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Phenotype-genotype correlations of pediatric patients with biallelic mutations in *ABCA3* and *SFTPB* surfactant-related genes

Manon Fleury, Alice Hadchouel, Harriet Corvol, Julie Mazonq, Jean-Christophe Dubus, Camille Fletcher, Nouha Jedidi, Myriam Benhamida, Jacques Brouard, Pierrick Cros, Christophe Delacourt, Carole Egrou, Ralph Epaud, Michael Fayon, Aude Forgeron, Lisa Giovannini-Chami, Caroline Perisson, Hortense Petat, Marie-Catherine Renoux, Léa Roditis, Caroline Thumerelle, Clémentine Vigier, Aurore Coulomb L'Herminé, Laureline Berteloot, Chiara Sileo, Alix de Becdelièvre, Pascale Fanen, Camille Louvrier, Marie Legendre, Nadia Nathan

Affiliations: Reference center for rare lung diseases (RespiRare) and Reference network for rare lung diseases (RespiFIL)

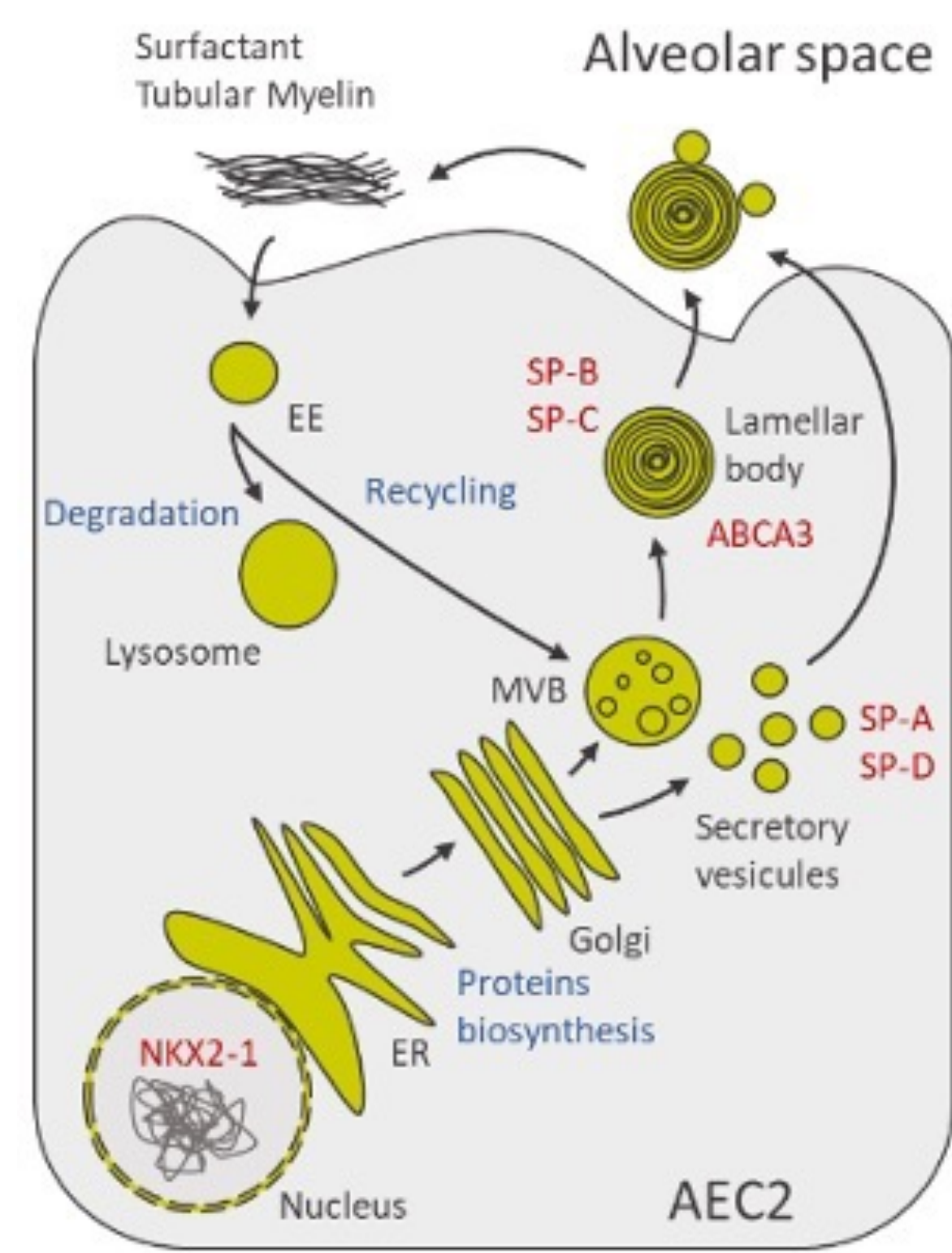
Introduction

Among childhood interstitial lung diseases (chILD) etiologies, the main genetic causes are due to **surfactant metabolism abnormalities**.

Mutations in the ATP-binding-cassette transporter A3 (*ABCA3*) and in *SFTPB* genes lead to ABCA3 and SP-B deficiencies respectively. Both **recessive diseases**, they are the most severe causes of chILD. Cohort studies remain limited.

→ The **main goal** of this study was to describe the clinical presentation and the evolution of patients with ABCA3 and SP-B deficiency in the French paediatric RespiRare cohort in order to establish phenotype-genotype correlations.

→ The **secondary objective** of the ABCA3 cohort was to attempt to predict, through sequences homology with CFTR (ABCC7), the potential effect of CFTR modulators in patients.



