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Philippe Perot, Danielle Seilhean, Franck Bielle, Delphine Chrétien, Thomas Bigot, Charles Duyckaerts, Marc Eloit

► **To cite this version:**

Philippe Perot, Danielle Seilhean, Franck Bielle, Delphine Chrétien, Thomas Bigot, et al.. Role of pathogens in life-threatening encephalitides analyzed by untargeted transcriptomic analysis of pathological brain tissues. 3rd International Conference on Clinical Metagenomics, Oct 2018, Genève, Switzerland. . pasteur-01887124

**HAL Id: pasteur-01887124**

**<https://pasteur.hal.science/pasteur-01887124v1>**

Submitted on 3 Oct 2018

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# Role of pathogens in life-threatening encephalitis analyzed by untargeted transcriptomic analysis of pathological brain tissues

Pérot, Philippe.\*<sup>2</sup> ; Seilhean, Danielle.\*<sup>1</sup> ; Bielle, Franck.<sup>1</sup> ; Chrétien, Delphine.<sup>2</sup> ; Bigot, Thomas.<sup>2,3</sup> Duyckaerts, Charles.<sup>1</sup> ; Eloit, Marc.<sup>2</sup>

<sup>1</sup> Département de Neuropathologie Raymond Escourolle, Groupe Hospitalier Universitaire Pitié-Salpêtrière, APHP, UPMC-Sorbonne Universités, Paris, France

<sup>2</sup> Pathogen Discovery Laboratory, Biology of Infection Unit, Institut Pasteur, Paris, France

<sup>3</sup> Centre de bioinformatique, biostatistique et biologie intégrative (C3BI), Institut Pasteur, Paris, France

\* Contributed equally

## BACKGROUND

About half of the encephalitis remains of undetermined etiology. Blood- and CSF-based assays are used routinely but their diagnostic efficiency remains poor. Inflammatory lesions in biopsy/autopsy samples are often a challenge for pathologists. Specificity of positive results is critical for patient management, and negative predictive value is key when anti-inflammatory/immunosuppressive treatments are considered.

