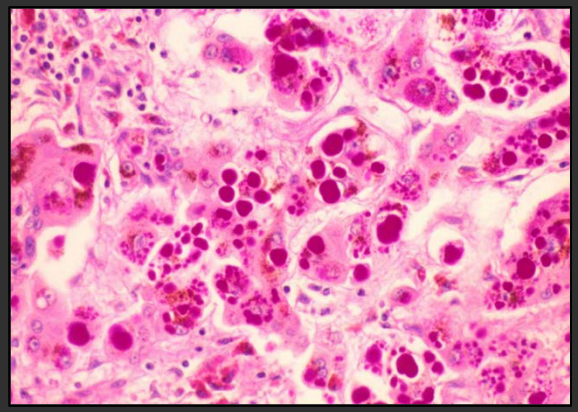
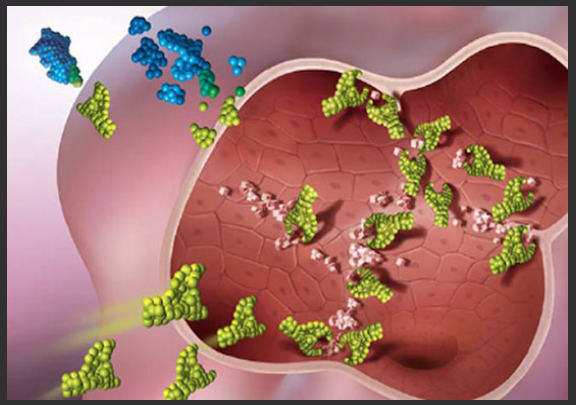
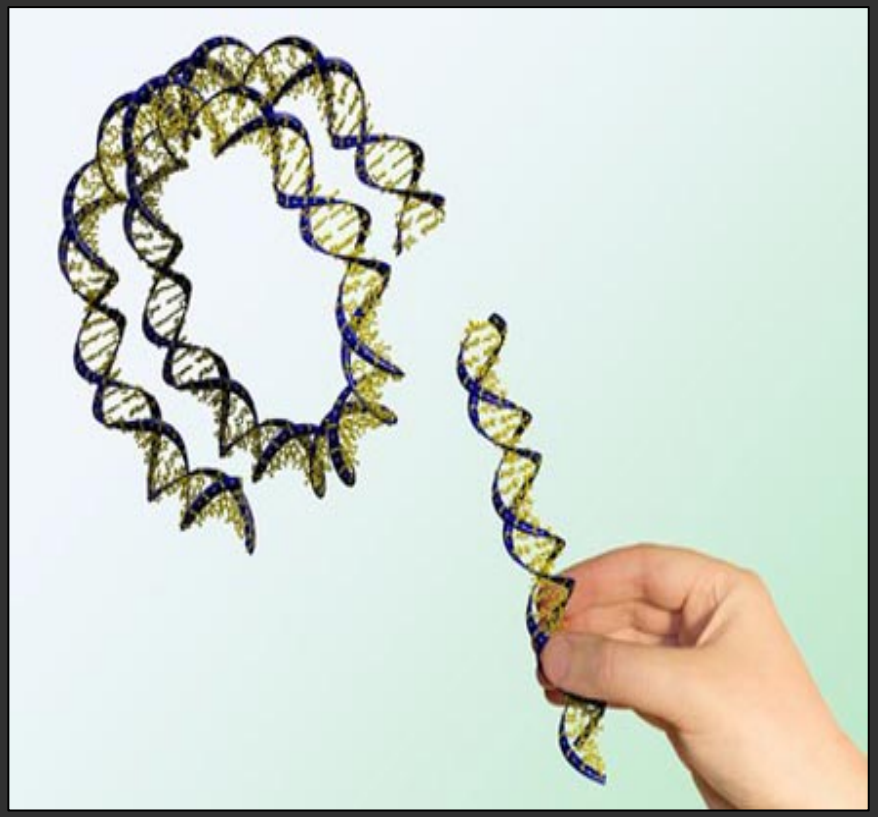
Alfa-1-antitrysin mangel hos børn





