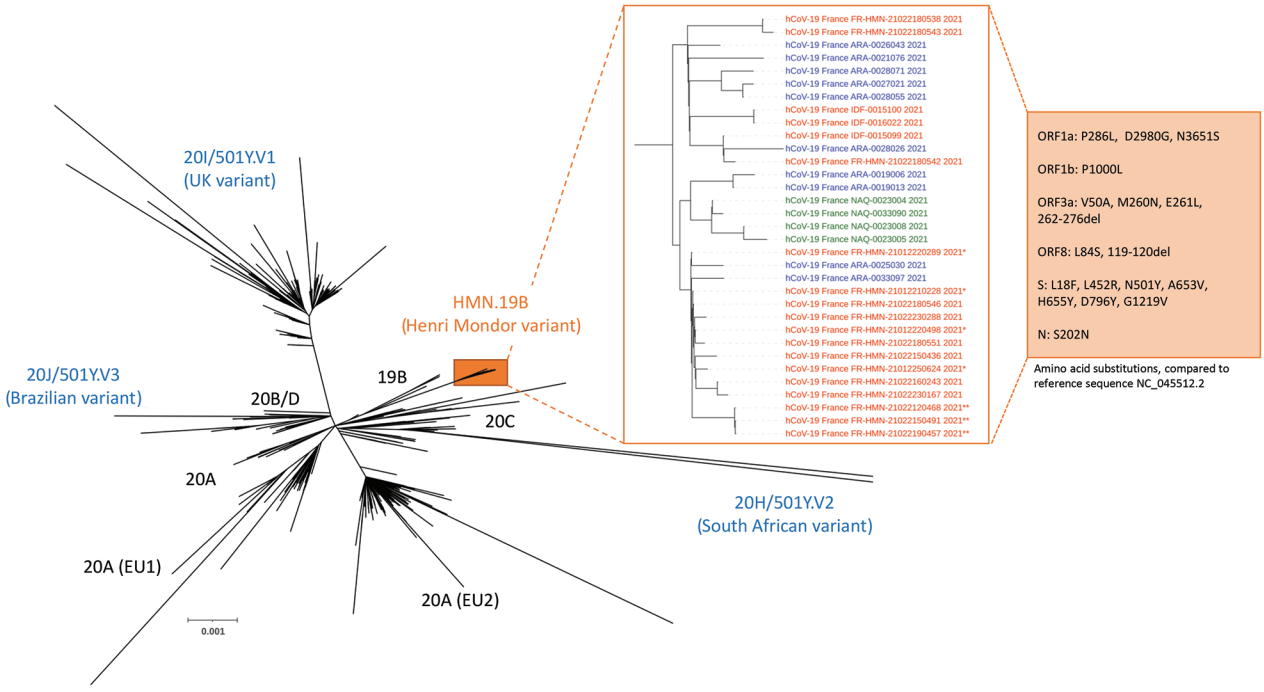

Figure. Phylogenetic tree built with sequences from the 33 patients infected with the new HMN.19B or Henri Mondor variant and from 1,537 SARS-CoV-2–infected patients in France sampled during January 18–February 23, 2021, sequenced in 9 successive series. Phylogeny was performed after full-length genome alignment with Muscle 3.8.31 (maximum-likelihood model general time-reversible plus invariant sites model, 1,000 bootstrap replicates) by means of IQ-Tree 1.3.11.1 and iTOL. The HMN.19B (Henri Mondor) variant cluster is considerably different from all the others, with a 99% bootstrap value. HMN.19B sequences are colored according to the geographic origin of the patients: red, greater Paris area (IDF or HMN); blue, southeast France (ARA); green, southwest France (NAQ). *Original cluster in an occupational health unit; **cluster in the hematology department of our institution. Amino-acid substitutions and deletions detected in all sequences are described in the orange box. ARA, Auvergne-Rhône-Alpes; HMN, Henri Mondor; IDF, Ile-de-France; NAQ, Nouvelle-Aquitaine.

sequencing surveillance platforms in France, found the HMN.19B variant in 12 patients from the greater Paris area (Figure). These patients were 1 prison administration staff member from northeast of the Paris area, tested February 9 during a prison screening campaign; 3 epidemiologically related subjects from a cluster in the hematology department of our hospital (an asymptomatic nursing student tested February 12, his mentor nurse tested February 14, and a hospitalized patient tested February 15); and 8 epidemiologically unrelated cases found positive for SARS-CoV-2 RNA during February 3–23 in different hospitals in the greater Paris area (GISAID identification numbers in Appendix Table).

