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

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BACKGROUND

About half of the encephalitides 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

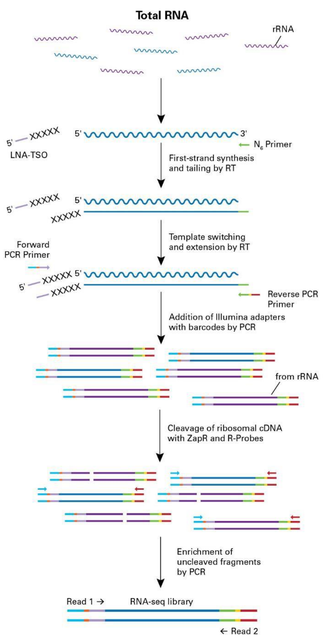
We present the methodology and results of examples of RNA-NGS of brain biopsies in actionable diagnostic, together with interim results of a retrospective study where RNA-NGS is conducted on brain biopsy or necropsy samples of very severe or lethal encephalitis of unknown origin.

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

Institut Pasteur

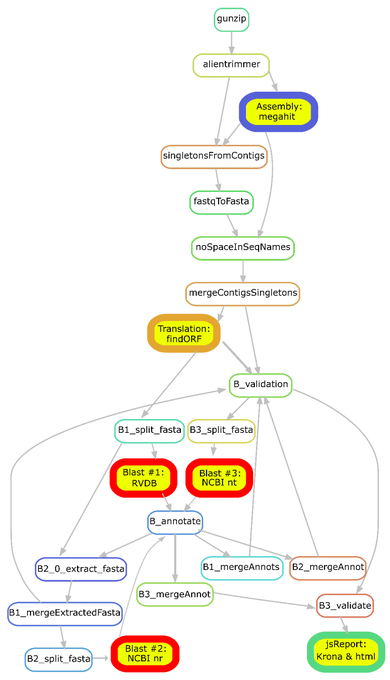
RVDB database, proteic version

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 nucleotidic 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

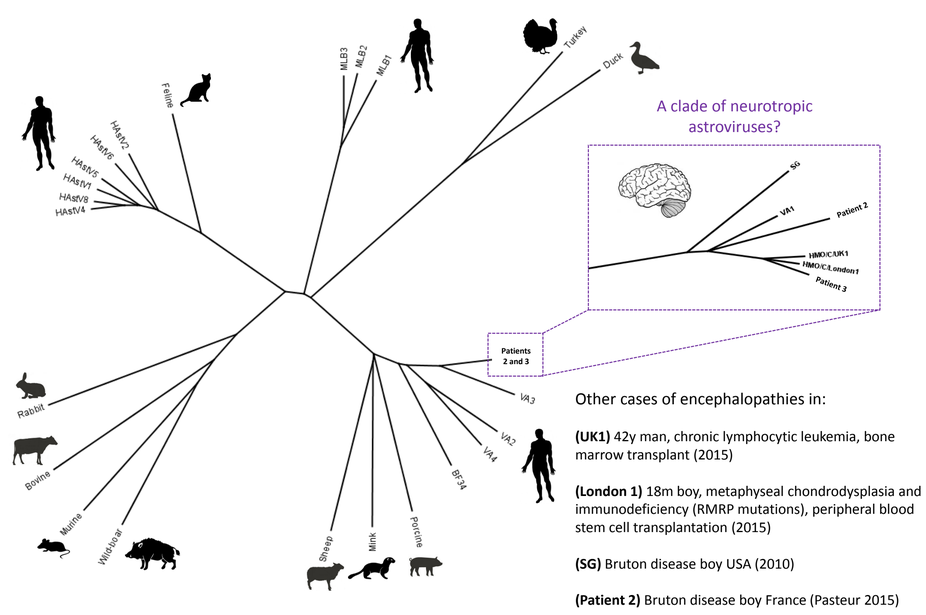
Three patients with actionable diagnostic with direct impact on the treatment are shown. Among 16 patients with currently available results in the retrospective cohort, an etiology was identified in 4, including one new viral species or distant strains and three known viruses in an atypical presentation.