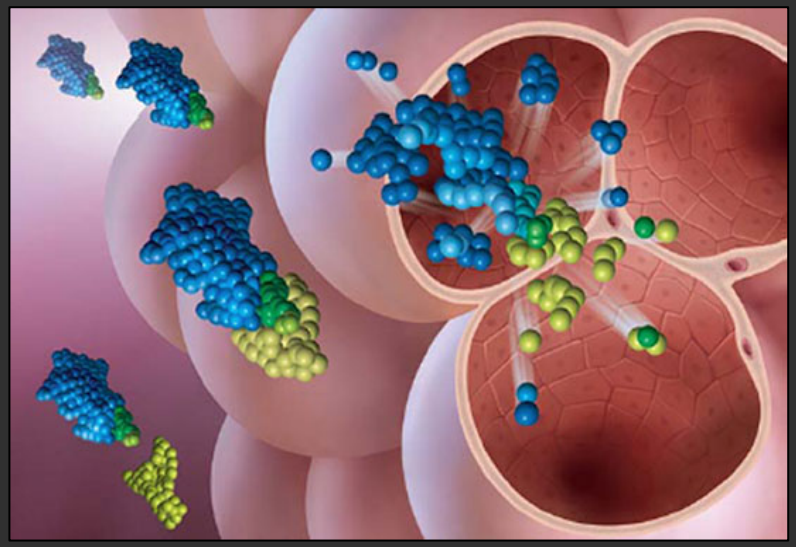


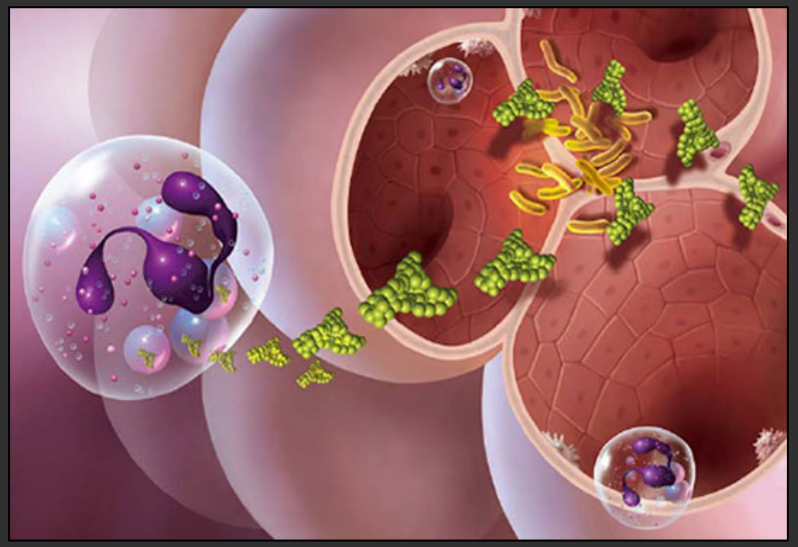
Elisabeth Stenbøg, Afd.læge, PhD
Børneafd. A, AUH

Alfa-1-antitrypsin

Hvad er det?

- Proteinstof
  - Produceres i leveren
  - Fungerer i lungerne
  - Regulerer neutrofil elastase balancen

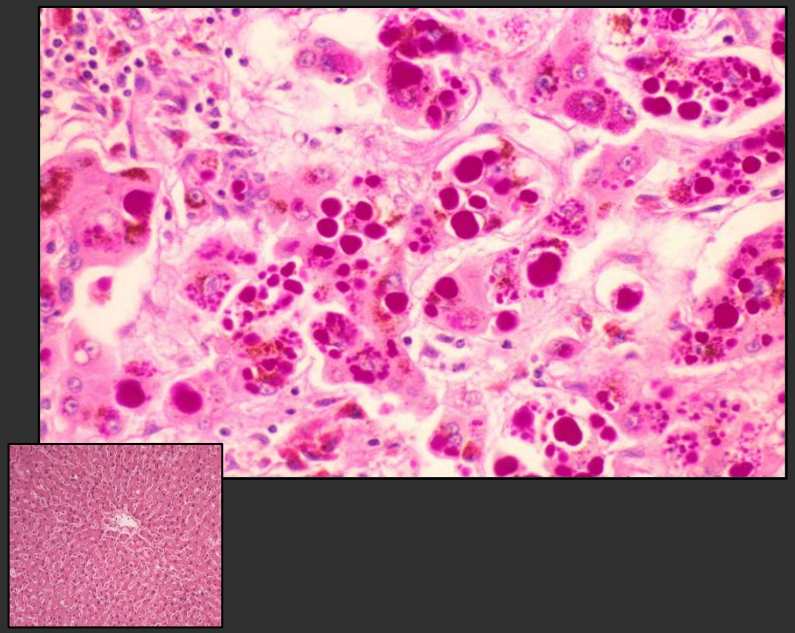


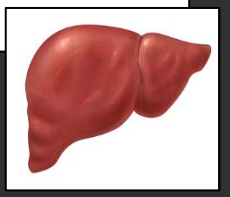


Alfa-1-antitrypsin mangel

Hvad sker i leveren?

- Defekt levertoksisk Alfa-1-antitrypsin ophobes i levercellerne
- Fremadskridende arvævsdannelse

