(semi)personalized antisense oligonucleotide treatments for otogenetic disorders

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Otogenetic disorders

- 430 million people suffer from disabling hearing loss (> 35 dB)
- ~50% has an underlying genetic cause
- Highly heterogeneous
- Syndromic vs non-syndromic
- Different modes of inheritance

Hearing aids and cochlear implants often fall short

(semi)personalized treatments

For genetic disorders, gene or genetic therapies are (becoming) reality

- Mutation-specific and individual therapies for inherited disorders will be extremely expensive
- No market potential for ultra-rare mutations and individual therapies
- Finding the right balance with semi-personalized treatments

Antisense oligonucleotides (ASO), and RNA technology in general offer interesting treatment options -> no genetic manipulation

Two examples with different ASO mechanisms:

- Usher syndrome
- DFNA9 hearing loss

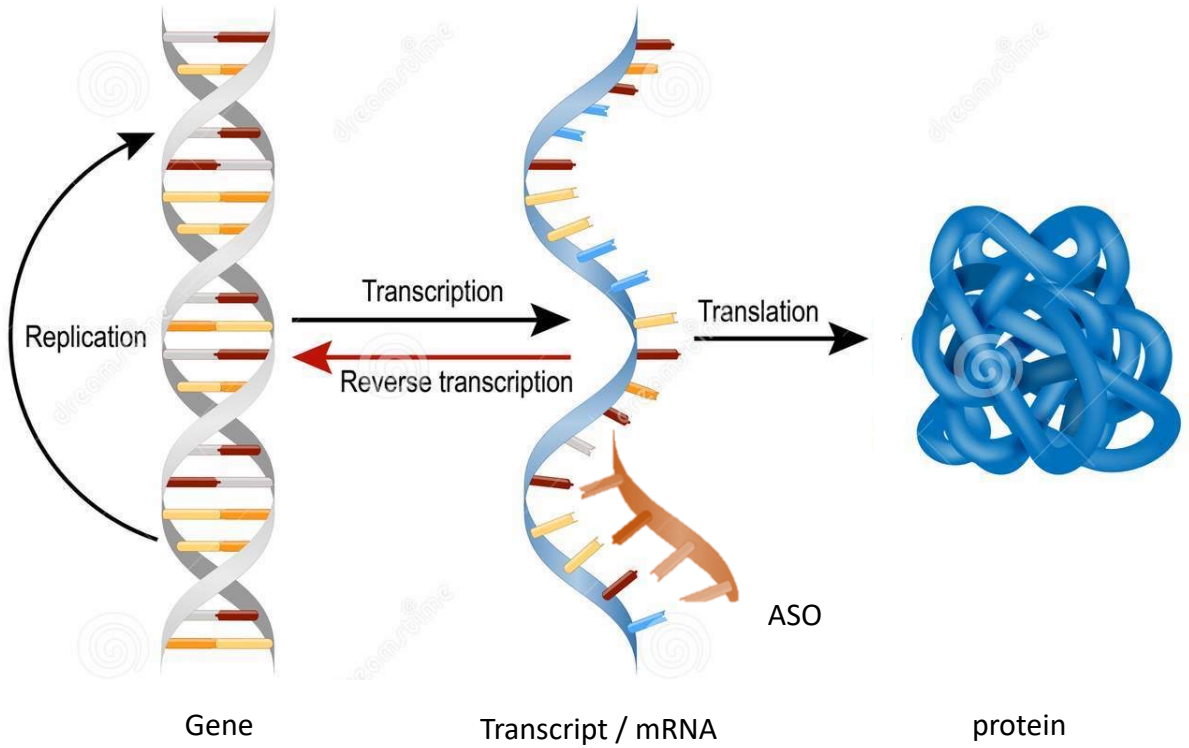
Antisense oligonucleotides

- Chemically modified, single stranded RNA or RNA/DNA molecules (16-25nt in lenght)
- Complementary to (pre-)mRNA
- Proven safety in animal models and man (several ASOs have FDA/EMA approval)

