Cardiomyopathy in recessive dystrophic epidermolysis bullosa (RDEB)

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European Reference Networks | SKIN

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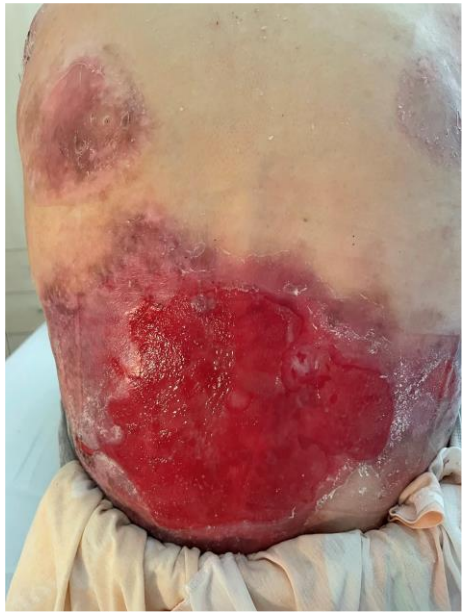
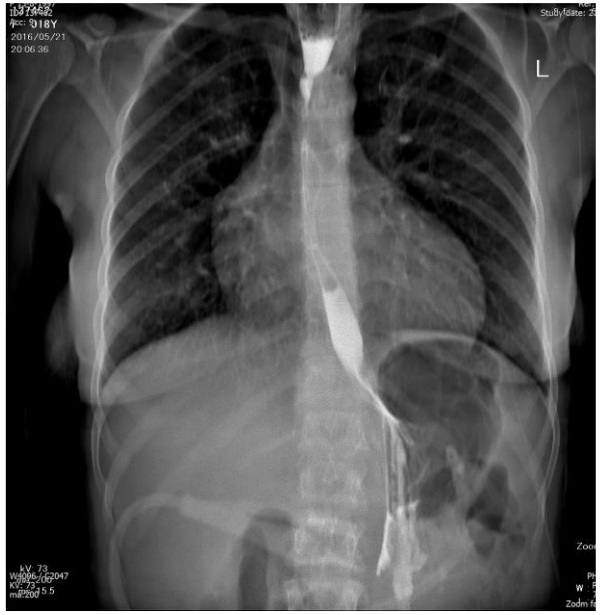
Cardiac disease in RDEB

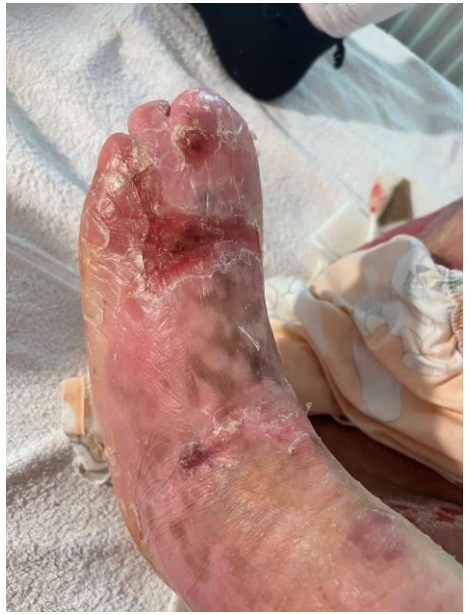
- CPMS: Case RDEB with cardiomyopathy > deceased
- Literature, own experiences
- Not all centers screen on a regular base
- **Suggestion for screening baseline and follow-up**

Case Groningen, NL:
Female, 25 yo, RDEB severe, no type VII collagen

- *COL7A1*:c.4767delA, p.Asp1590fsX / c.4767delA, p.Gly1590fsX

- Severe RDEB: wounds, scarring skin and mucosae, low BMI (18), chronic anemia with multiple transfusions, often skin infections



Laboratory

- Recurrent anemia 5,7 mmol/L (n 7,5-10) > recurrent transfusions iron, RBC
- Iron deficiency, normal selenium
- CRP: >100, long term
- Normal kidney function till recently
- Recurrent wound infections with bacteriemia lately

Cardiac/internal situation

- 2016: ‘myocarditis’, since then progressive dilated cardiomyopathy with reduced ejection fraction
- rr around 90/70mmHg, heart rate >90/min in rest
- Family: no cardiomyopathy/cardiac disease/sudden death
- DNA WES panel CM genes: no (likely) pathogenic variants
- Deceased in January 2023 following bacteriemie with 1. progressive cardiac failure and 2. kidney failure likey due to 1.