During the same period, the National Reference Center for Respiratory Viral Infections (Lyon, France) identified 17 additional patients infected with closely related viruses, which carried ≥7 similar substitutions in spike (some were lacking Q677H in spike [Figure]). Three patients were from the greater Paris area, 10 from southeastern France, and 4 from southwestern France (Figure).

We identified a new, previously undescribed variant of SARS-CoV-2 (HMN.19B or Henri Mondor variant) within a cluster of hospital staff in Paris. This variant stems from an older SARS CoV-2 clade, 19B, which emerged in late 2019 but have been rarely detected since early 2020, overtaken by clades 20A, 20B, and 20C, which harbor the D614G substitution believed to improve viral transmission (*1*). The HMN.19B variant is characterized by the presence of 2 deletions and 18 amino acid substitutions over the entire sequence, including 8 substitutions within the spike protein, some of which are common with other recently described variants, a finding in keeping with the ongoing evolutionary convergence of SARS-CoV-2 variants. The acquisition of spike substitutions, including N501Y and L452R, has been suggested to enhance the interaction of spike with the angiotensin-converting enzyme 2 viral receptor. The resulting substantial fitness acquisition could explain the reappearance of clade 19B (*2*; Yang et al., unpub. data, https://doi.org/10.1101/2020.12.29.42469).

New variants with several spike mutations (20I/501Y.V1) have been associated with increased transmissibility. Whether HMN.19B will be less susceptible to protection by natural, therapeutic, or vaccine-induced immune responses remains to be determined. Several of its spike substitutions (N501Y, L452R, and H655Y) have been shown to require higher levels of neutralizing antibodies to be controlled, both in vitro and in vivo (*3*,*4*; Liu et al., unpub. data, https://doi.org/10.1101/2020.11.06.372037).

In conclusion, we report a new SARS-CoV-2 variant circulating in France. Our results emphasize the need for careful molecular surveillance of SARS-CoV-2 evolution to track emergence of any new variant of interest with potential epidemiologic or pathophysiologic consequences.

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About the Author

Dr. Fourati is a researcher at University of East Paris, Créteil, France. He is also a clinical virologist in the Department of Microbiology, Henri Mondor Hospital, Créteil, France. His primary research interests include viral evolution and adaptation, and viral hepatitis and respiratory viruses including SARS CoV-2.

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Address for correspondence: Slim Fourati, Virology Department, Henri Mondor Hospital, 51 Av. du Maréchal de Lattre de Tassigny, 94010 Créteil, France; email: slim.fourati@aphp.fr

Undocumented Migrants Reintroducing COVID-19, Yunnan Province, China

Meiling Zhang,[1] Jienan Zhou,[1] Senquan Jia, Xiaonan Zhao, Yaoyao Chen, Yanhong Sun, Zhaosheng Liu, Xiaofang Zhou, Duo Li, Chunrui Luo, Yong Zhang, Violet Magoma Onsongo, Yong Shao, Xiaoqing Fu

Author affiliations: Yunnan Provincial Center for Disease Control and Prevention, Kunming, China (M.L. Zhang, J.N. Zhou, S.Q. Jia, X.N. Zhao, Y.Y. Chen, Y.H. Sun, Z.S. Liu, X.F. Zhou, D. Li, C.R. Luo, Y. Zhang, X.Q. Fu); Kunming Institute of Zoology, Kunming (V.M. Onsongo, Y. Shao)

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To limit the spread of severe acute respiratory syndrome coronavirus 2, the government of China has been monitoring infected travelers and minimizing cold-chain contamination. However, other factors might contribute to recurring outbreaks. We analyze the role of undocumented migrants as potential transmitters of severe acute respiratory syndrome coronavirus 2 in China.

China's efforts to suppress coronavirus disease (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rely on rigorous quarantine measures. These measures contributed to a decline in COVID-19 cases; no new locally acquired cases were reported in China on March 18, 2020 (http://www.nhc.gov.cn/xcs/yqtb/list_gzbd_10.shtml). As a result, the focus of epidemic control and prevention work has shifted from local to imported cases of COVID-19. Although viral spread has been contained by mandates minimizing travel and cold-chain contamination (*1*), recurring COVID-19 outbreaks might be caused by other factors and pathways. On September 14, 2020, the discovery of 2 SARS-CoV-2–infected undocumented migrants from Myanmar prompted large-scale testing of >280,000 persons in Ruili, Yunnan Province, China (Figure).