	Case #	Symptoms	Antecedent/Context	Raw reads # (10^6)	Hit	Confirmation RT-PCR	IHC	ISH	Treatment
Actionable diagnostic	1	Encephalitis	Bruton's agammaglobulinemia	40,7	Dengue virus 2 (4 reads)	✓			Immunoglobulins
(biopsies)	2	Encephalitis	Bruton's agammaglobulinemia	75,6	Astrovirus VA1/HMO-C (14 contigs)	✓		◌	Ribavirin + PEG IFN
3/5 positive (60%)	3	Myeloencephalitis	B cell lymphoma	120,8	Astrovirus VA1/HMO-C (16 reads)	✓		◌	Ribavirin + PEG IFN
	4	Encephalitis	Leukemia ; Allograft	60,5	No significant hit				
	5	Encephalitis	Malaria	72,2	No significant hit				
Retrospective cohort	6	Encephalitis	HIV+ ; Patient from Togo	26,7	Dengue virus 1 (full genome)	✓	◌		
(post-mortem tissues)	7	Acute necrotic encephalitis	Dog bite in Bangladesh 16 months before death	19,0	Rabies lyssavirus (full genome)	✓	✓		
4/16 positive (25%)	8	Encephalitis		28,3	Not disclosed	✓	✓		
	9	Encephalitis		116,8	Orthobunyavirus (>100 reads)	✓	◌	◌	
	10	Progressive encephalitis	Langerhans cell histiocytosis	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)



Other cases of encephalopathies in:

(UK1) 42y man, chronic lymphocytic leukemia, bone marrow transplant (2015)

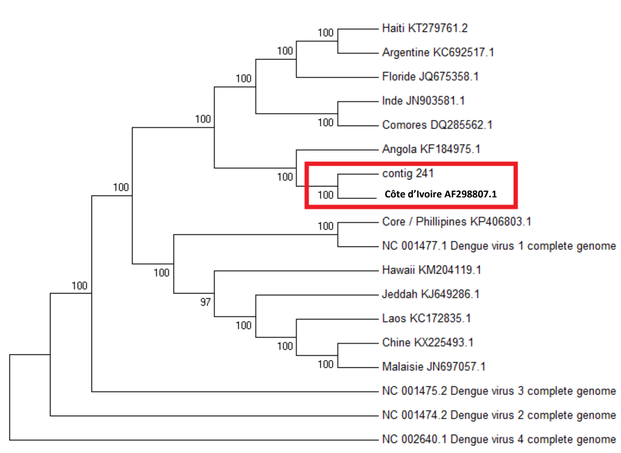
(London 1) 18m boy, metaphyseal chondrodysplasia and immunodeficiency (RMRP mutations), peripheral blood stem cell transplantation (2015)

(SG) Bruton disease boy USA (2010)

(Patient 2) Bruton disease boy France (Pasteur 2015)

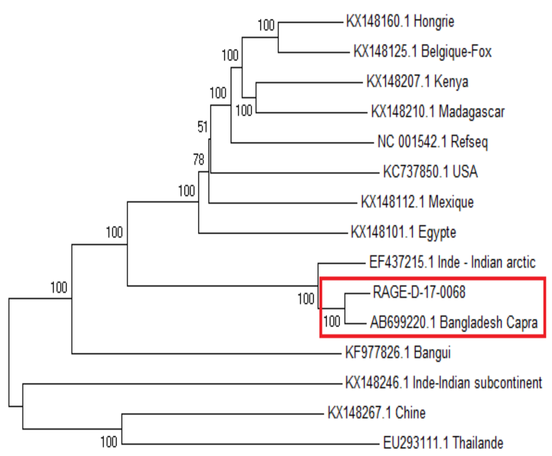
(Patient 3) France (Pasteur 2017)

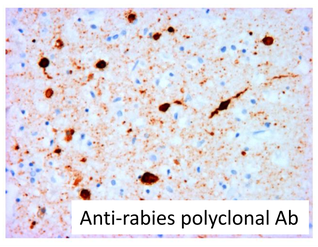
DENGUE 1 (patient 6)

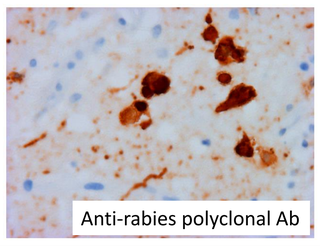


Strain « Côte d'Ivoire »
(a few hundred km from Togo)

RABIES (patient 7)




Anti-rabies polyclonal Ab


Anti-rabies polyclonal Ab

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 encephalitides, a methodology that could be later tested in a clinical trial.

Institut Pasteur · UPMC Sorbonne Universités · Assistance Publique Hôpitaux de Paris · Hôpitaux Universitaires Pitié Salpêtrière Charles Foix · Third International Conference on Clinical Metagenomics