Questions

- CM in RDEB, how often in other centers?
- Literature?
- Screening, how often? How?
- Pathomechanisms?
  - Chronic inflammation&anemia and/or
  - systemic fibrosis and/or
  - micronutrient (selenium) deficiency and/or
  - molecularly (COL7A1) driven?
- More relevant with novel therapies in development?

Literature, results

- **Search: ‘cardiomyopathy’ and ‘dystrophic epidermolysis bullosa’: 24 hits**
- Cardiomyopathy (mainly dilated): both RDEB intermediate and **severe**
- Wide variation in age, also below 2 y of age
- Numbers varying from to 0-30% of RDEB population: ~10%
- Lethal in number of cases
- Limitations: often subtype not well defined, retrospective & chart-based

Next steps

- Clinical evaluation of our RDEB cohorts within ERN according to same basic protocol, suggestion (next slide)
- Molecular underpinning etiology > directly *COL7A1* related?

Suggestion for screening and follow-up

Credits also to C. Prodinger and team in Salzburg

Prospective follow-up, suggestion for ERN-Skin EB > RDEB

Children <18 years of age:

Investigations	Frequency
Anamnesis *Especially asking for*: shortness of breath, increased breathing work, change in intensity of fatigue, frequent rest breaks while playing, falling asleep when feeding, lack of appetite, nausea; poor growth, failure to thrive, excessive sweating, episodes of blueness (lips, face), dizziness and fainting; chest pain;	At time of diagnosis (baseline), then **yearly** (does not have to be done by a cardiologist)
Physical status *Especially looking for*: Peripheral edema; swelling of eyelids, face, abdomen; Change of skin color, cyanosis; peripheral perfusion (cool extremities); growth parameters; heart and breathing rate, blood pressure; Auscultation: murmurs, pulmonary crackles	
Lab: NTproBNP, Hemoglobin, Hematocrit, iron, MCV, ferritin, selenium, zink, carnitine, TSH, T4, BSE, CRP	
Electrocardiogram (ECG) Cave: use (weakly) adhesive electrodes (no suction buttons)	At time of diagnosis, then **yearly** until age of 3 years, afterwards **every 2 years**
Echocardiography* In case of wounded thoracic skin: use e.g. MepitelFilm	

***Earlier echocardiography** if one of the following findings are present

- Suspicious anamnesis regarding heart failure
- Suspicious physical status regarding heart failure
- Increased pBNP

