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### ► To cite this version:

Manon Fleury, Alice Hadchouel, Harriet Corvol, Julie Mazonq, Jean-Christophe Dubus, et al.. Phenotype-genotype correlations of pediatric patients with biallelic mutations in ABCA3 and SFTPB surfactant-related genes. European Respiratory Society, Sep 2023, Milan (Italie), Italy. inserm-04212335

**HAL Id: inserm-04212335**

**<https://inserm.hal.science/inserm-04212335>**

Submitted on 20 Sep 2023

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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

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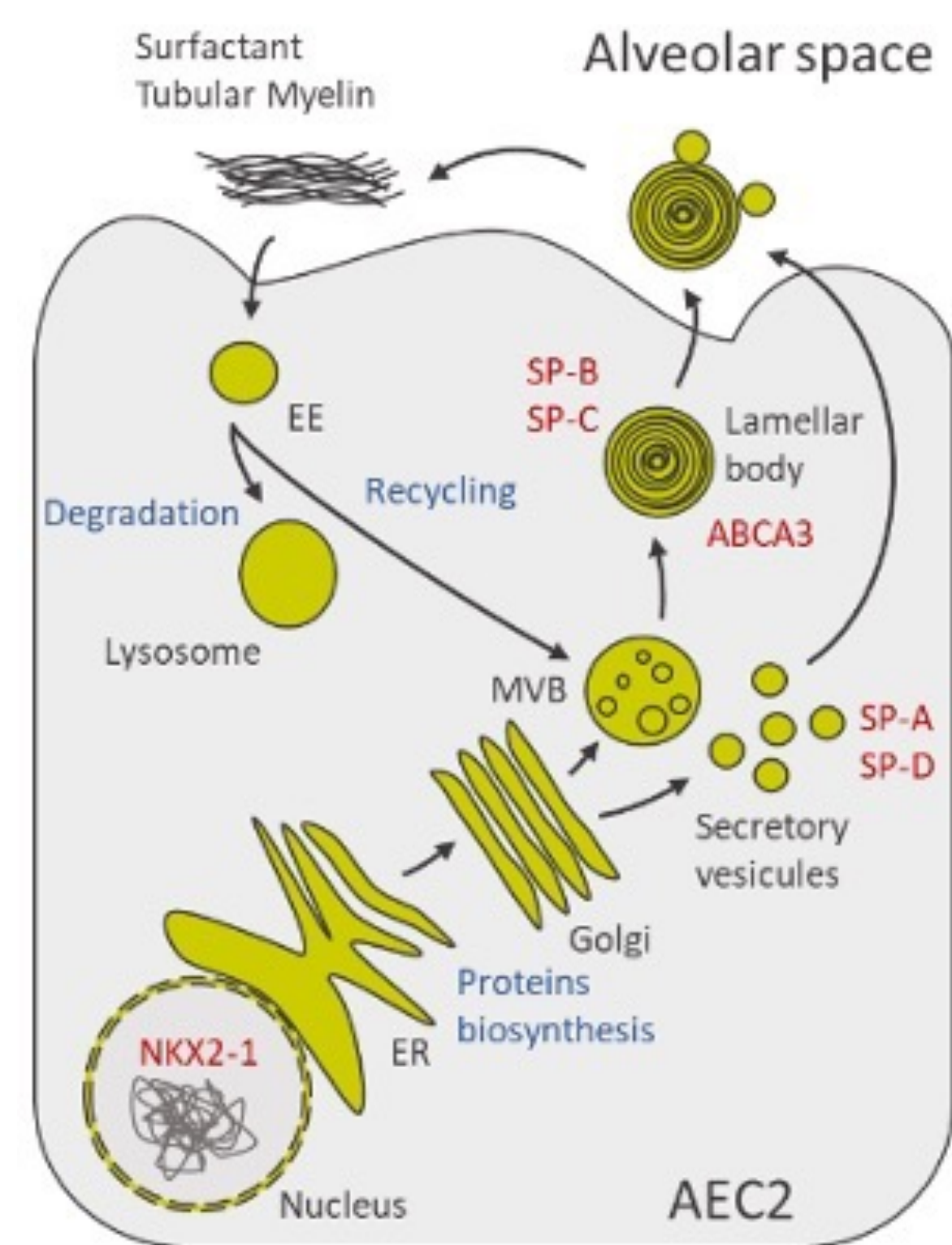
## Introduction