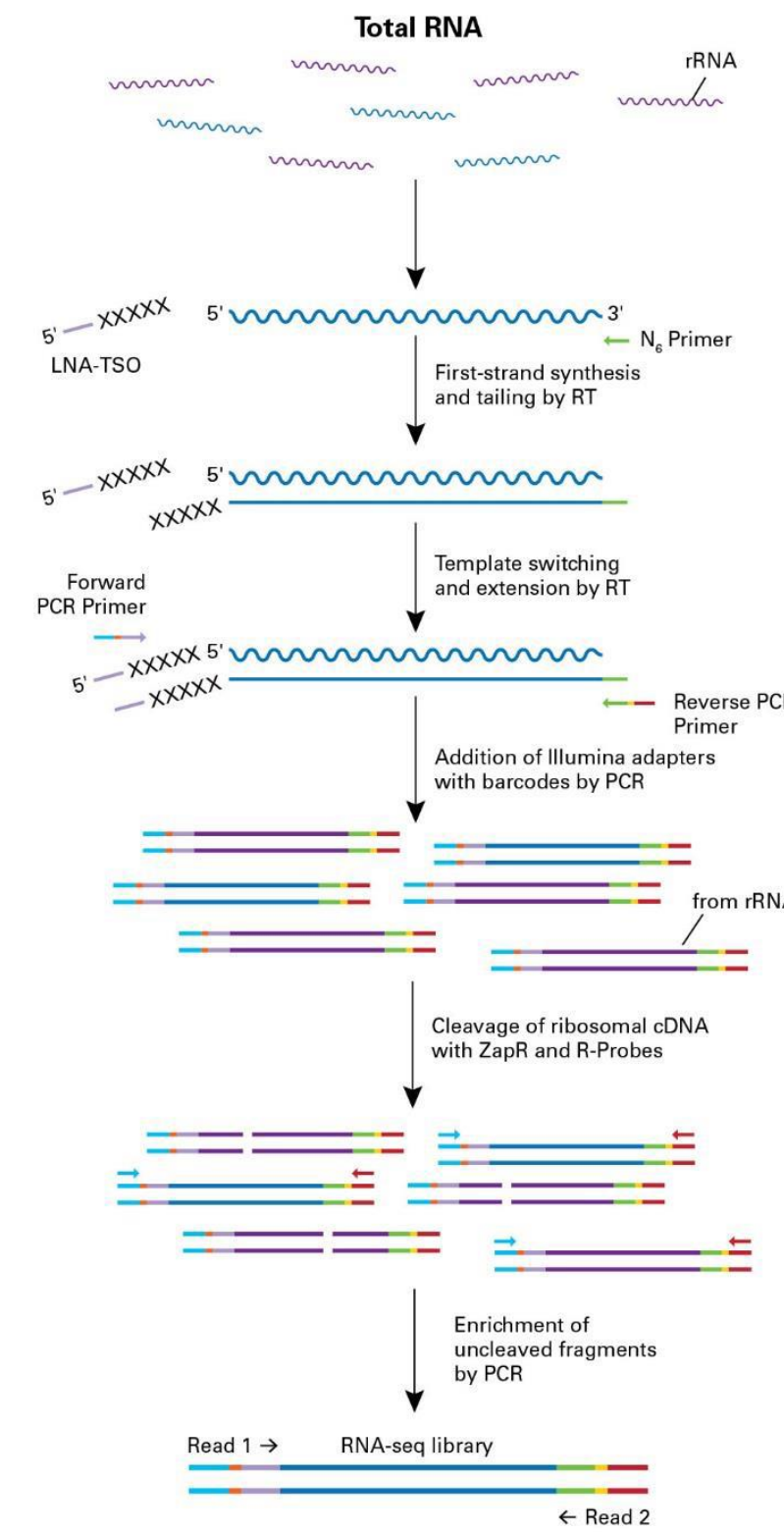
## METHODS

We present the methodology and results of examples of RNA-NGS of brain biopsies in actionable diagnostic, together with interim results of a retrospective study where RNA-NGS is conducted on brain biopsy or necropsy samples of very severe or lethal encephalitis of unknown origin.

### 1. Inclusion criteria

- Acute encephalitis
- Inflammatory lesions
- Not a Creutzfeldt-Jakob disease
- A possible context of immunosuppression (transplant recipient, PID...)
- Unknown etiology (neurodegenerative diseases were not included)

