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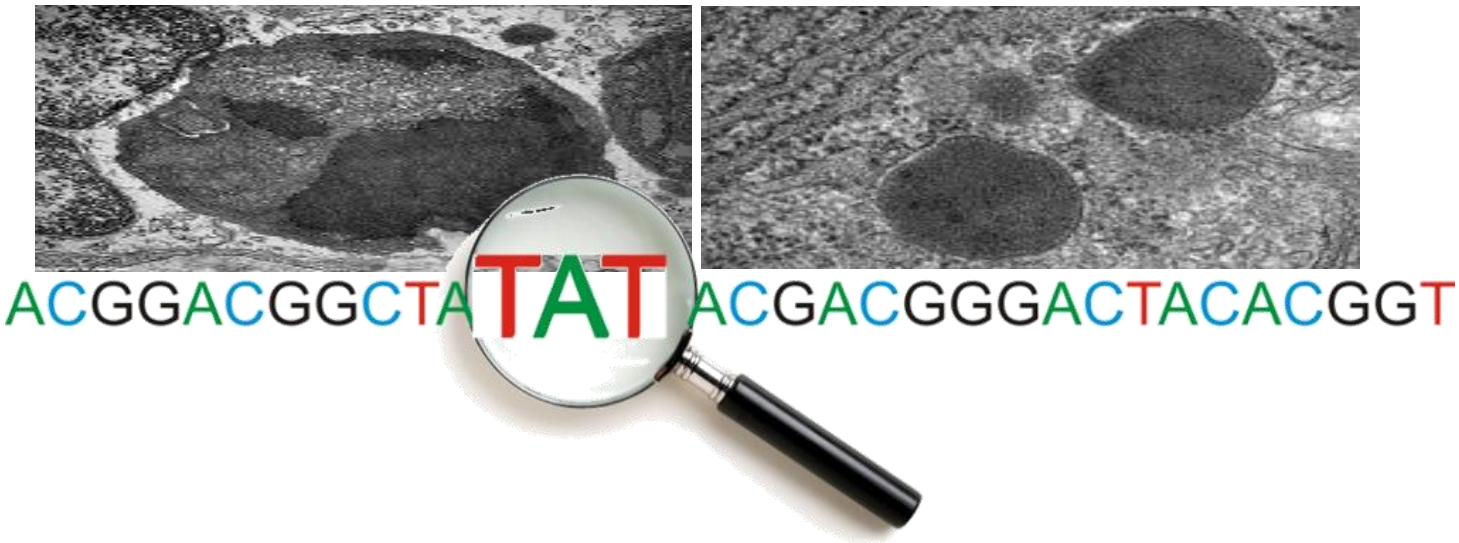
NGS AND LYSOSOMAL DYSFUNCTION
NOVEL MUTATIONS ASSOCIATED WITH NEURODEGENERATIVE DISORDERS



Marisa Encarnação, Francisca Coutinho, Liliana Matos, Lisbeth Silva, Diogo Ribeiro, Célia Nogueira, Laura Vilarinho, and Sandra Alves

Research and Development Unit - Porto
Human Genetics Department

LSD diagnosis can be difficult due to considerable clinical overlap and variability

Multiple samples and test are often required before a diagnosis is reached (is time consuming)