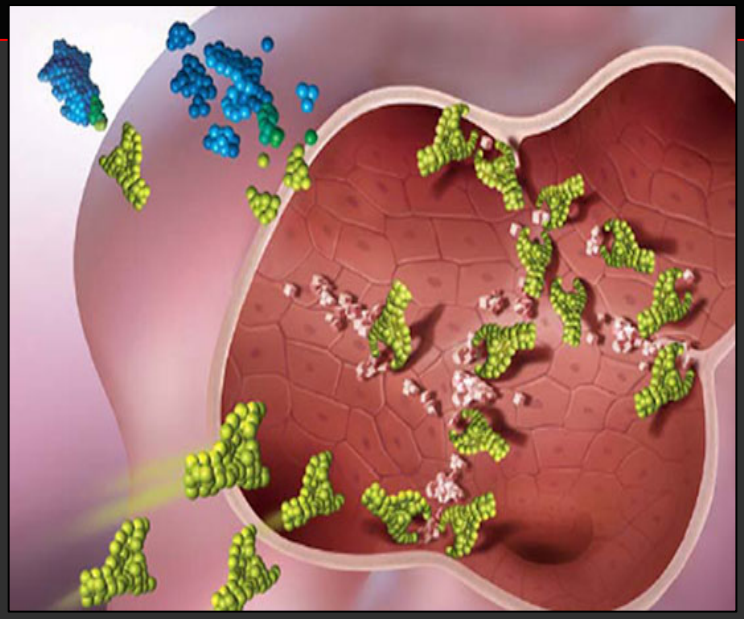


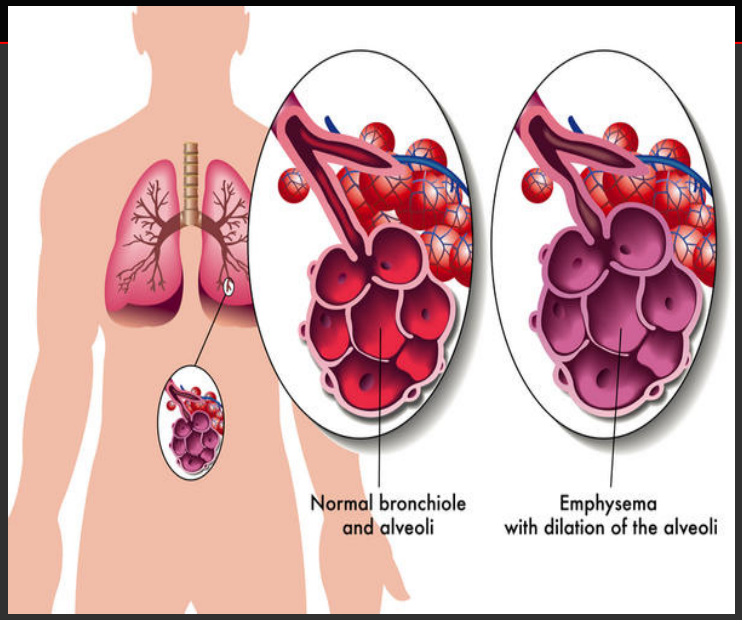


Alfa-1-antitrypsin mangel

Hvad sker i lungerne?

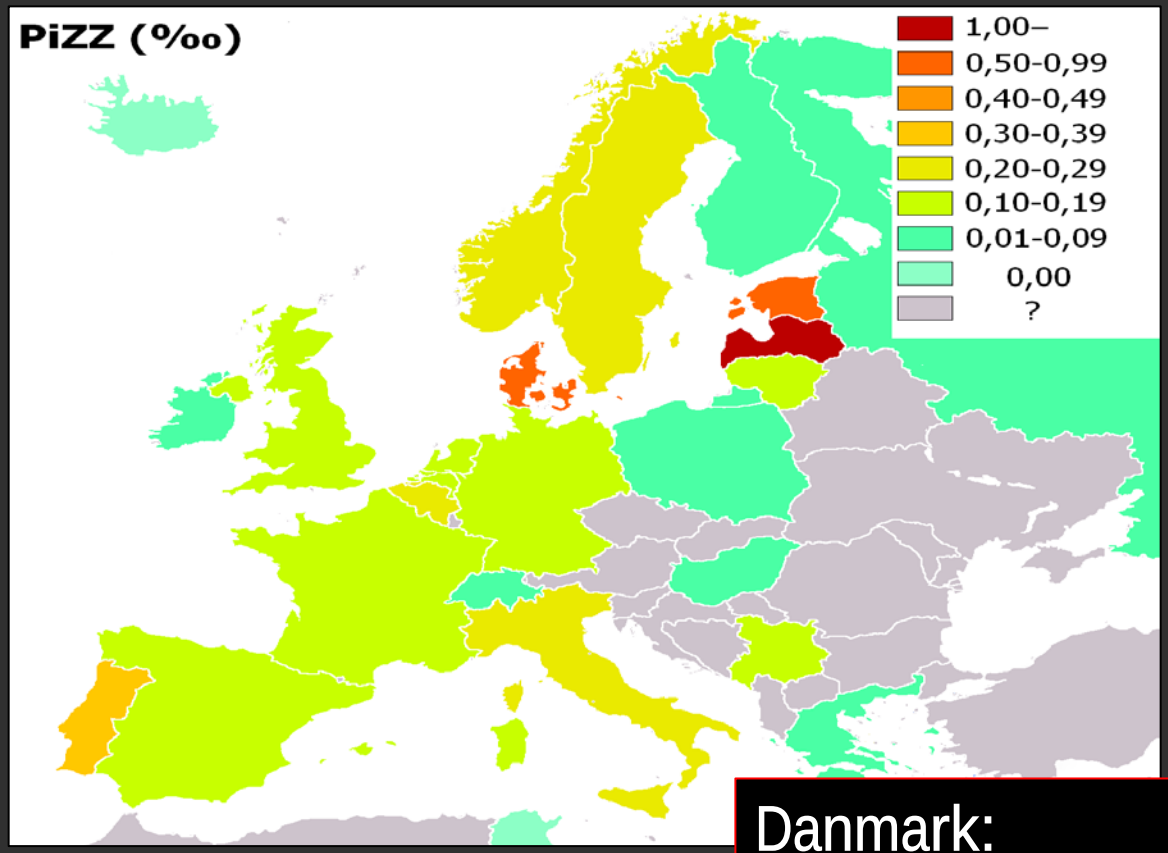
- Neutrofil elastase nedbrydes ikke
- Lungernes elastiske protein (elastin) nedbrydes)
- Alveolevæggen ødelægges