### 2. Sample prep



### 3. Viral proteic database



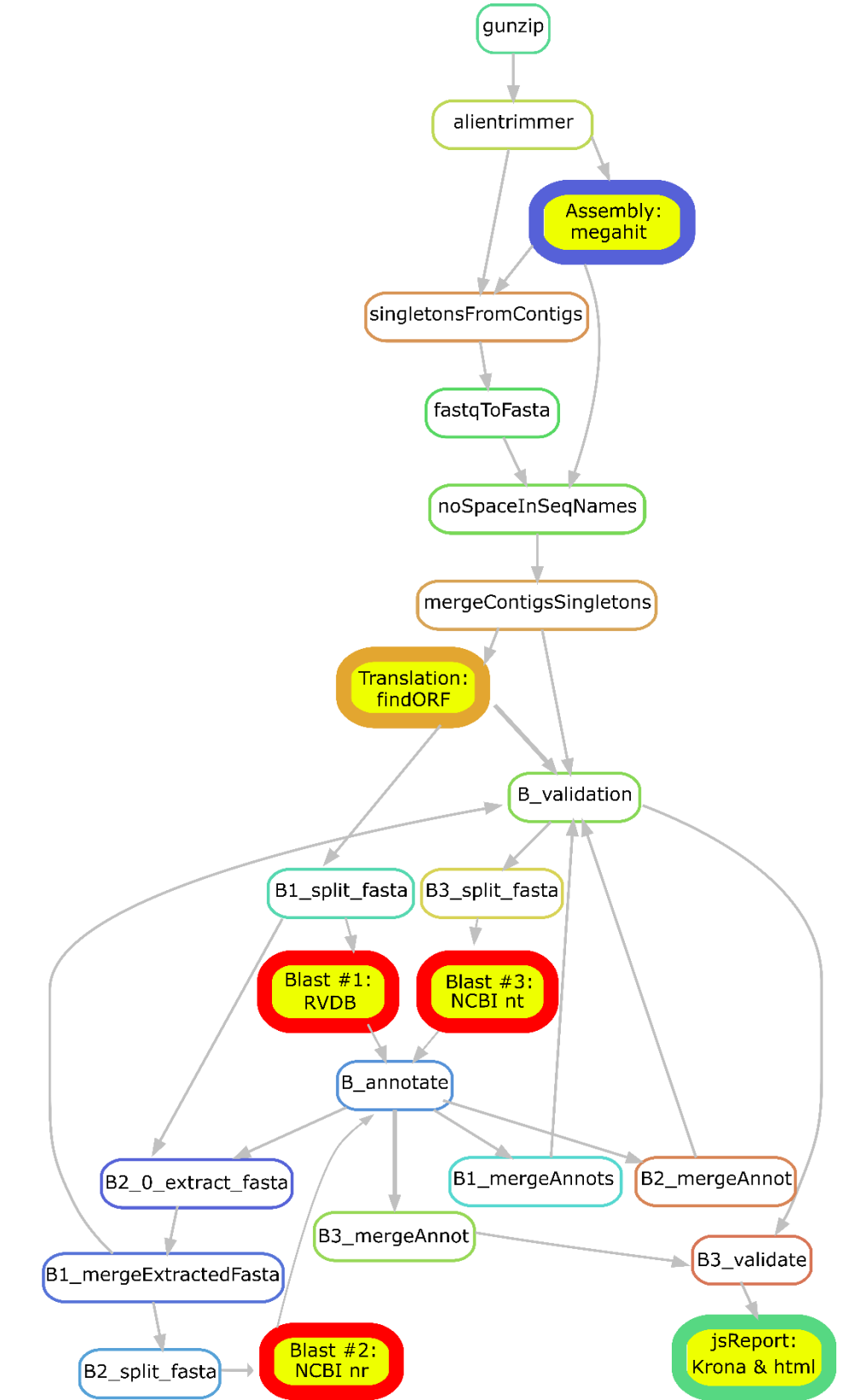
#### RVDB database, proteic version

##### Description

Reference Viral Databases (RVDB-prot and RVDB-prot-HMM) were developed by Thomas Bigot in Marc Eloit's Pathogen Discovery group in collaboration with Center of Bioinformatics, Biostatistics and Integrative Biology (C3BI) at Institut Pasteur, for enhancing virus detection using next-generation sequencing (NGS) technologies. They are based on the reference Viral DataBase, courtesy of Arifa Khan's group at CBER. They are updated after each new release of the nucleotide database. The version number of the proteic databases follows the one of the original nucleic database.