High-throughput sequencing is cost and time effective

Custom-targeted panel for LSD genes

Identification of disease-causing mutations in LSD

Unidade de Rastreio Neonatal Porto

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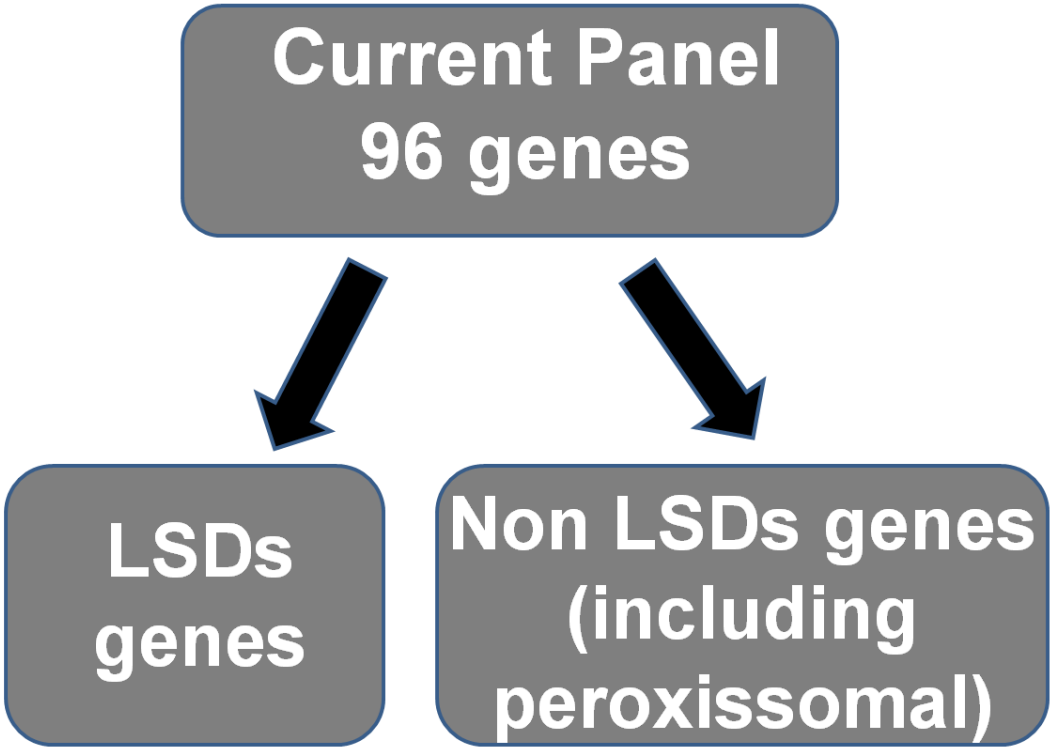
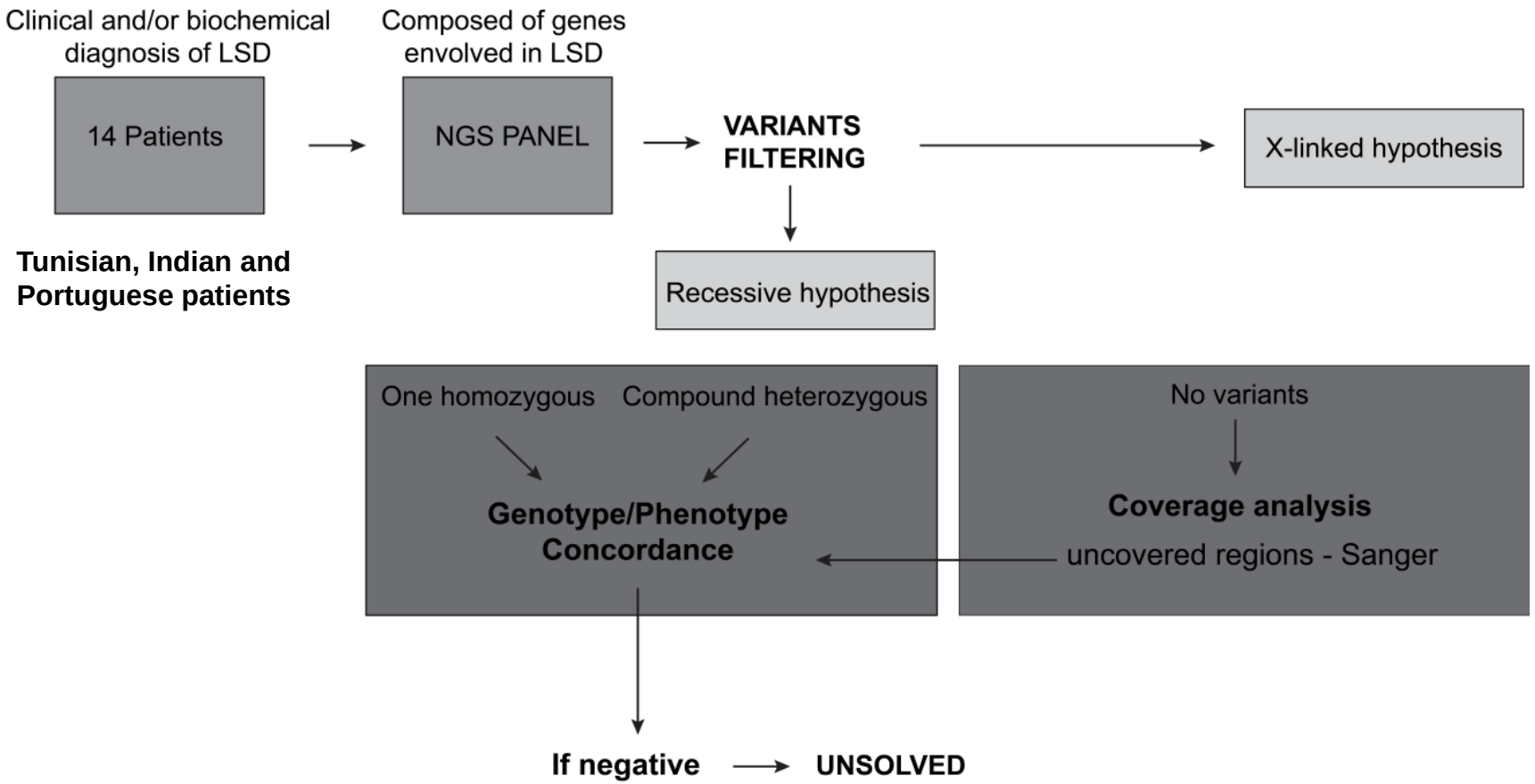
Our NGS Panel