Adapted from Schindlbeck, Hum Mut 2015

Surfactant metabolism

Methods

Type of study

- Observational
- Retrospective (1995 - 2022)
- National, multicentric (all the RespiRare centres in France)
- Legal issue: ethics committee gave their authorization

Inclusion criteria

- Bi-allelic mutations of *ABCA3* or *SFTPB* genes (ACMG class 4 and 5)
- Patients aged 0-18 years

Exclusion criteria

- Not followed in France



Data collection

- e-Respirare database
- Multidisciplinary team meetings (MDT) for chILD
- Direct emails to the centres

Eligibility of ABCA3 mutations for CFTR modulators

Eligibility	Code	Type of pathogenic variants		
Not eligible	0	Non sense mutations, with a stop before the 1160 position corresponding to the NBD2 domain (not essential for the activity of the protein)	All deletions or insertions resulting in a frameshift mutations	Splice mutations known to be non-responders
Eligible	1	All other situations		
Very eligible	2	Mutation that corresponds to an amino acid identical to CFTR or belonging to the same amino acid family		
Undefined eligibility	?	Mutation that does not match a CFTR amino acid		

Results

A total of 47 patients were included:
ABCA3 = 37 patients, SP-B = 10 patients

	ABCA3 cohort	SP-B cohort
Sex ratio	0.76	1.5
Full-term birth	35 (95%)	7 (70%)
Family history of ILD	15 (41%)	8 (80%)
Invasive ventilation	27 (73%)	7 (70%)
Fan score 5	11 (30%)	4 (40%)

Distribution of ABCA3 genotype:

- 70% hypo/hypo
- 22% hypo/nul
- 8% nul/nul

Age at onset of symptoms:

→ In the ABCA3 cohort:

- Majority (86%) of presentation at birth
- Minority (14%) of later onset disease beyond 1 year

→ In the SP-B cohort:

- 90% of presentation at birth

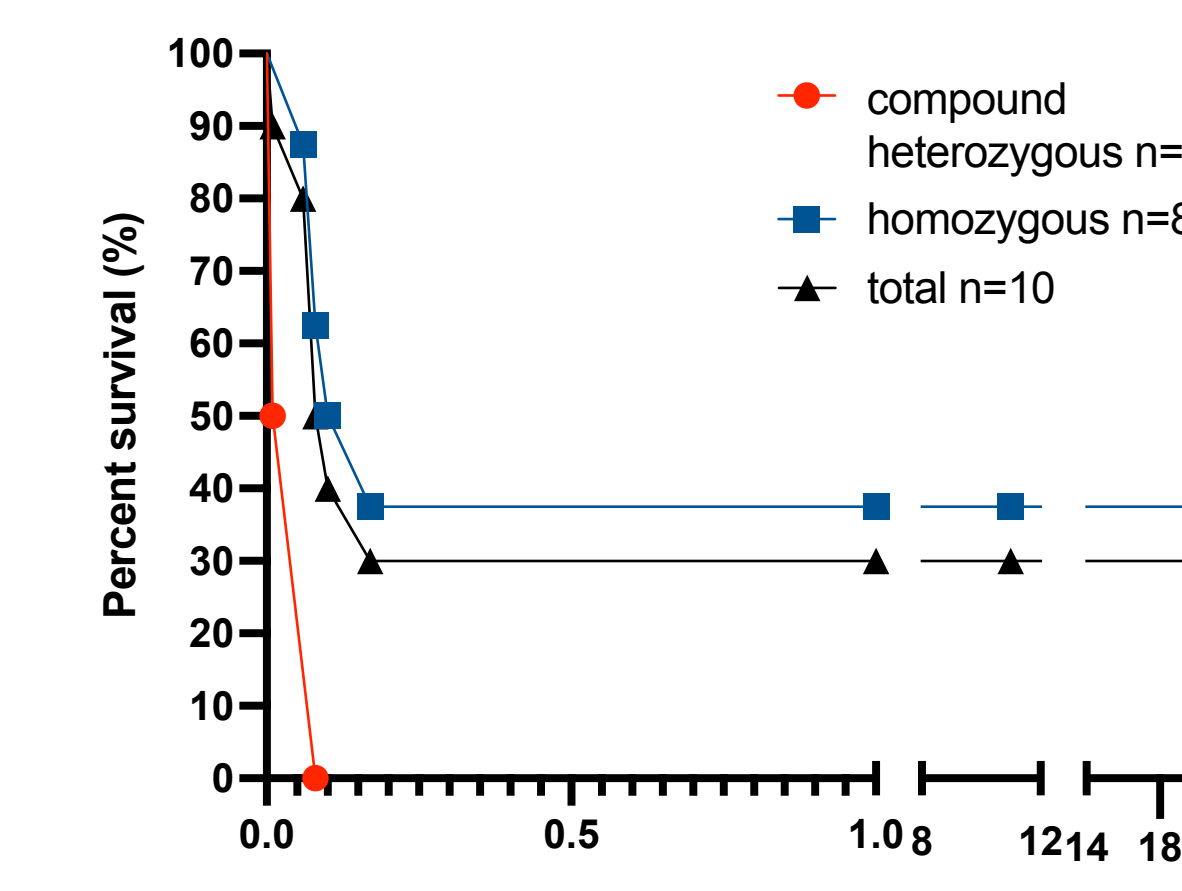