<u>Upon ASO binding:</u>

Alter pre-mRNA splicing

Sequence specific mRNA degradation



Two examples

Two examples, using distinct ASO mechanisms of action

1. Usher syndrome
2. DFNA9 hearing loss

Part 1: Usher syndrome

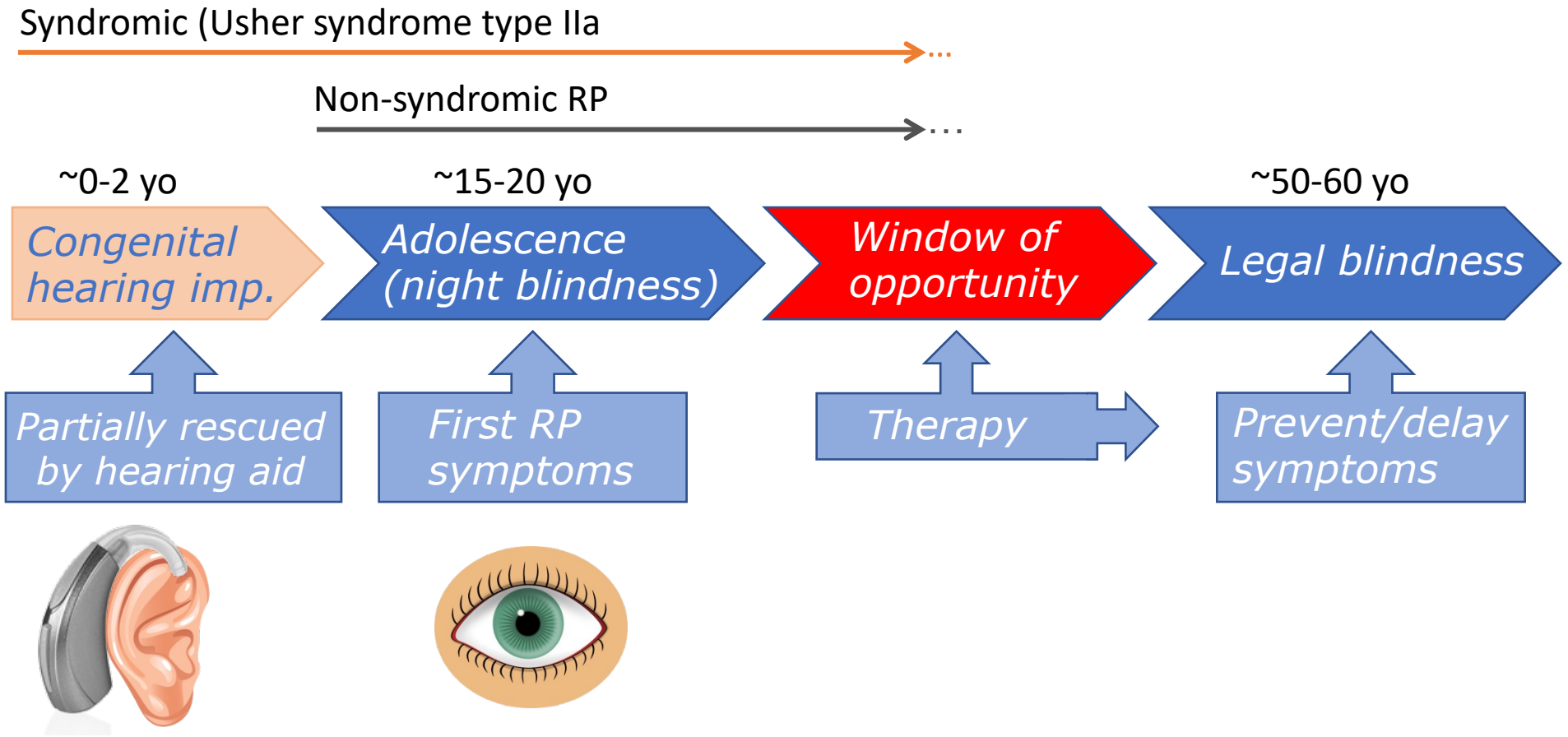
- Most common cause of combined hereditary deaf-blindness in man
- Rare condition: 1/20,000

- Autosomal recessively inherited disorder
- Genetically and clinically heterogeneous

