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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 Egron, 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)

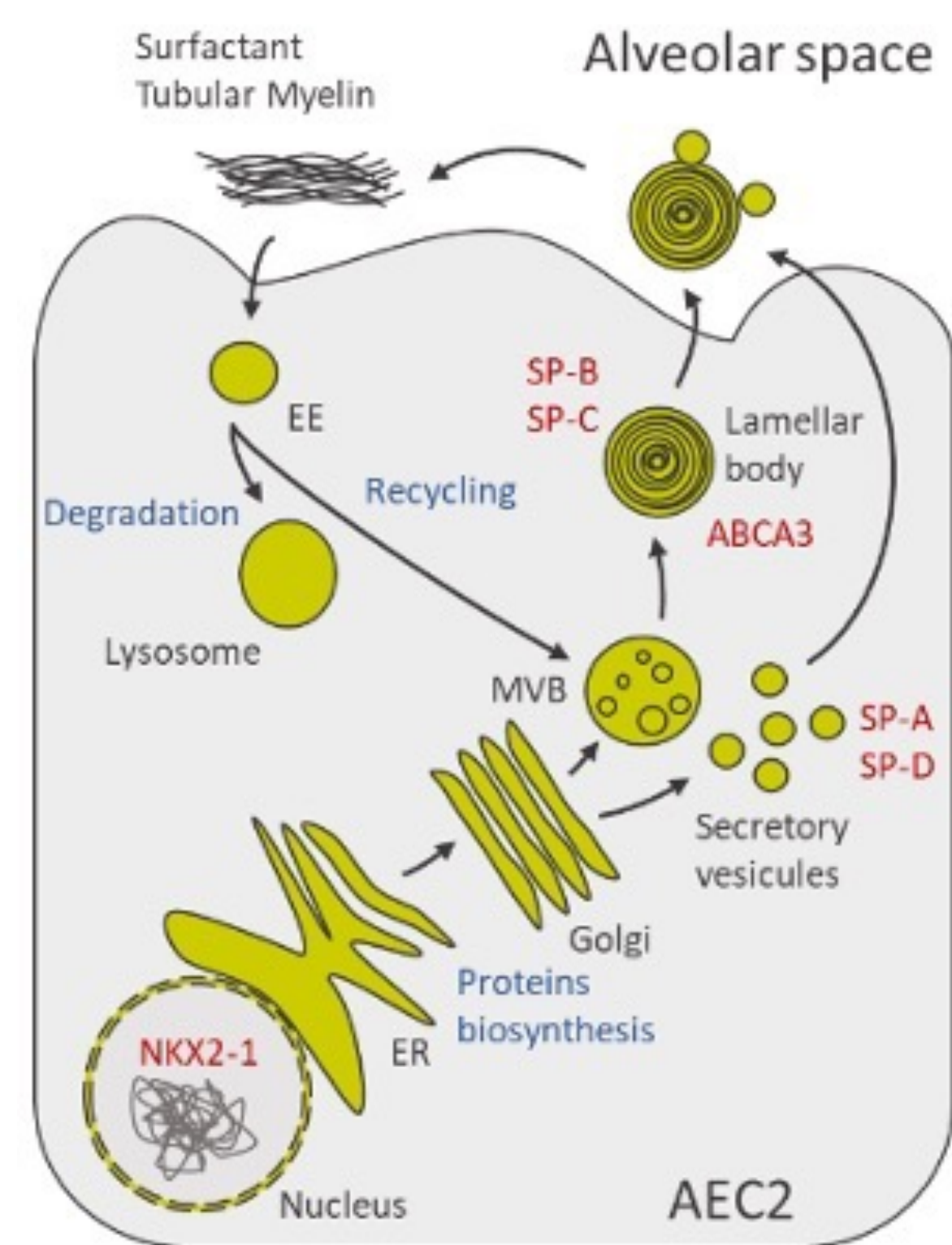
Introduction

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**