On March 31, 2020, the Yunnan Provincial Leading Group for COVID-19 Epidemic Response published Notice No. 15 (http://www.yn.gov.cn/ztgg/yqfk/zcfk/202004/t20200401_201604.html), which outlined strict measures to prevent COVID-19 importation from land and water ports. This notice discouraged citizens of adjacent countries from entering Yunnan Province; if entry was required, then those

[1]These authors contributed equally to this article.

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Novel SARS-CoV-2 Variant Derived from Clade 19B, France

Appendix

Methods

The full-length SARS-CoV-2 genomes from the 4 infected patients were sequenced by next-generation sequencing. Viral RNA was extracted from nasopharyngeal swabs with a NucliSENS easyMAG kit on an EMAG device (bioMérieux, https://www.biomerieux.com). Sequencing was performed with the COVIDSeq Test (Illumina, https://www.illumina.com), which uses 98-target multiplex amplifications along the full SARS-CoV-2 genome (Bhoyar et al. unpub. data, https://doi.org/10.1101/2020.08.10.242677). The libraries were sequenced with NextSeq 500/550 High Output Kit 2.5 on a NextSeq 500 device (Illumina). The sequences were demultiplexed and assembled as full-length genomes with the DRAGEN COVIDSeq Test Pipeline on a DRAGEN server (Illumina). Lineages and clades were interpreted with Pangolin and NextClade (*1*). Phylogeny was performed after full-length genome alignment with Muscle 3.8.31 (maximum-likelihood model general time-reversible plus invariant sites; 1,000 bootstrap replicates) by using IQ-Tree version 1.3.11.1 and iTOL (*2*,*3*).

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Appendix Table. Amino acid substitutions observed in the spike protein of the 19B.HMN variants*

	Amino acid position in spike protein													
Lab identification number submitted to GISAID	18	49	70	346	452	501	653	655	677	796	798	1113	1191	1219
hCoV-19/France/FR-HMN-21022180538/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y	G798D			G1219V
hCoV-19/France/FR-HMN-21022180543/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y	G798D			G1219V
hCoV-19/France/ARA-0026043/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/ARA-0021076/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/ARA-0028071/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/ARA-0027021/2021	L18F	H49Y			L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/ARA-0028055/2021	L18F	H49Y			L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/IDF-0015100/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/IDF-0016022/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/IDF-0015099/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/ARA-0028026/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/FR-HMN-21022180542/2021	L18F				L452R	N501Y	A653V	H655Y		D796Y				G1219V
hCoV-19/France/ARA-0019006/2021	L18F			R346I	L452R	N501Y	A653V	H655Y	Q677H	D796Y			K1191N	G1219V
hCoV-19/France/ARA-0019013/2021	L18F			R346I	L452R	N501Y	A653V	H655Y	Q677H	D796Y			K1191N	G1219V
hCoV-19/France/NAQ-0023004/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y			K1191N	G1219V
hCoV-19/France/NAQ-0033090/2021	L18F		V70F		L452R	N501Y	A653V	H655Y	Q677H	D796Y			K1191N	G1219V
hCoV-19/France/NAQ-0023008/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y			K1191N	G1219V
hCoV-19/France/NAQ-0023005/2021					L452R	N501Y	A653V	H655Y	Q677H	D796Y			K1191N	G1219V
hCoV-19/France/FR-HMN-21012220289/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/ARA-0025030/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/ARA-0033097/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y		Q1113K		G1219V
hCoV-19/France/FR-HMN-21012210228/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022180546/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022230288/2021					L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21012220498/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022180551/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022150436/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21012250624/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022160243/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022230167/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022120468/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022150491/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V
hCoV-19/France/FR-HMN-21022190457/2021	L18F				L452R	N501Y	A653V	H655Y	Q677H	D796Y				G1219V

*HMN.19B spike sequences are colored based on geographic region of origin of patients: greater Paris area (IDF or HMN) in red, southeast France (ARA) in blue, and southwest France (NAQ) in green.