Alfa-1-antitrysin mangel

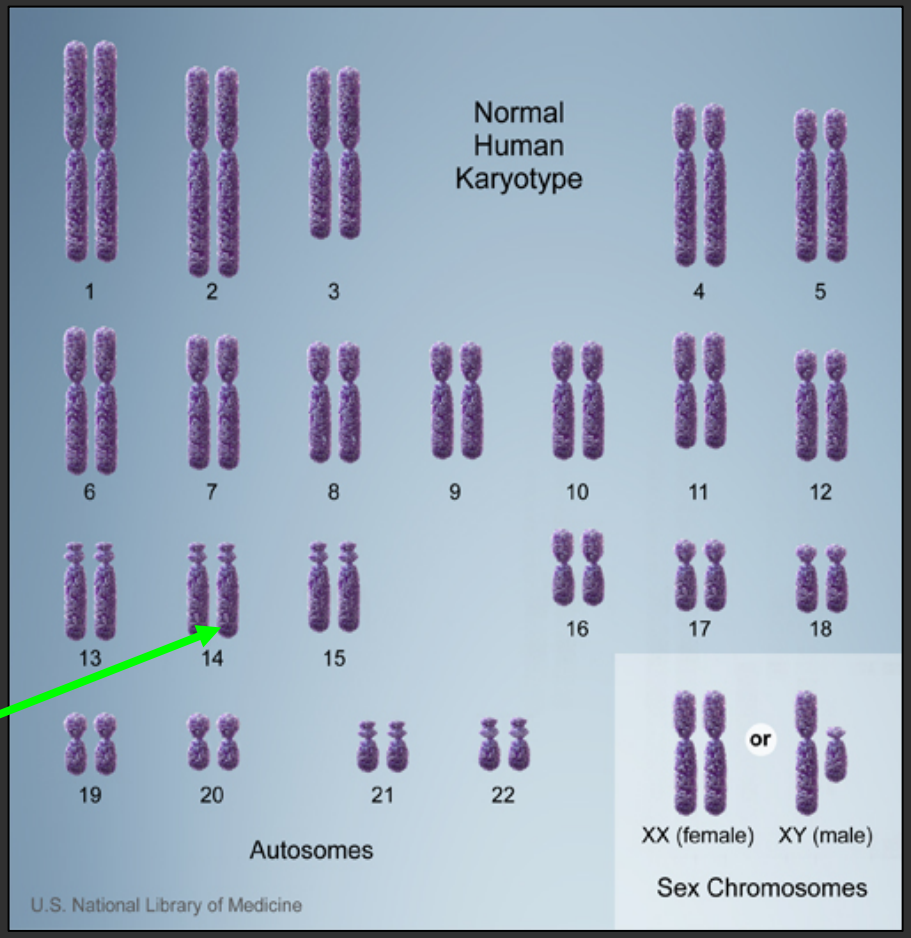
Forekomst

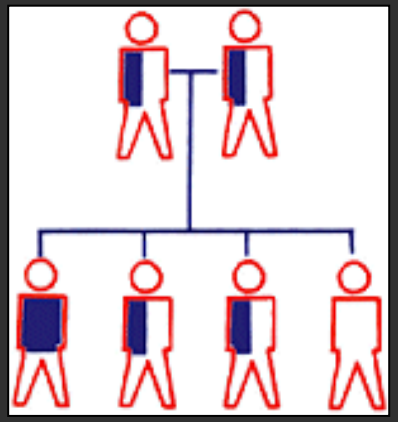


Danmark:
1 / 1600 nyfødte = 40 børn / år
5% af befolkningen er raske bærer

Monogen arvelig sygdom

Alfa-1-antitrysin mangel





Genotyper

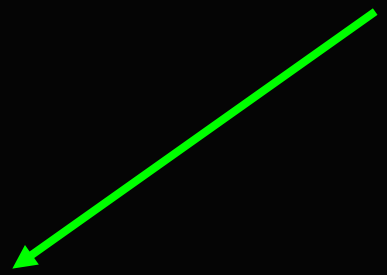
- > 100 genotyper
- M er den normale allel
- Z og S udgør 95% med kliniske symptomer
- S 50-60% expression af A1AT
- Z 10-20% expression af A1AT

	S	Z
M	MS	MZ
Z	SZ	ZZ

Alfa-1-antitrypsin mangel

Fænotyper

Fænotype	Alfa-1-antitrypsin koncentration (%)
MM	100%
MZ	60%
SS	60%
FZ	60%
M-	50%
PS	40%
SZ	42%
ZZ	15%
Z-	10%
-	0%