Our NGS Workflow

Sample Preparation and Sequencing (Illumina MiSeq) (2-3 days)

Analysis Software (1-2 days)



RESULTS-TRAINING SET

Total number of studied patients → **18**

Number of diagnosed patients → **7**

	Gene	Mutation	Impact on Protein	Molecular Diagnosis
Novel Mutations	***MFSD8***	p.G455R/G455P	YES	Neuronal Ceroid Lipofuscinosis 7
	NAGLU	p.D312N/D312N	YES	Mucopolysacchari-dosis type IIIB
	GM2A	p.G104Gfs*14/G 104Gfs*14	YES	GM2 Gangliosidosis AB variant*
	GALC	p.Y205X/Y205X	YES	Krabbe
	NPC1	p. V505G/V562V	*Unclear*	
Described	***NPC1***	p.A3T/N961S	YES	Niemann-Pick type C
	MAN2B1	p.802Qfs*128/ 802Qfs*128	YES	Alpha-mannosidosis

Patients with Neurodegenerative LSD

Mutation p.G455R in *MFSD8*

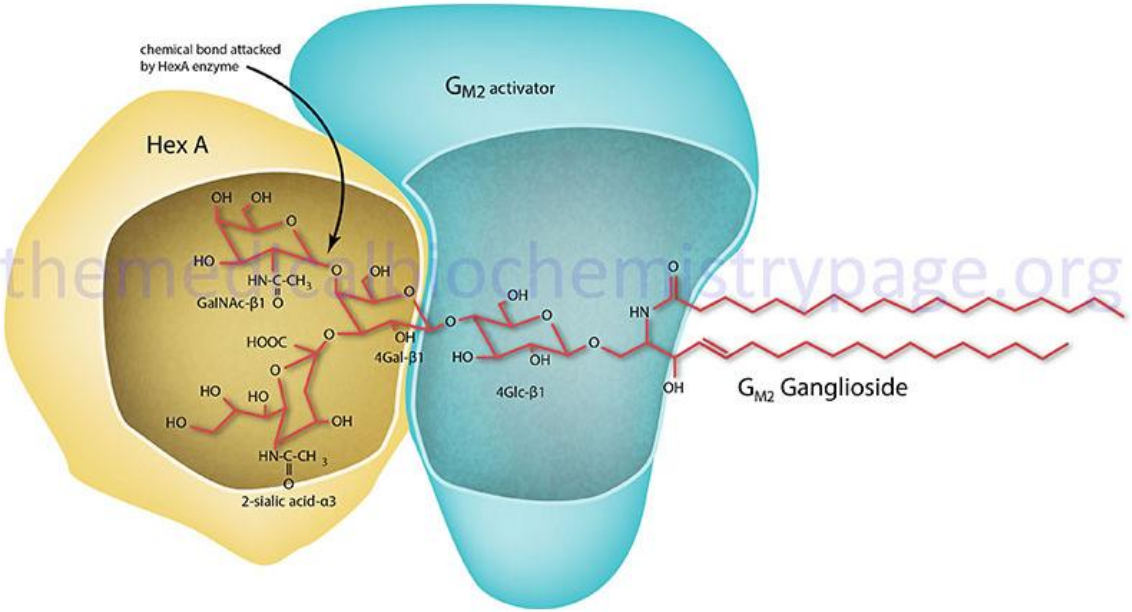
CLN7 protein (unclear function)
Lysosome membrane mainly