Adults ≥ 18 years of age

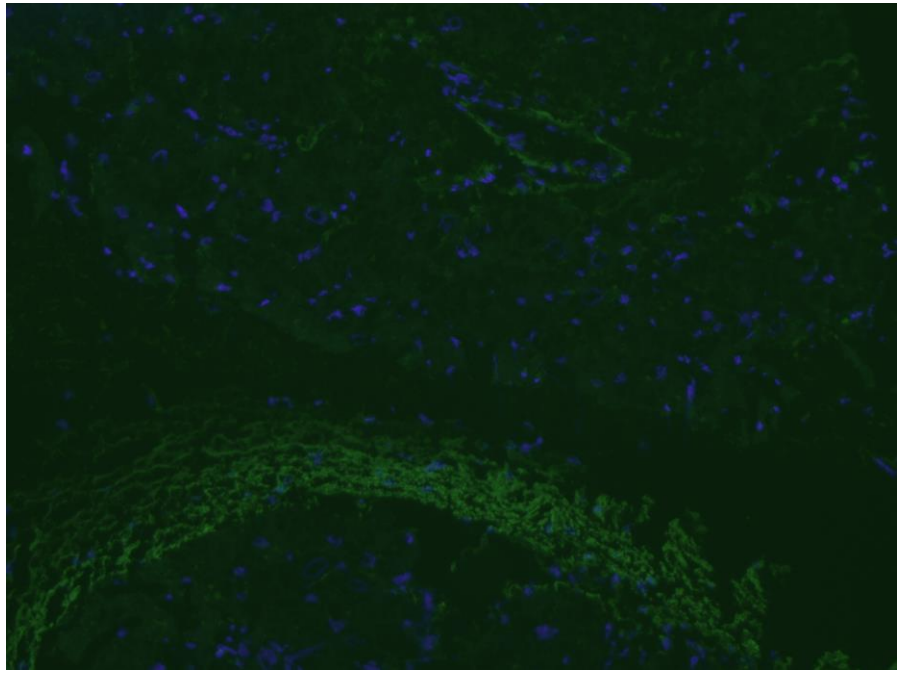
Investigations	Frequency
Anamnesis *Especially asking for*: exertional dyspnea, reduced exercise tolerance; (change in intensity of) Fatigue or physical weakness; (new, progressive) peripheral edema; unexpected weight gain (fluid retention); palpitations/fluttering; increased pulse rate; chest pain	**Yearly** (does not have to be done by a cardiologist)
Physical status *Especially looking for*: jugular venous pressure; Peripheral edema; skin color, cyanosis; blood pressure; heart rate, breathing rate; Auscultation: murmurs, pulmonary crackles;	
Electrocardiogram (ECG) Cave: use (weakly) adhesive electrodes (no suction buttons)	
Lab: NTproBNP	
Echocardiography° In case of wounded thoracic skin: use e.g. MepitelFilm	**Every 3 years**

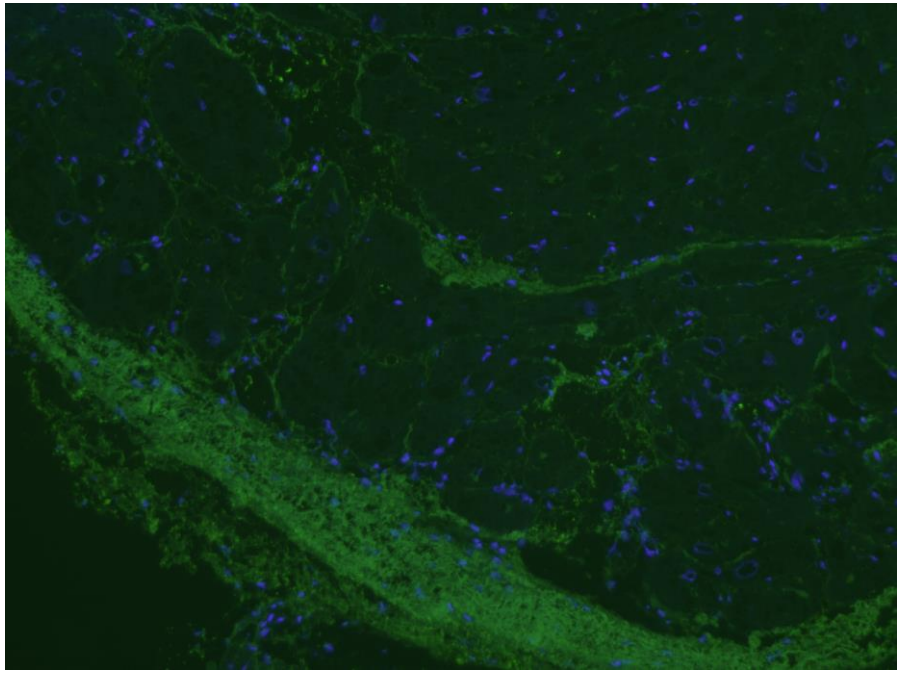
°**Earlier echocardiography** if one of the following findings are present

- Suspicious anamnesis regarding heart failure
  - Leading symptoms: exertional dyspnea, reduced exercise tolerance, leg edema,…