Alfa-1-antitrypsin mangel

Præsentation

Alfa-1-antitrypsin mangel

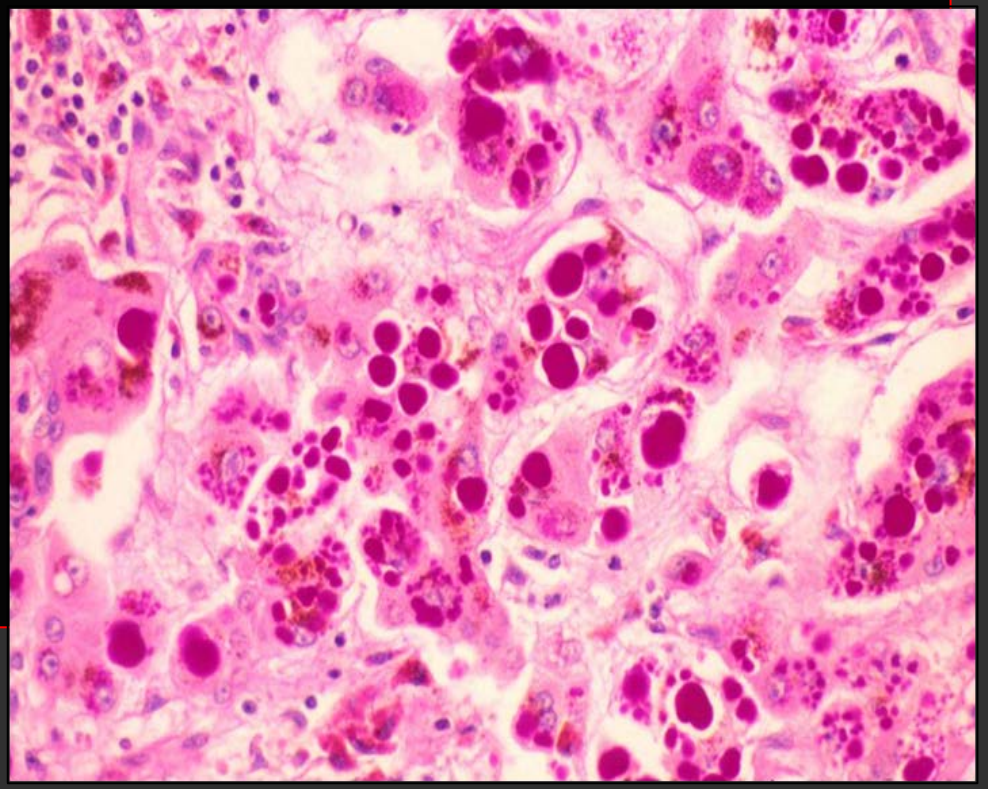
Præsentation

Sygdomsdebut i nyfødthedsperioden

- Ikterus
- Dårlig trivsel
- Påvirkede levertal (ALAT)
- Forlænget blødningstid

Diagnostiske undersøgelser

- Gen undersøgelse
  - Barnet
  - Forældre
  - Søskende
- Leverbiopsi



Prognose

- 50% God prognose
  - 25% helt raske
  - **25% ↑ ALAT, men raske**
- 50% Dårlig prognose
  - 25% udvikler hurtigt leversvigt
  - 25% udvikler langsomt leversvigt