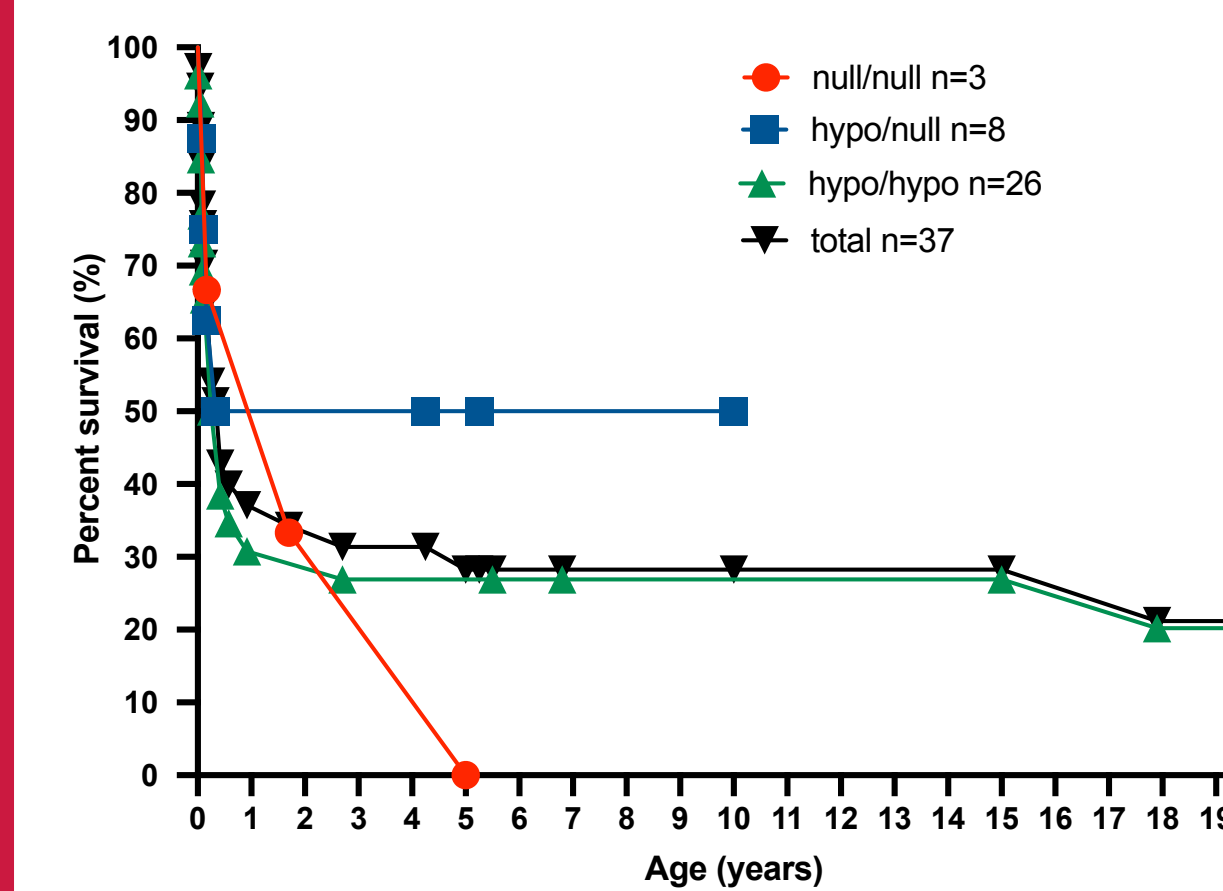
Evolution