- Loss-of-Function disease mechanism

Charles Howard Usher

Window for interventions

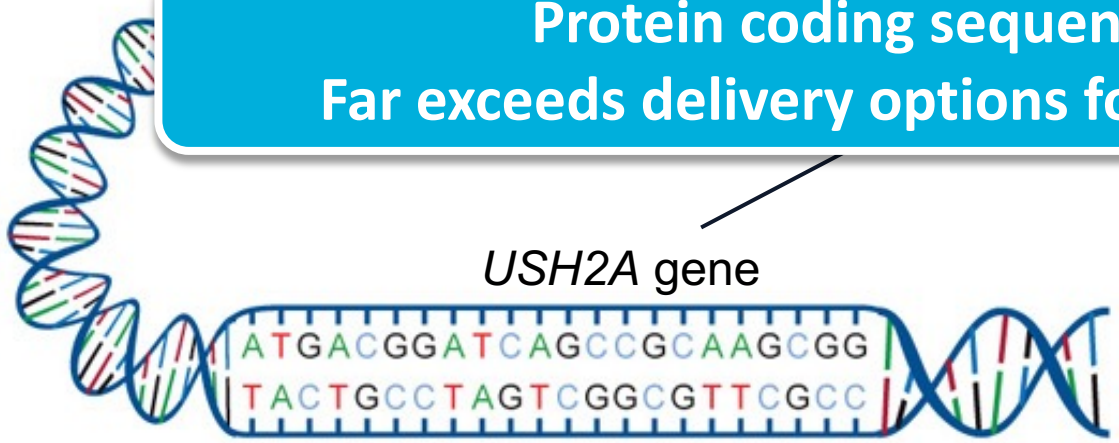


Most important genetic cause

~170.000 people

Protein coding sequence of 15.6 kb!
Far exceeds delivery options for gene augmentation

USH2A gene



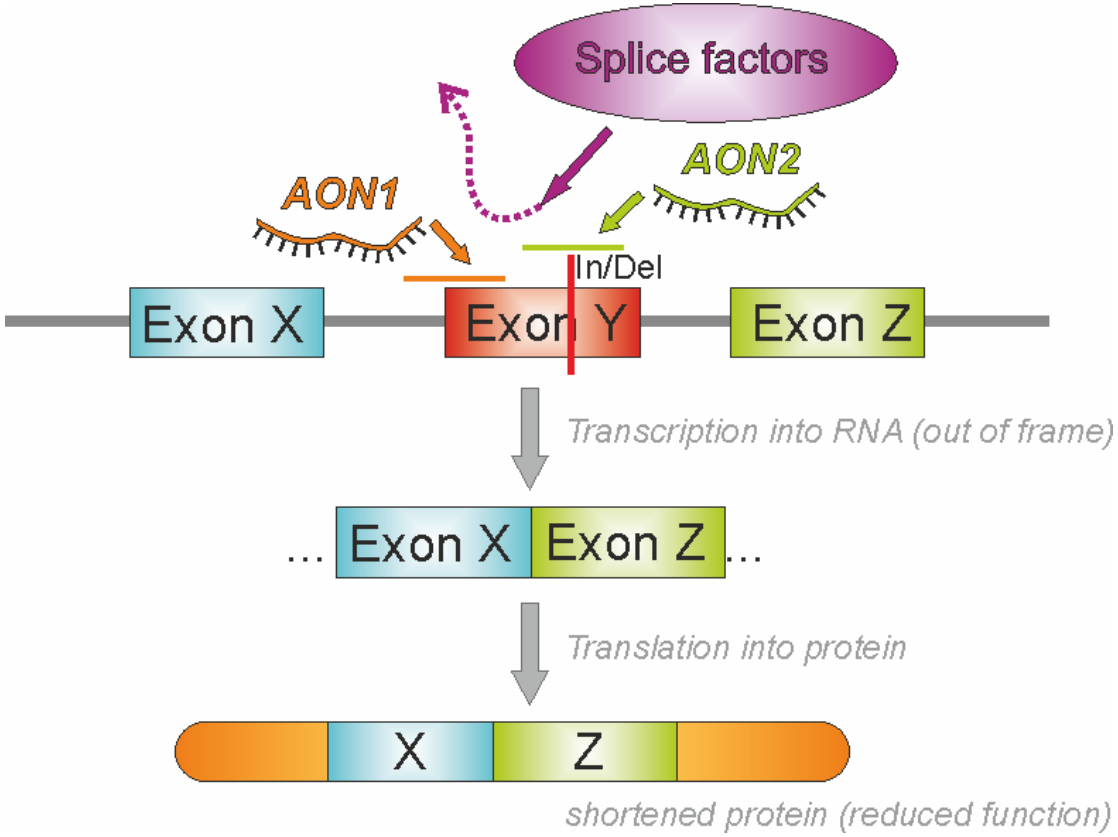
~250.000 people

ASO action: splice-modulation

Sequence-specific ASOs interferes with binding of splice factors

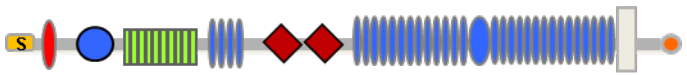
Results in skipping of target exon

- Exclude mutant exons
- Correct pre-mRNA splicing defects
- Exclude pseudoexons



Exon skipping

mRNA **Protein** **Function ?**



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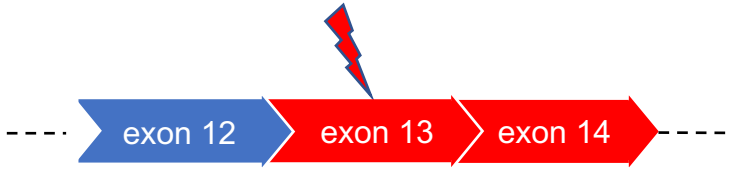
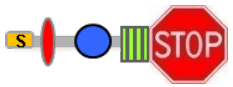
2 founder LoF mutations (24 unique pathogenic variants)