<https://rvdb-prot.pasteur.fr/>

### 4. BioIT pipeline



## RESULTS

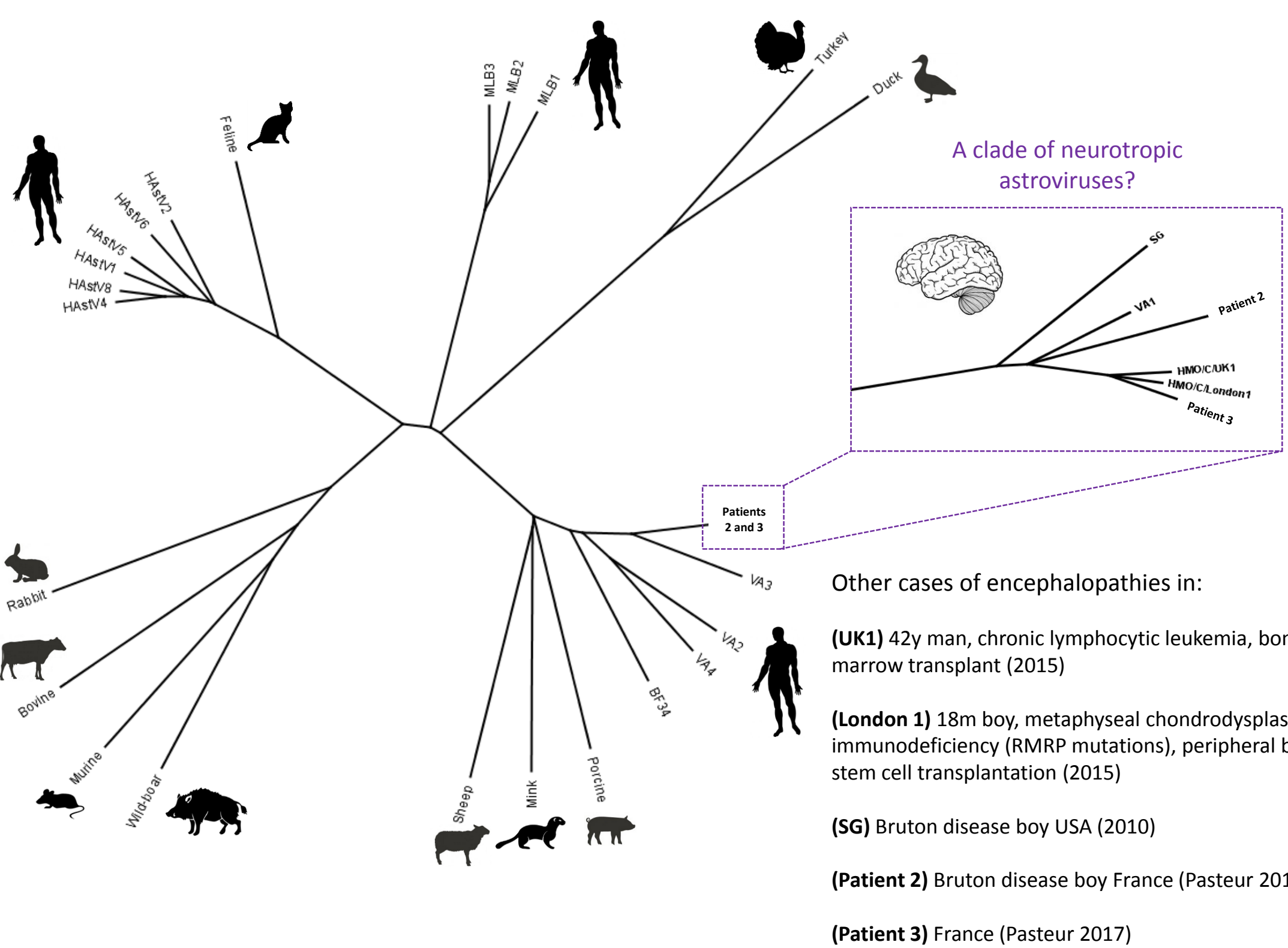
Three patients with actionable diagnostic with direct impact on the treatment are shown. Among 16 patients with currently available results in the retrospective cohort, an etiology was identified in 4, including one new viral species or distant strains and three known viruses in an atypical presentation.

Case #	Symptoms	Antecedent/Context	Raw reads # (10%)	Hit	Confirmation			Treatment
					RT-PCR	IHC	ISH	
<b>Actionable diagnostic</b> (biopsies) 3/5 positive (60%)	1	Encephalitis	40,7	Dengue virus 2 (4 reads)	✓			Immunoglobulins
	2	Encephalitis	75,6	Astrovirus VA1/HMO-C (14 contigs)	✓	✗	✗	Ribavirin + PEG IFN
	3	Myeloencephalitis	120,8	Astrovirus VA1/HMO-C (16 reads)	✓	✗	✗	Ribavirin + PEG IFN
	4	Encephalitis	60,5	No significant hit				
	5	Encephalitis	72,2	No significant hit				
<b>Retrospective cohort</b> (post-mortem tissues) 4/16 positive (25%)	6	Encephalitis	26,7	Dengue virus 1 (full genome)	✓	✗	✗	
	7	Acute necrotic encephalitis	19,0	Rabies lyssavirus (full genome)	✓	✓	✓	
	8	Encephalitis	28,3	Not disclosed	✓	✓	✓	
	9	Encephalitis	116,8	Orthobunyavirus (>100 reads)	✓	✗	✗	
	10	Progressive encephalitis	61,8	No significant hit				
	11	Diffuse vascular lesions	76,4	No significant hit				
	12	Vasculitis	114,5	No significant hit				
	13	Encephalitis	88,7	No significant hit				
	14	Encephalitis	90,0	No significant hit				
	15	Diffuse pan-encephalitis	117,9	No significant hit				
	16	Encephalitis	101,7	No significant hit				
	17	Encephalitis	78,4	No significant hit				
	18	Encephalitis	97,2	No significant hit				
	19	Meningo-encephalitis	44,6	No significant hit				
	20	Encephalitis	58,4	No significant hit				
	21	Encephalitis	32,2	No significant hit				