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

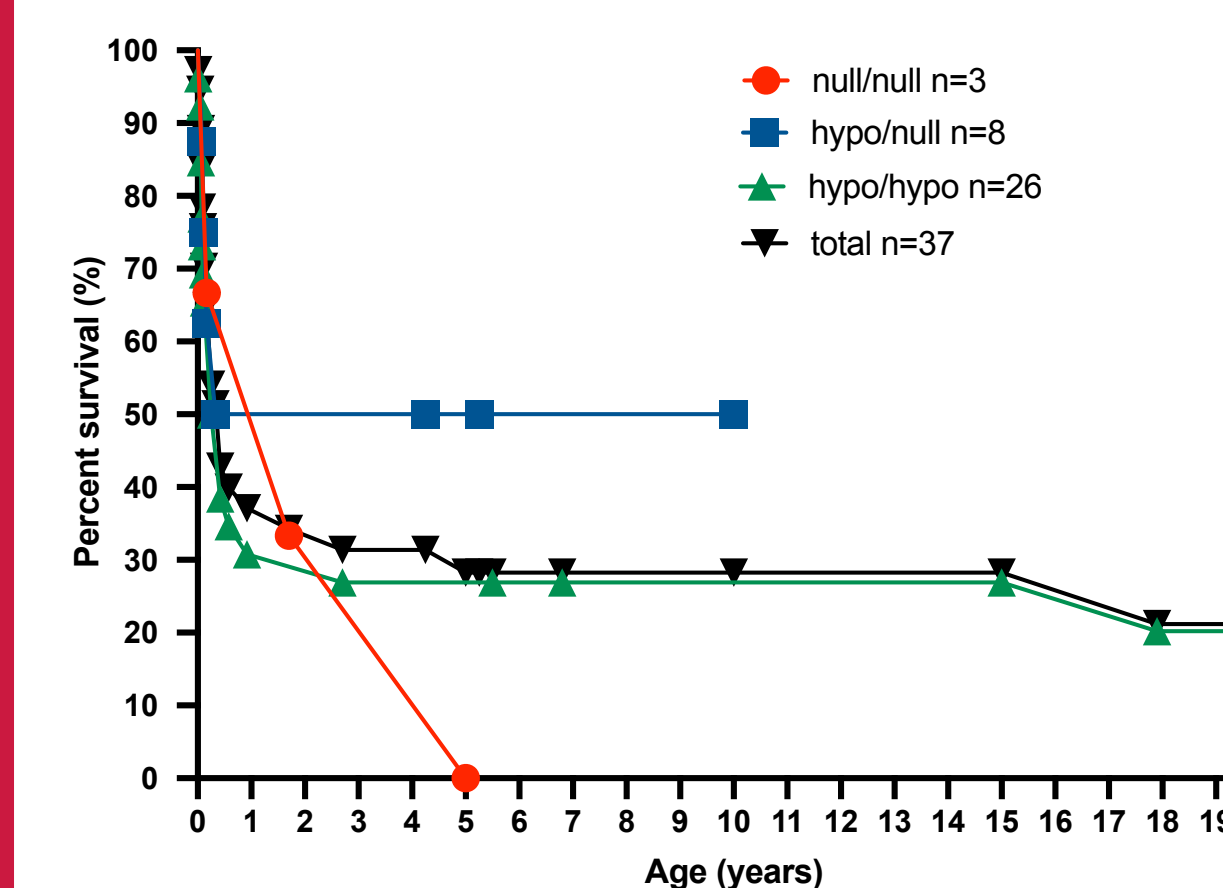
→ In the *SP-B* cohort:

- 90% of presentation at birth

Evolution

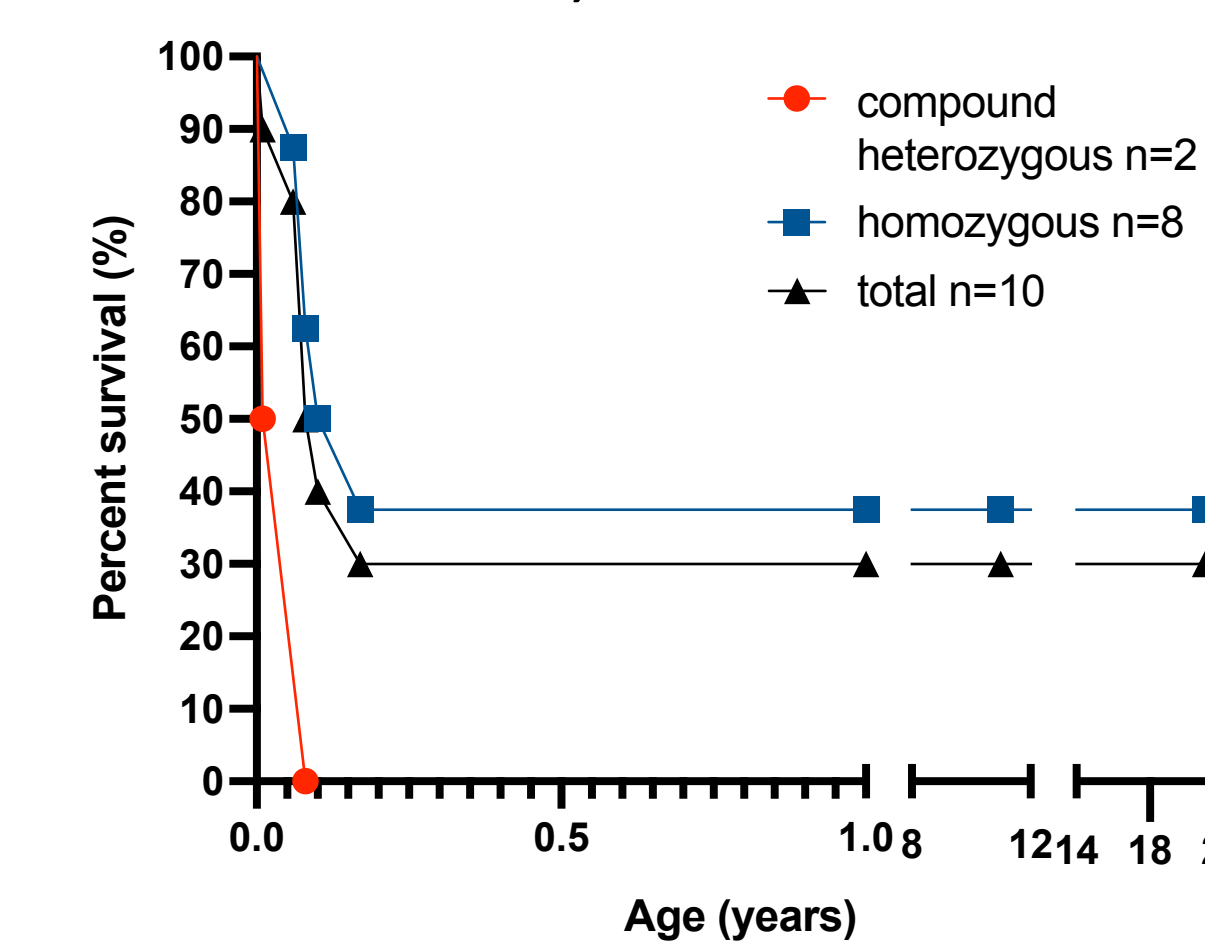
→ In the *ABCA3* cohort:

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



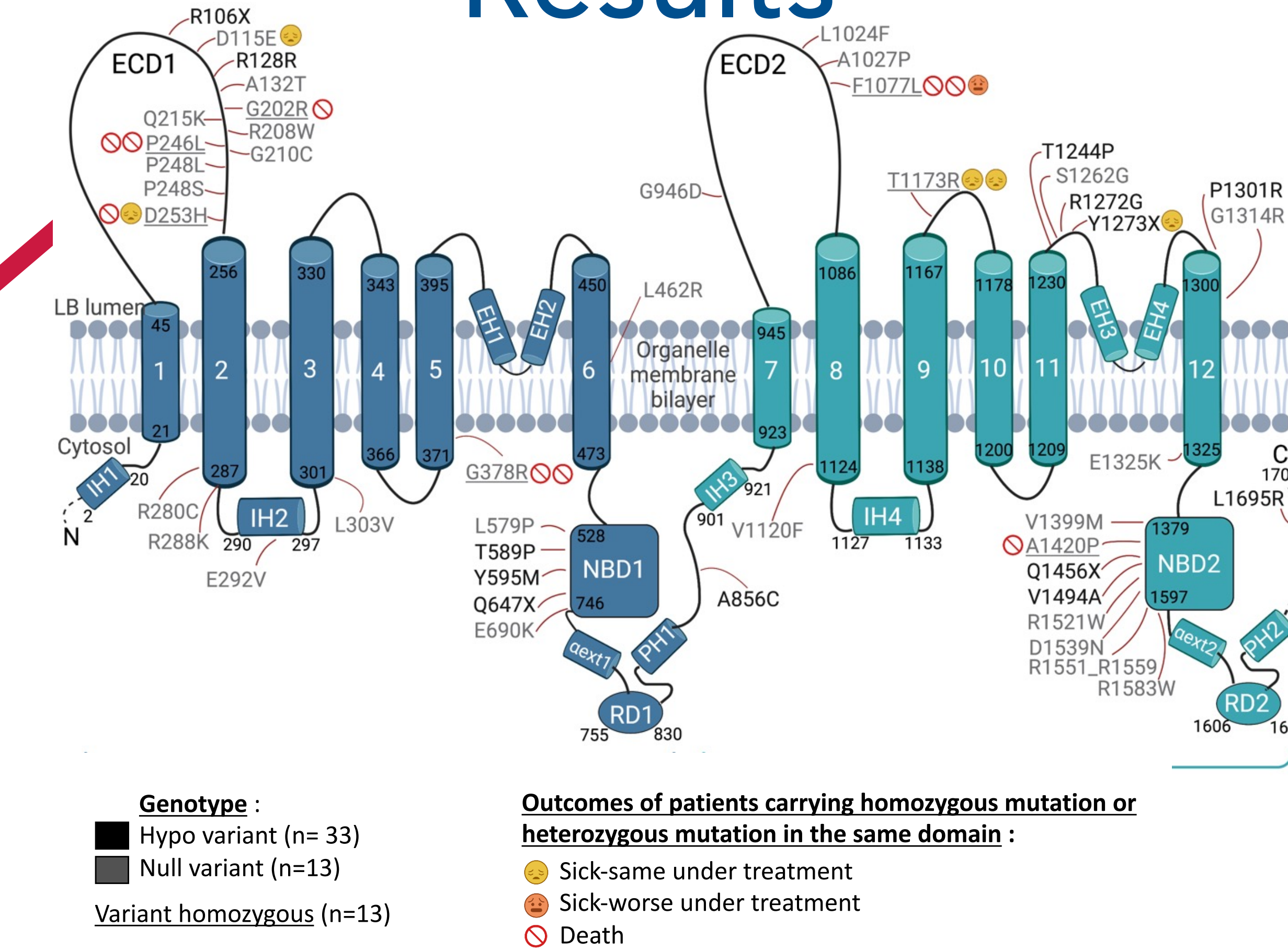
→ In the *SP-B* cohort:

- . 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.