CLN7- Late infantile form of NCL

There are at least 14 different genes associated with NCL

Mutation p.G104Gfs14 in *GM2A*

GM2 activator protein (necessary for substrate solubilisation)
Lysosome lumen



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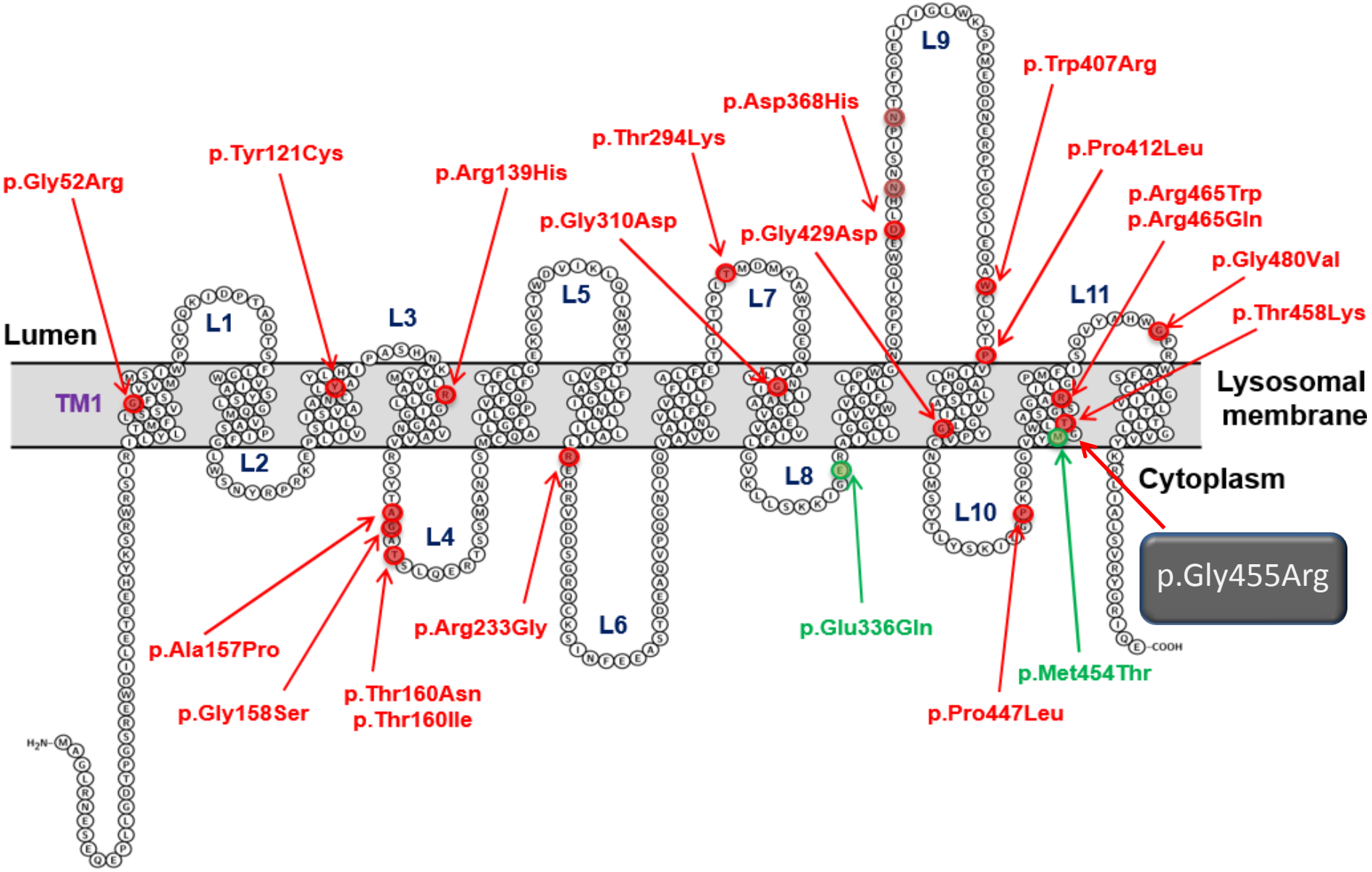
Clinically and biochemically undistinguishable of the other two variants (Sandhoff and Tay-Sachs)