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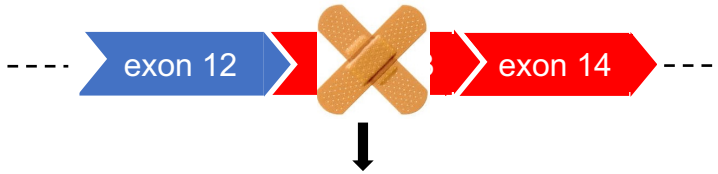
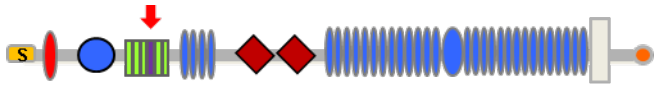


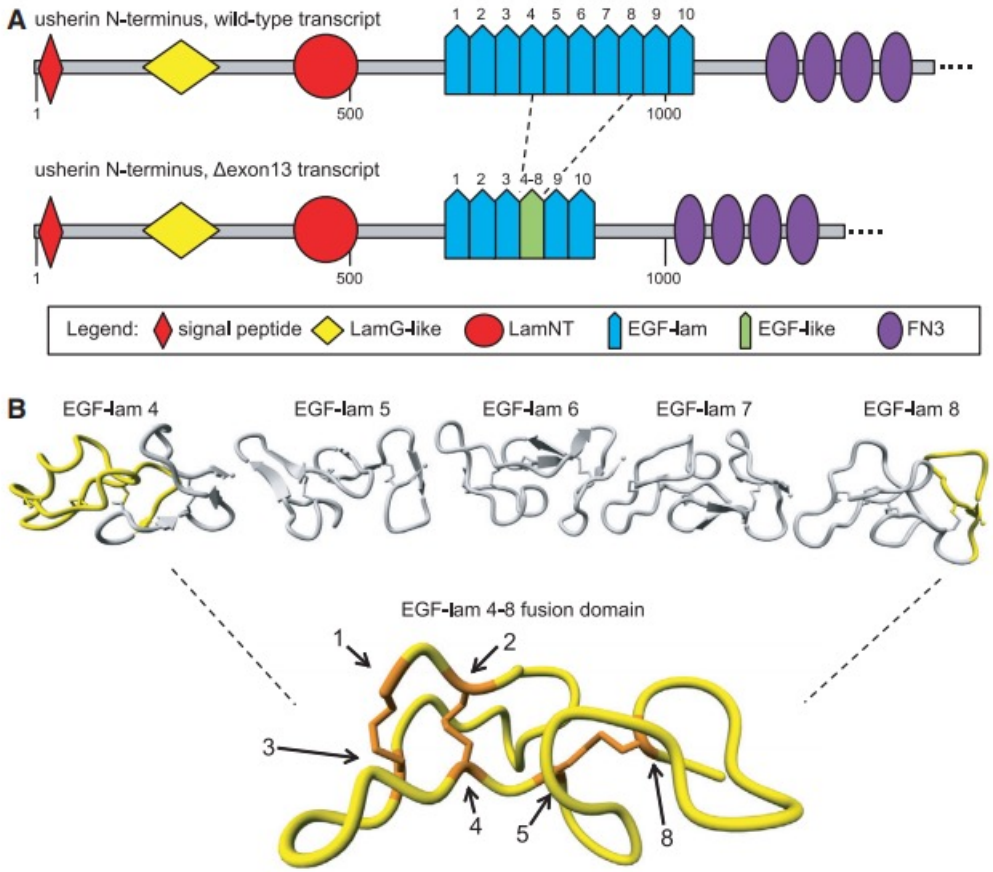
In frame skipping



+ ?

Is USH2A Δexon 13 functional?

In silico prediction of resulting protein domains



EGF Lam domains 5, 6 and 7 are lost

Fusion of EGF Lam domains 4 and 8 into a functionally related EGF-like domain