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**

### General characteristics

	<i>ABCA3</i> cohort	<i>SP-B</i> 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

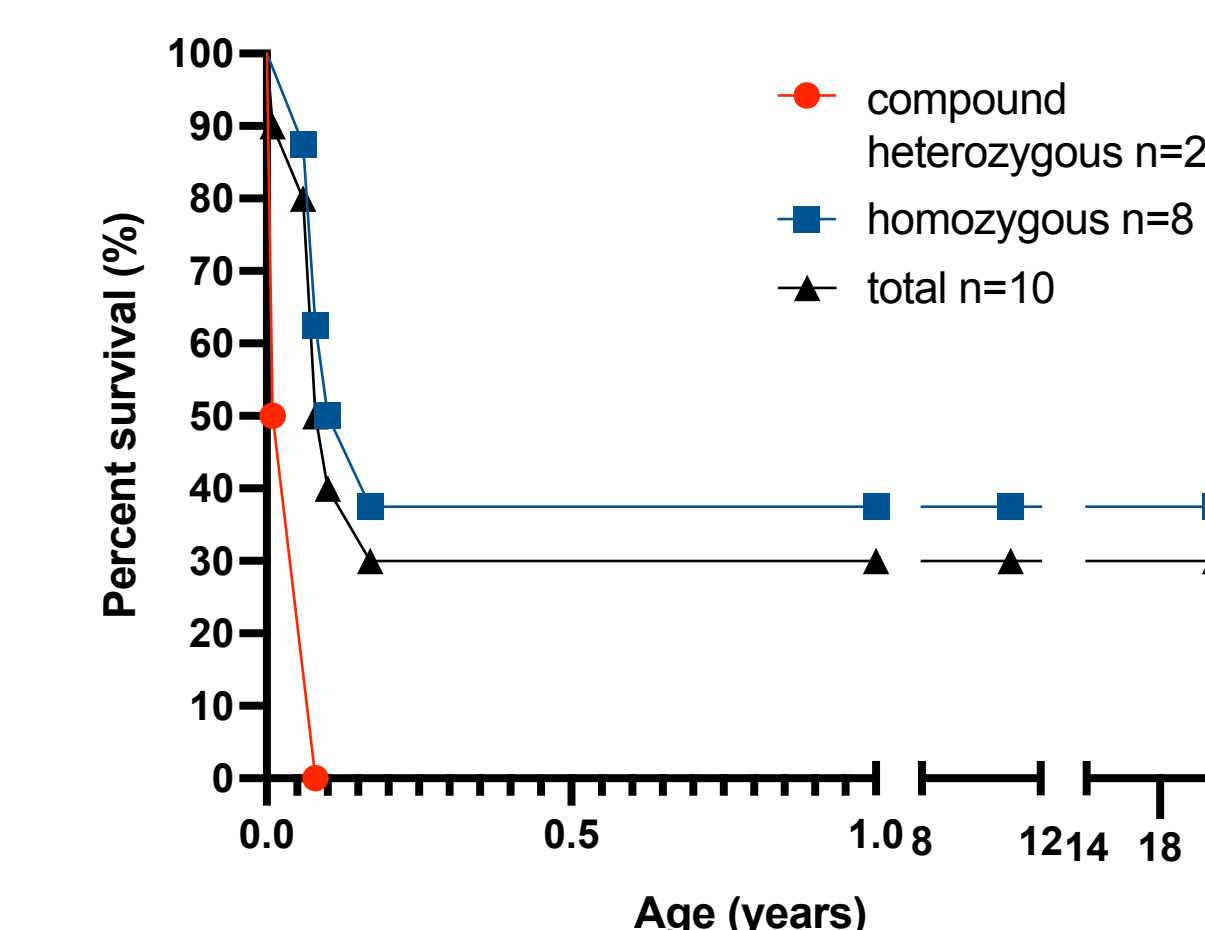
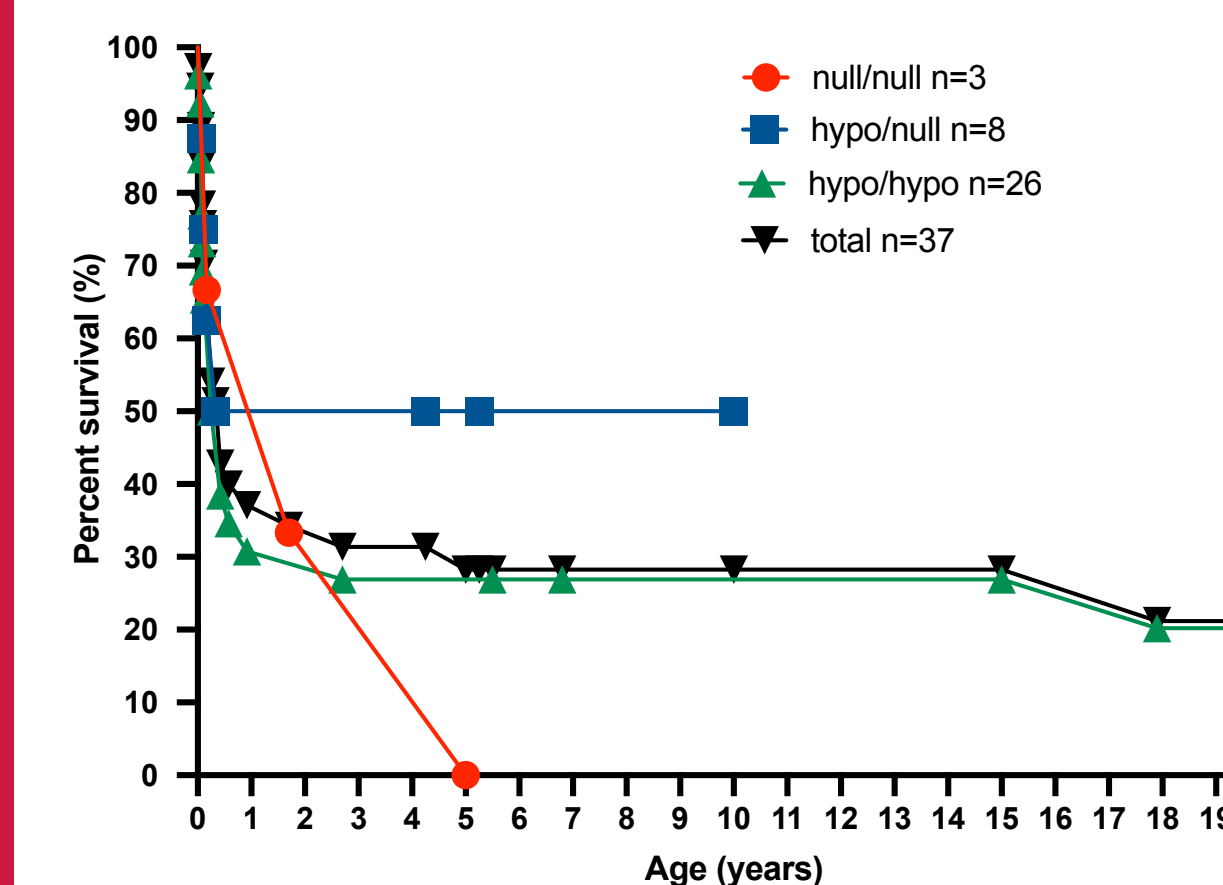
### Evolution