Our NGS approached allowed a rapid and precise diagnosis in these patients

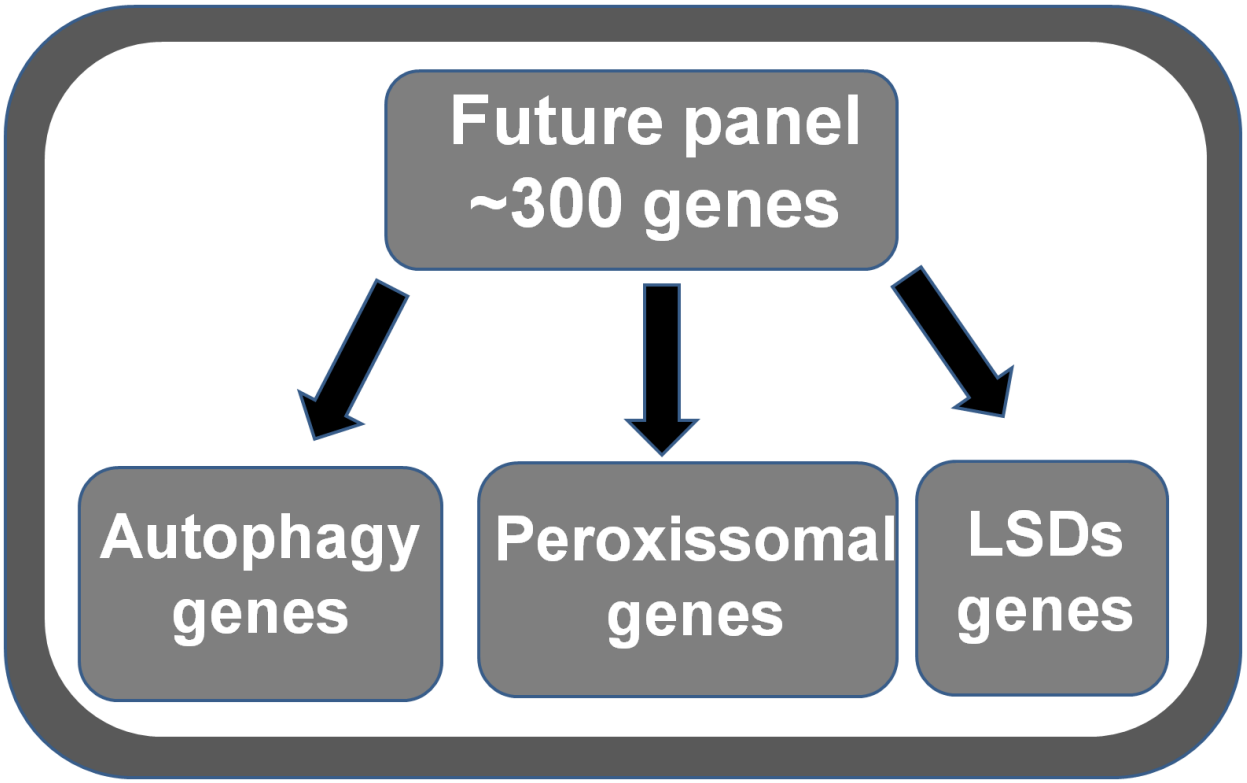
CLN7 protein



Future perspectives

- Expand the present NGS panel in order to include more genes involved in the Lysosomal Function.

- For the cases where a diagnostic is not reached even after using the extended panel perform other NGS analysis (WES and WGS).



For further informations about these two customized gene panels, please contact Dr. Sandra Alves: sandra.alves@insa.min-saude.pt

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