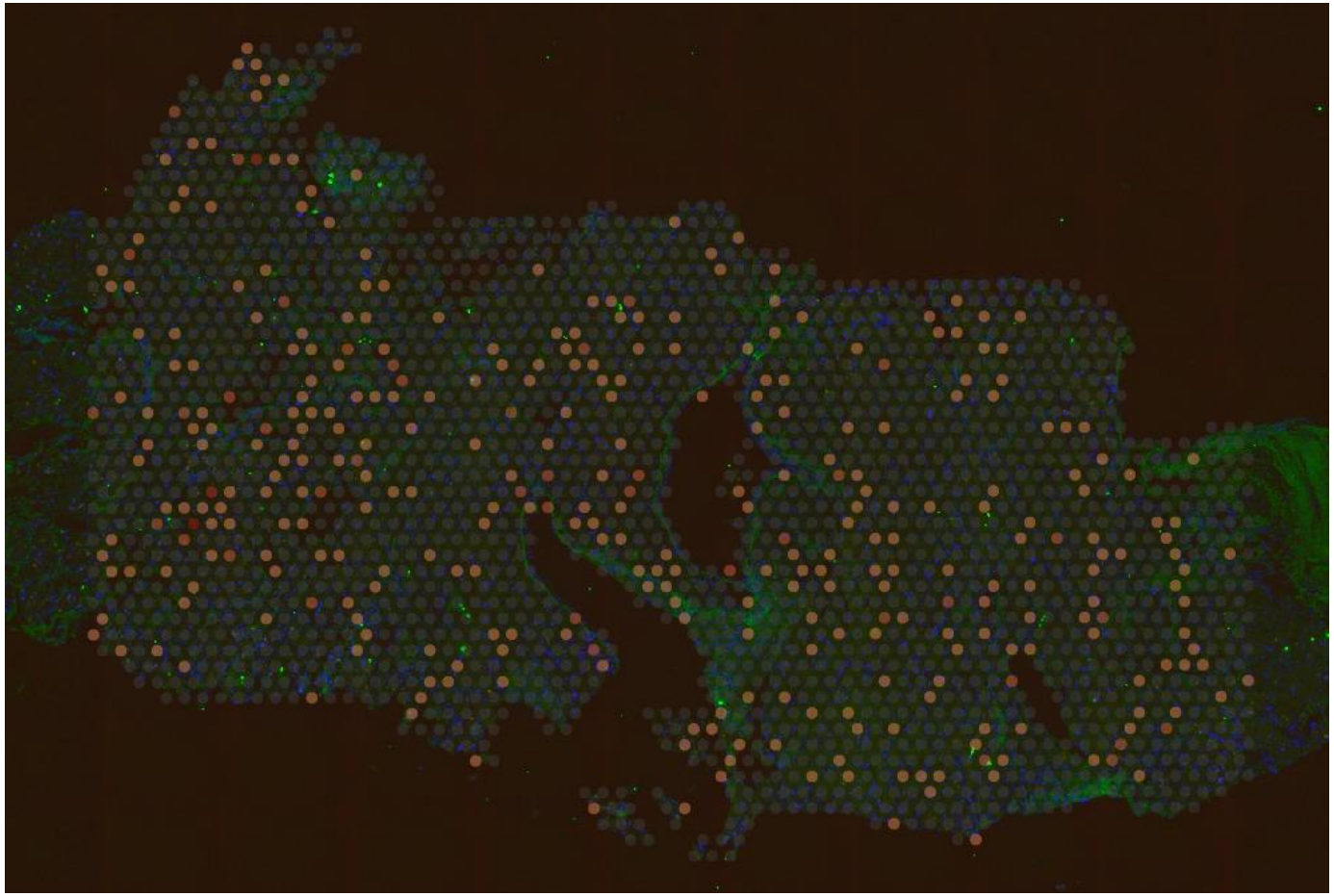
Pathomechanism: directly COL7A1 related?

- Protein: IF on ‘control’ cardiac tissue, LH7.2 and LH24 against type VII collagen > fibrous tissue in between cardiomyocytes





RNA: Spatial transcriptomics, data on COL7A1 RNA in cardiac tissue (heart failure)



Next steps:

- RNA COL7A1 expression in iPSC derived myocardial tissue (fibros en cardiomyocutes)

- If yes: iPSC derived 3D CM tissue under strain
  - Control versus patient RDEB
  - Mix mutated fibros, normal CMs and vice versa.