#### → In the *ABCA3* cohort:

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

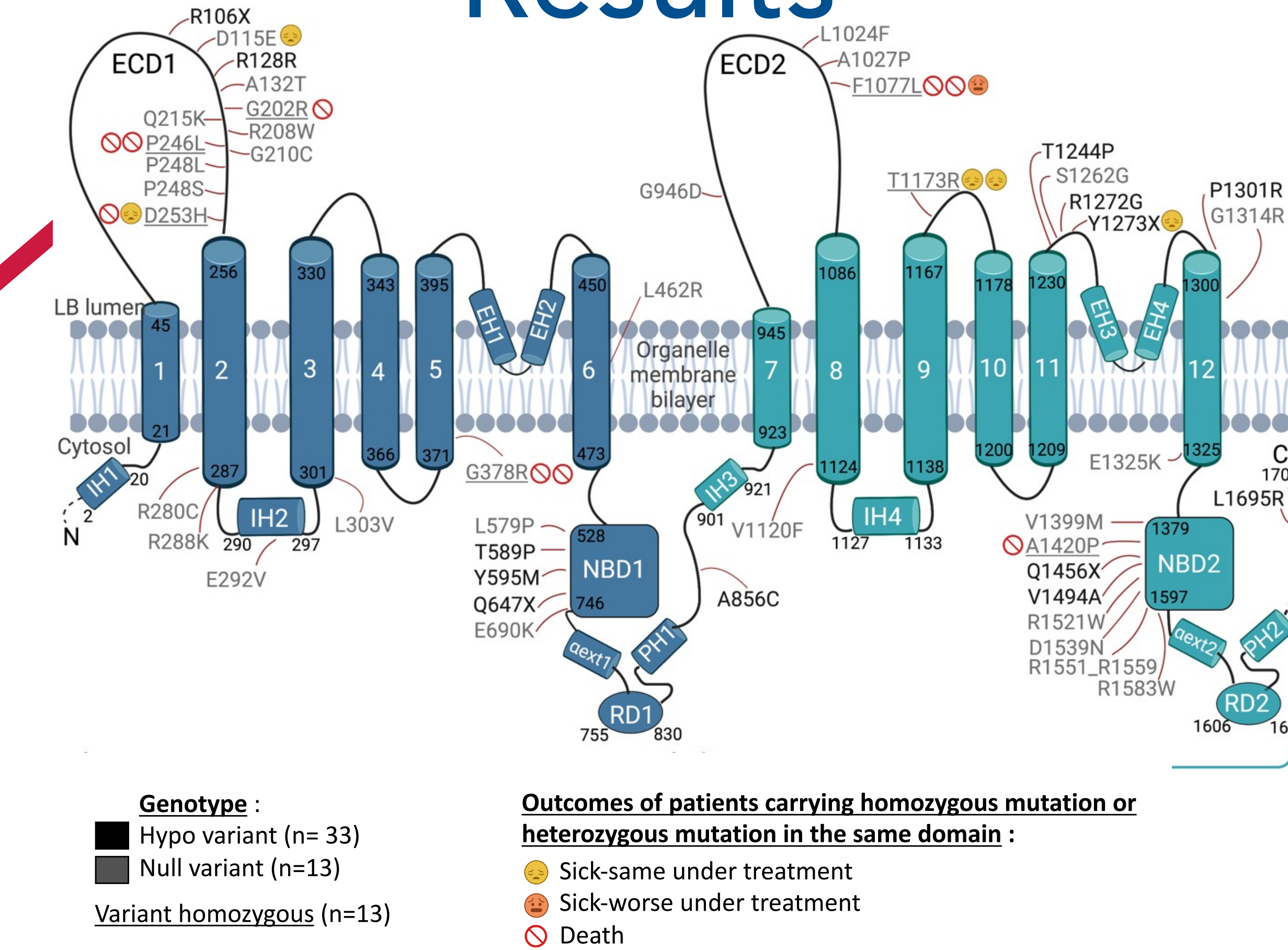
#### → In the *SP-B* cohort:

- . 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

### Predicted eligibility to CFTR modulators

Eligibility	n of patients
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.