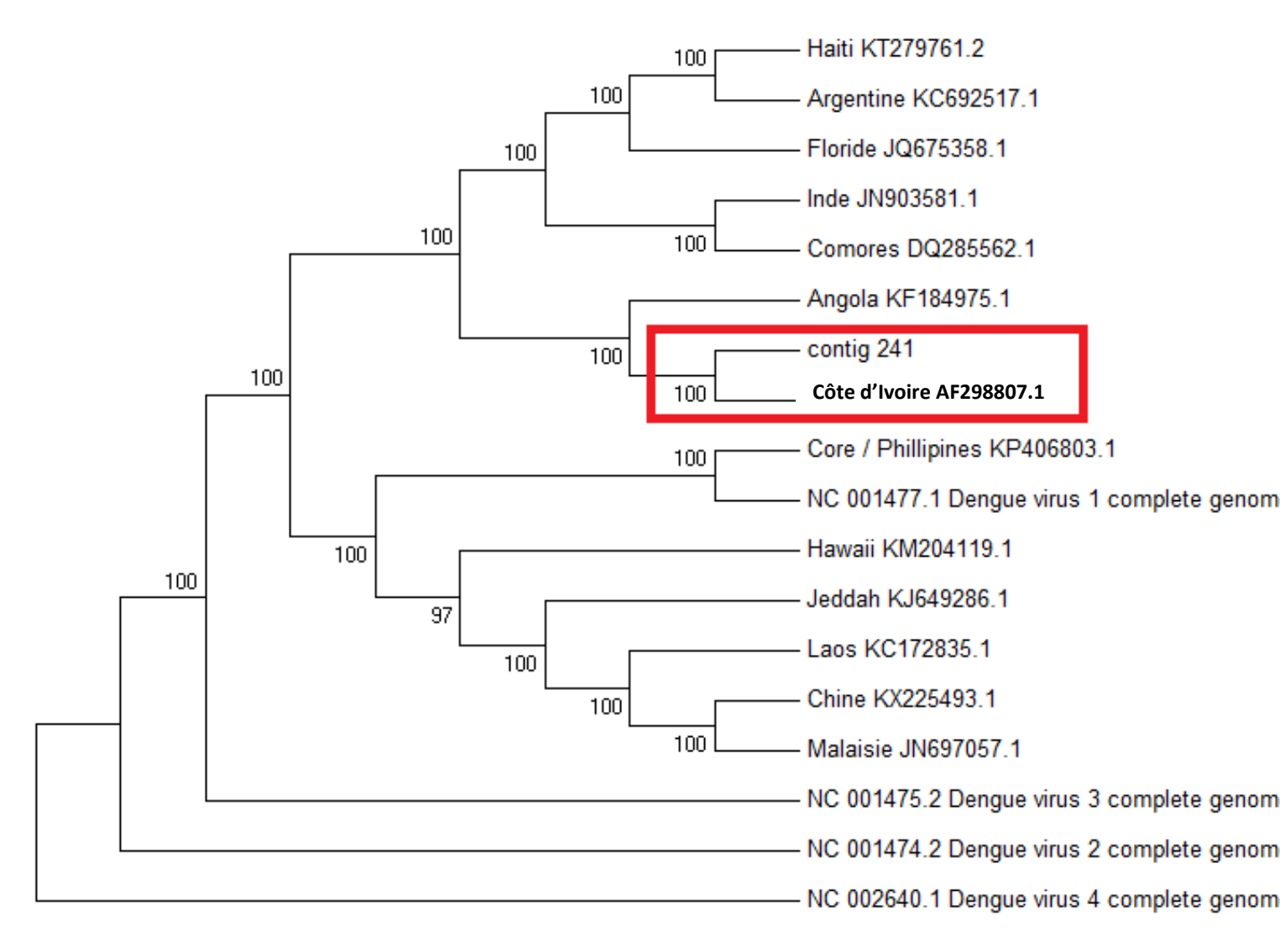
## AT A GLANCE

- 4 known viruses found in atypic presentations (2x dengue virus, rabies virus, 1 non-disclosed virus)
- 2 distant viruses with a neurotropic potential, newly described in immunosuppression cases (astroviruses)
- 1 new orthobunyavirus to be characterized