→ In the ABCA3 cohort:

- . 73% died at a median age of 3 months
- . Better prognosis of later onset disease ($p=0.0136$)

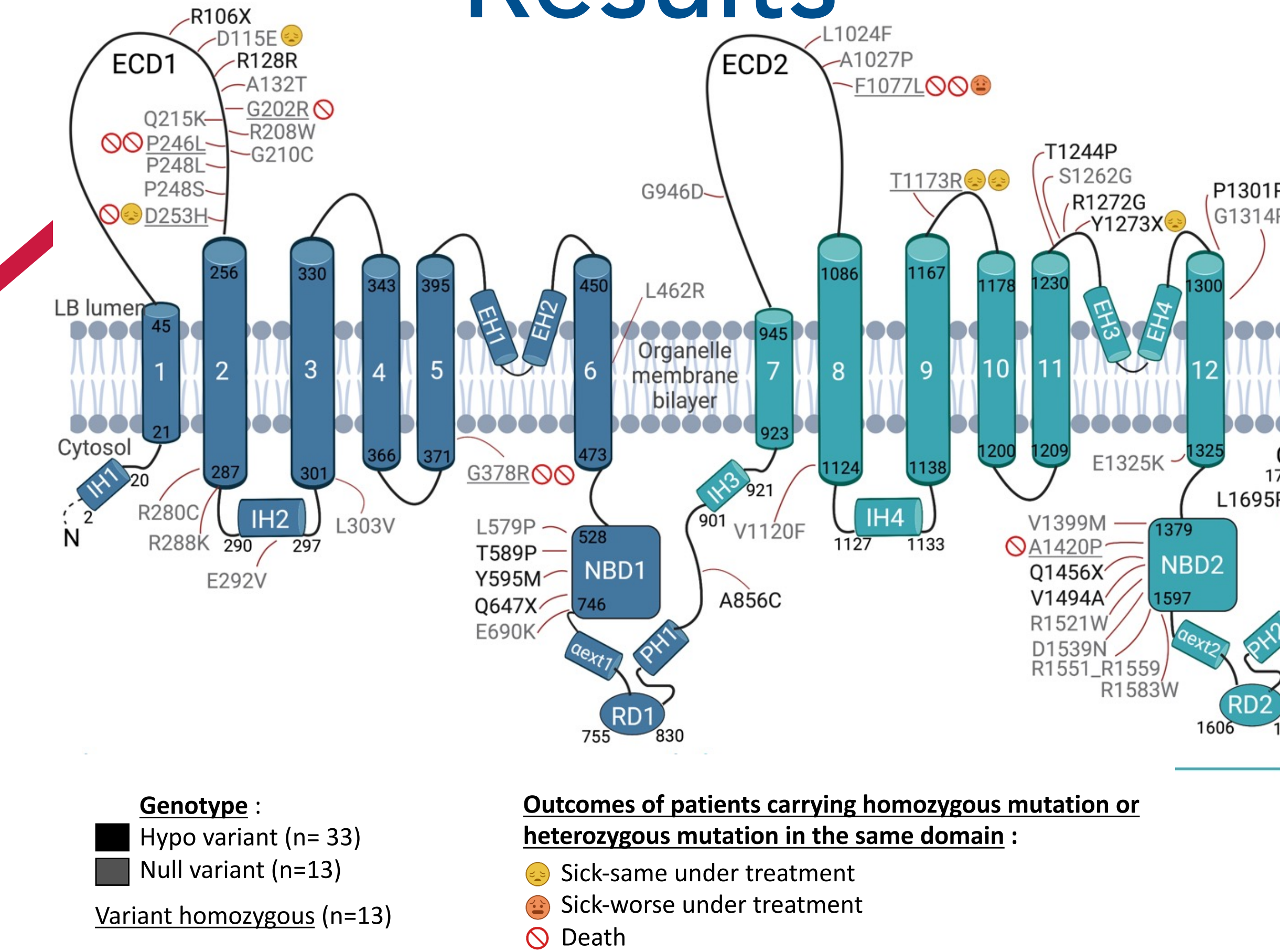
→ In the SP-B cohort:

- . 70% died at a median age of 1 m (remaining 30% = one family with *SFTPB* splice hypomorphic variant, Desroziers et al. *EJHG* 2023)



Kaplan Meier survival according to the genotype

Results



Domain organization of ABCA3 sequence variations observed in the cohort

	Eligibility	n of patients
Predicted eligibility to CFTR modulators	Non eligible	3 (8%)
	Eligible	33 (89%)
	Non determined	1 patient (1%)

Discussion and conclusion

This study confirms that the prognosis of ABCA3 patients with a null/null genotype appears to be fatal, as is the case for SP-B-deficient neonates.

At birth, it remains very difficult to distinguish both deficiency.

CFTR modulators may represent a **promising therapeutic approach**. The next challenge will be to develop international studies.