Alfa-1-antitrypsin mangel

Behandling

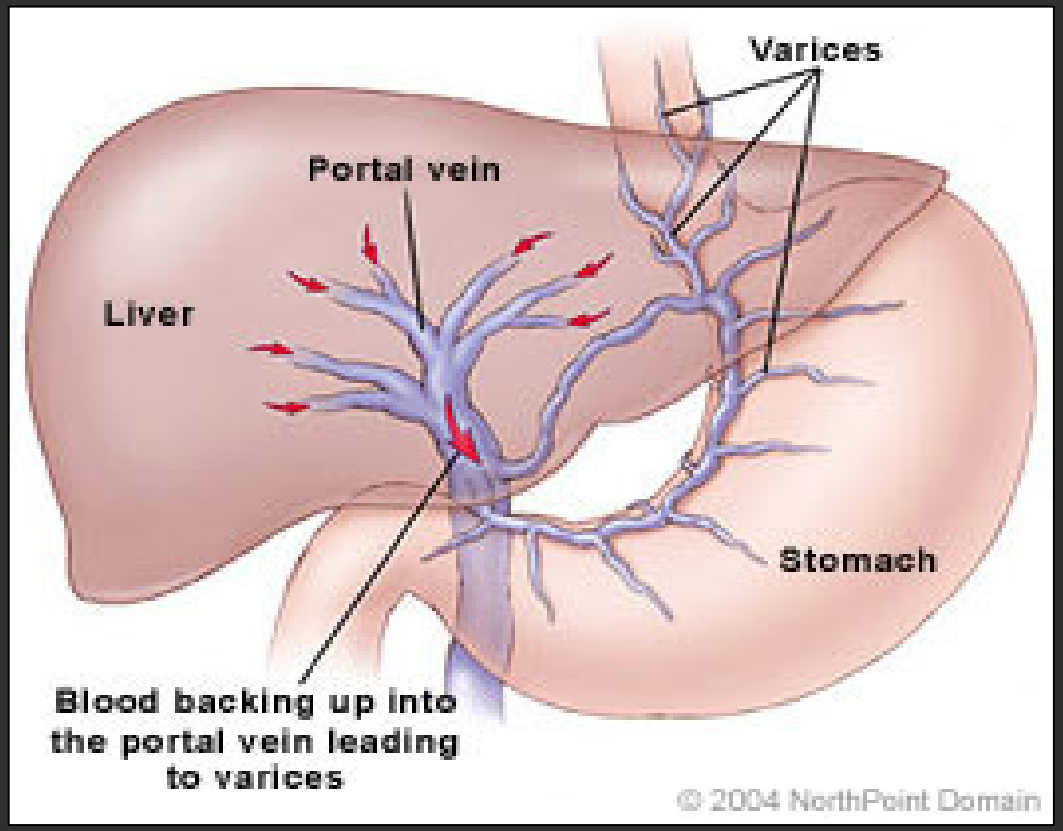
Understøttende behandling

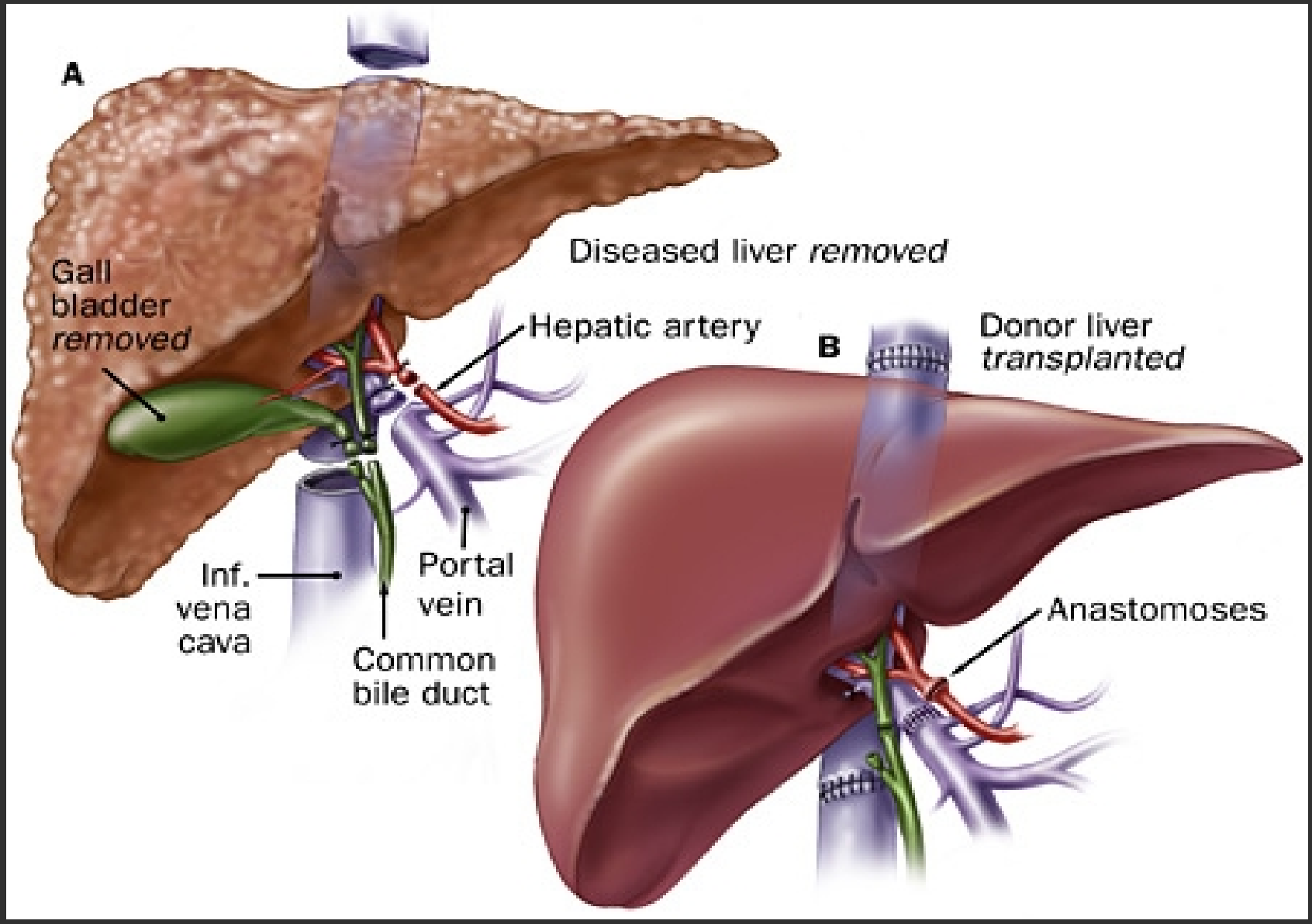
- Optimere ernæring og sikre vækst
  - MCT
  - Aquadeks

Alfa-1 antitrypsin mangel

Undgå komplikationer til leversvigt

PORTAL HYPERTENSION





Levertransplantation ved terminalt leversvigt

Alfa-1-antitrypsin mangel

Erstatningbehandling?

Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease

Peter C Gøtzsche1, Helle Krogh Johansen1

1The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark

Two trials were included (total 140 patients) that ran for two to three years. All patients were ex- or never-smokers and had genetic variants that carried a very high risk of developing chronic obstructive pulmonary disease. Mortality data were not reported. There was no information on harms in the first trial; in the second trial, serious adverse events were reported to have occurred in 10 patients in the active group and in 18 patients in the placebo group. Annual number of exacerbations and quality of life were similar in the two groups; none of the trials reported on average number of lung infections or hospital admissions. Forced expiratory volume in one second deteriorated a little more in the active group than in the placebo group (difference was -20 ml per year; 95% confidence interval

Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease (Review)

-41 to 1; p = 0.06). For carbon monoxide diffusion, the difference was -0.06 mmol/min/kPa per year (95% confidence interval -0.17 to 0.05; p = 0.31). Lung density measured by CT scan deteriorated a little less in the active group than in the placebo group (difference 1.14 g/l; 95% confidence interval 0.14 to 2.14; p = 0.03) over the total course of the trials.

Authors' conclusions

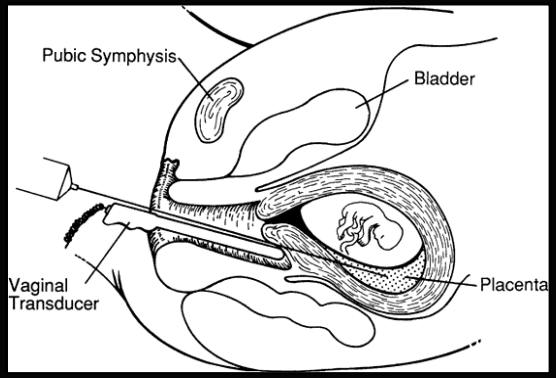
Augmentation therapy with alpha-1 antitrypsin cannot be recommended, in view of the lack of evidence of clinical benefit and the cost of treatment.

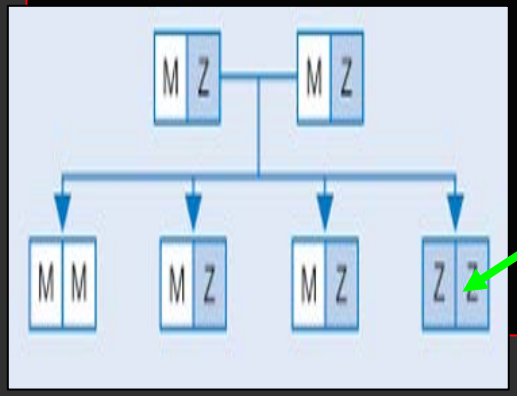
Alfa-1-antitrypsin mangel

Fosterdiagnostik

Moderkagebiopsi

- Meget tidligt i graviditeten
- Sikker diagnose





Alfa-1-antitrypsin mangel

Fremtidig behandling

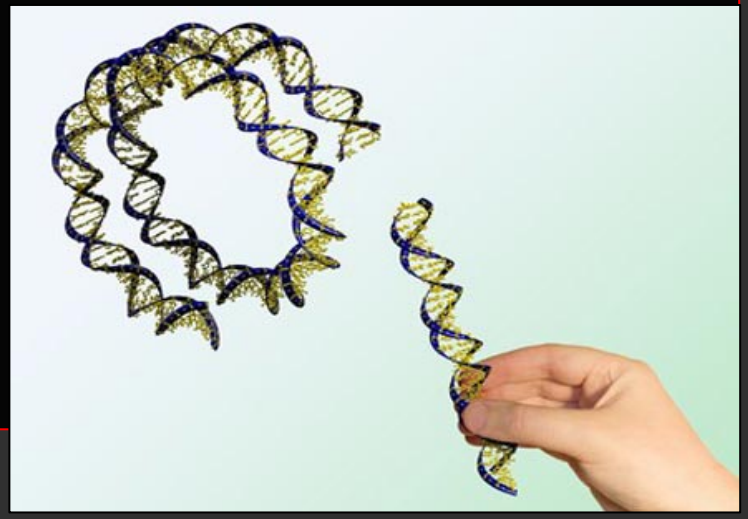
Alfa-1-antitrypsin mangel

Genterapi

- Cellerne tilføres det normale gen

↓

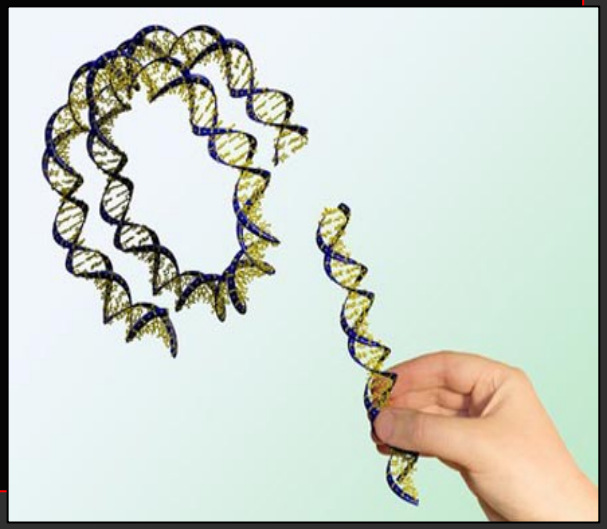
- Normalt genprodukt
- Sygdommen er kureret