### ASTROVIRUSES (patients 2 & 3)

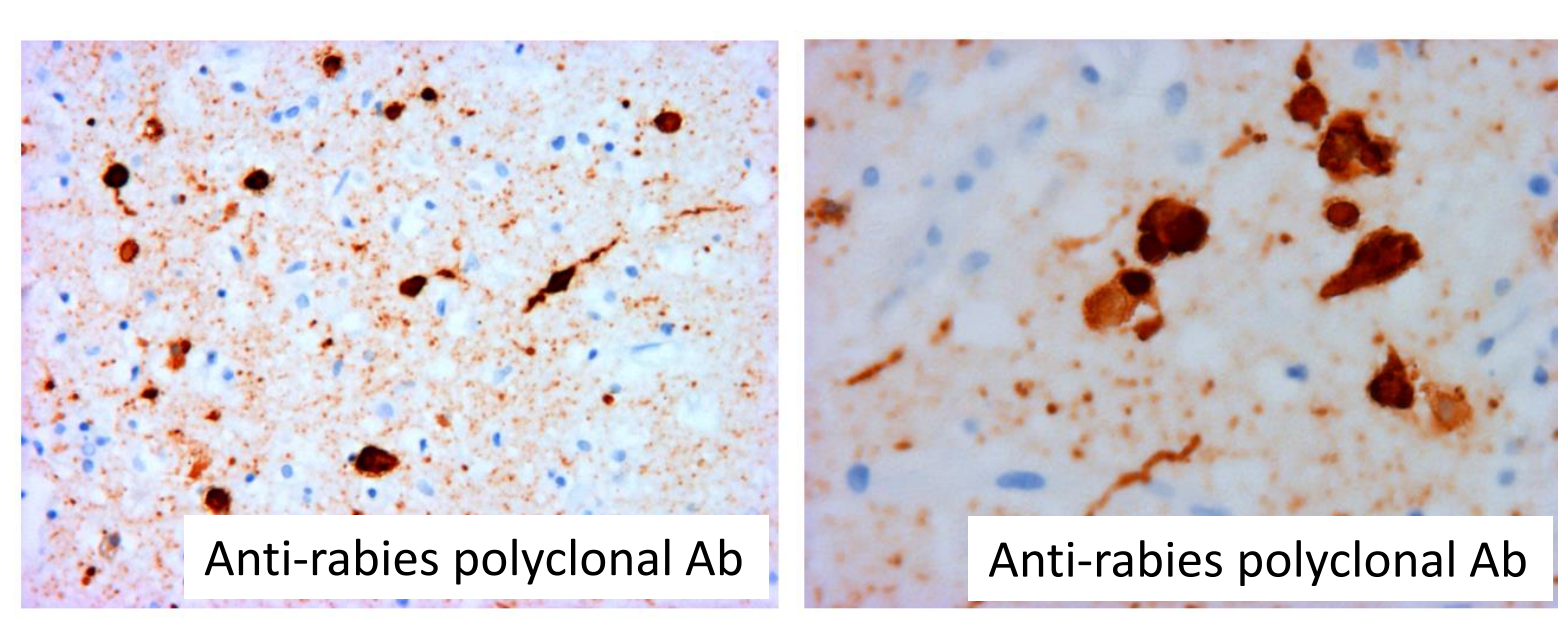
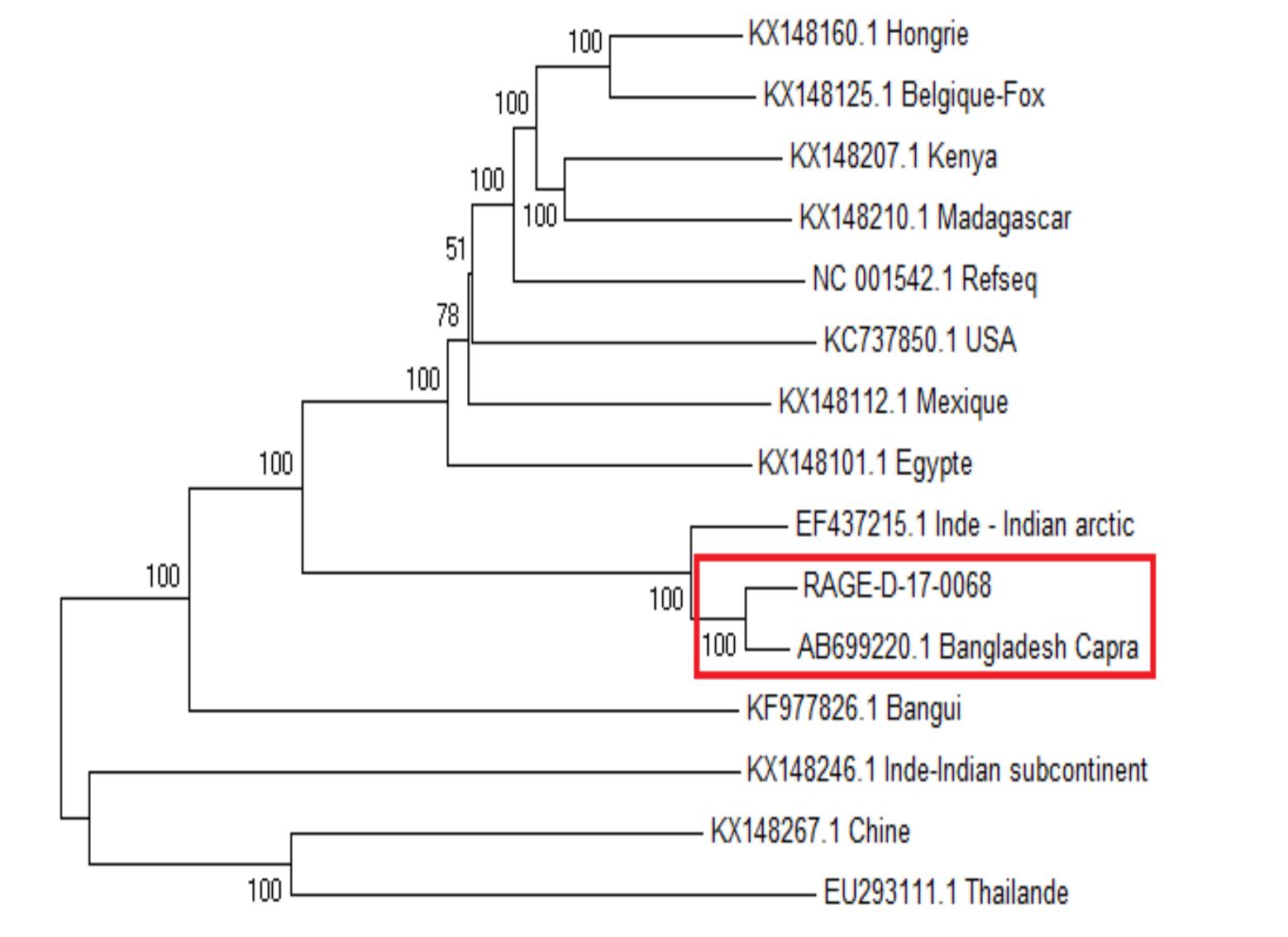


### DENGUE 1 (patient 6)



Strain « Côte d'Ivoire » (a few hundred km from Togo)

### RABIES (patient 7)



## CONCLUSION

Working in collaboration with neuropathologists allows identification of encephalitis cases on pathological criteria and selection of relevant brain sections, in which RNA-NGS allows broad range testing including unknown pathogens. Our final goal is to elaborate the place and the management of brain biopsy in the diagnostic process of severe encephalitis, a methodology that could be later tested in a clinical trial.