Alfa-1-antitrypsin mangel

Genoverførsel med virus (vektor)

- Princip:
- Virus generne bliver en del af cellens DNA
- Det raske gen kopieres sammen med cellens øvrige DNA ved celledeling
- Varig effekt



Alfa-1-antitrypsin mangel

Genterapi

HUMAN GENE THERAPY 22:1239–1247 (October 2011)
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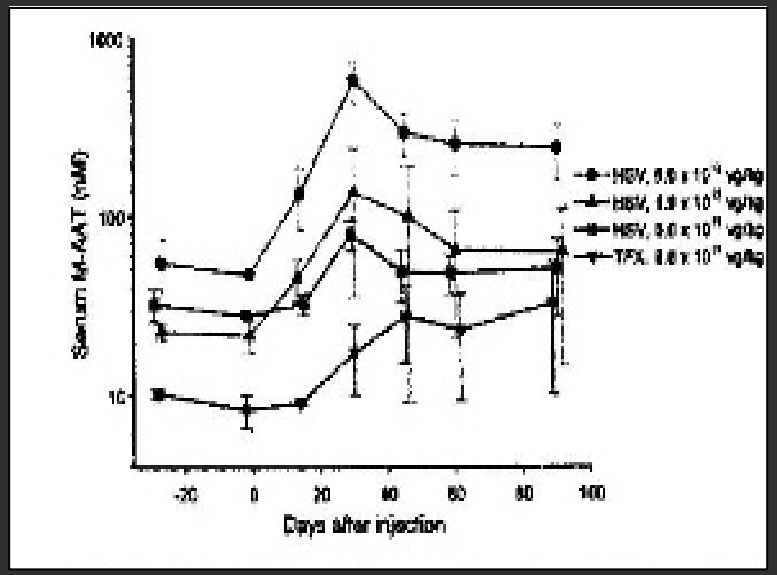
DOI: 10.1089/hum.2011.053

Brief Reports

Phase 2 Clinical Trial of a Recombinant Adeno-Associated Viral Vector Expressing α_1-Antitrypsin: Interim Results

Terence R. Flotte,[1] Bruce C. Trapnell,[2] Margaret Humphries,[2] Brenna Carey,[2] Roberto Calcedo,[3] Farshid Rouhani,[4] Martha Campbell-Thompson,[4] Anthony T. Yachnis,[4] Robert A. Sandhaus,[5] Noel G. McElvaney,[6] Christian Mueller,[1] Louis M. Messina,[1] James M. Wilson,[3] Mark Brantly,[4] David R. Knop,[7] Guo-jie Ye,[7] and Jeffrey D. Chulay[7]



Alfa-1-antitrypsin mangel

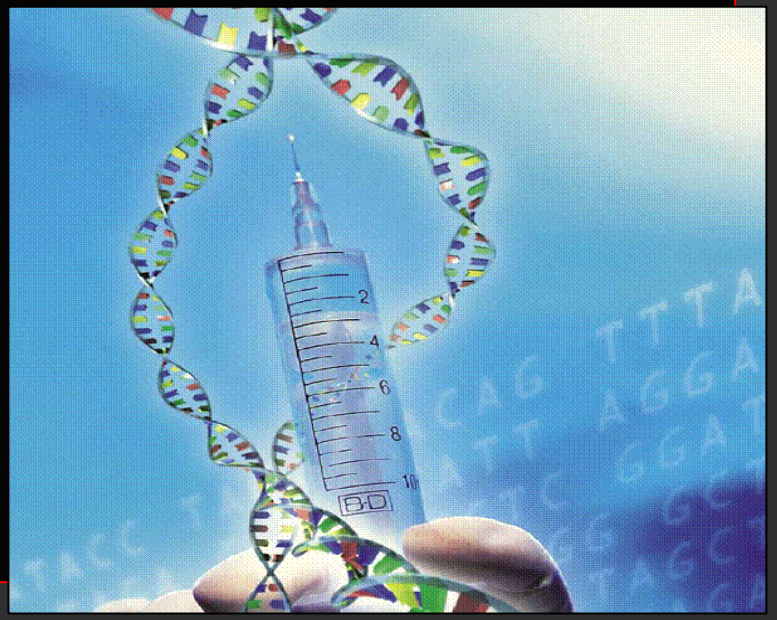
Genterapi

- Aktuel status
  1. Sikker og mulig behandling
  2. Lineær dosis – respons effekt
  3. Fortsatte studier er nødvendige for at opnå terapeutisk alfa-1-antitrypsin niveau

Alfa-1-antitrypsin mangel

Genoverførsel med virus (vektor)

- Udfordringen:
- Ikke alle vira kopieres ved celledeling
- Vira kan kun transportere små DNA stykker



Aktuelle tiltag

- National database

- Centralisering af kontrol og behandling

Tak for opmærksomheden