Genetics of Alström Syndrome

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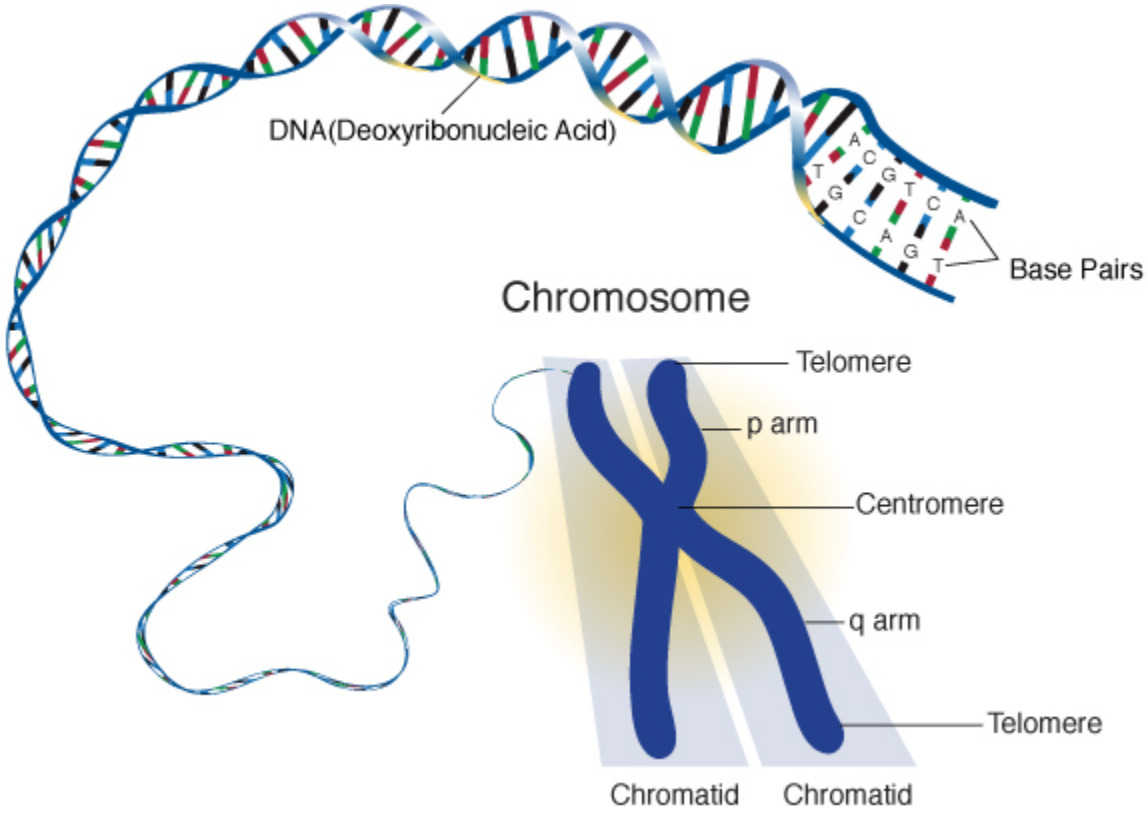
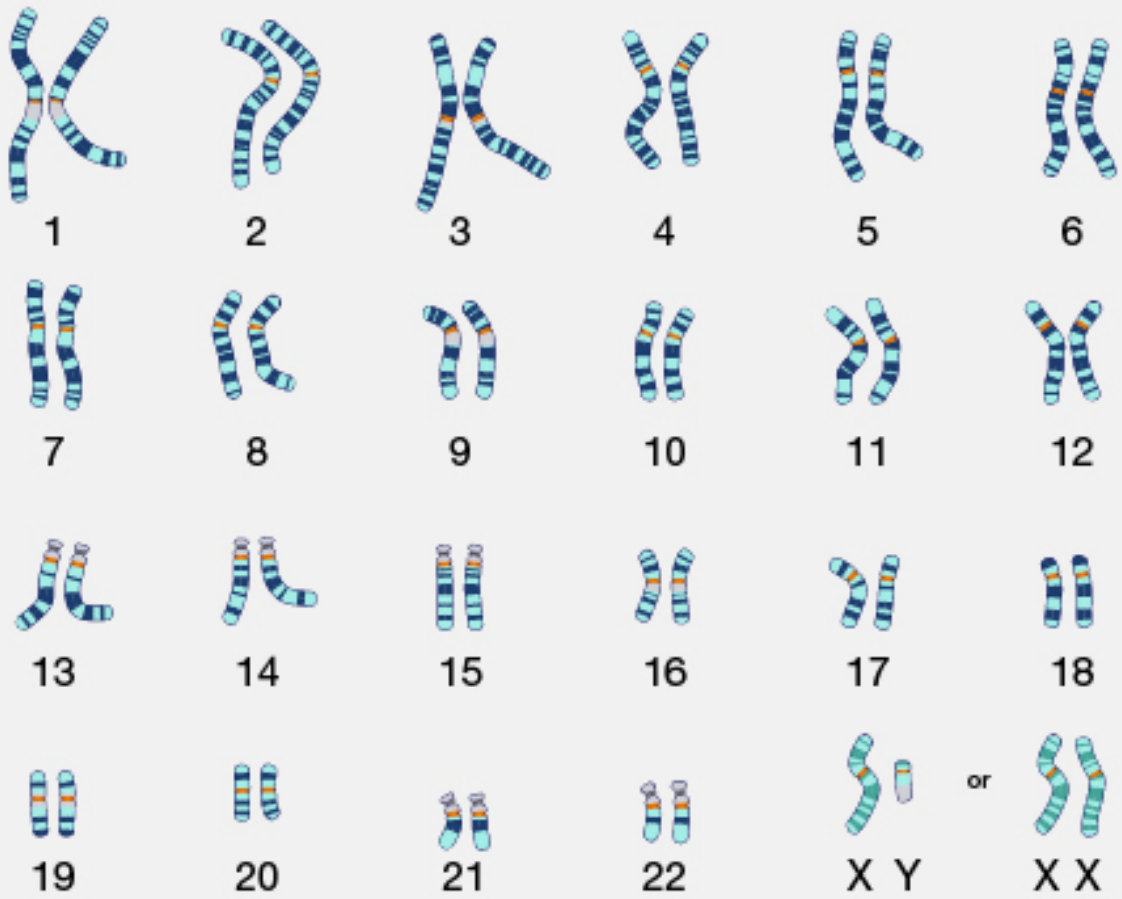
The Stuff of Inheritance: DNA, Genes and Chromosomes



The Human Body Has ....

- 30 Trillion Cells
- Each cell has 46 chromosomes (23 pairs)
- Chromosomes 1-22 are the same in males and females
- Males have an X and Y chromosome (XY)
- Females have two X chromosomes (XX)


1
2
3
4
5
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8
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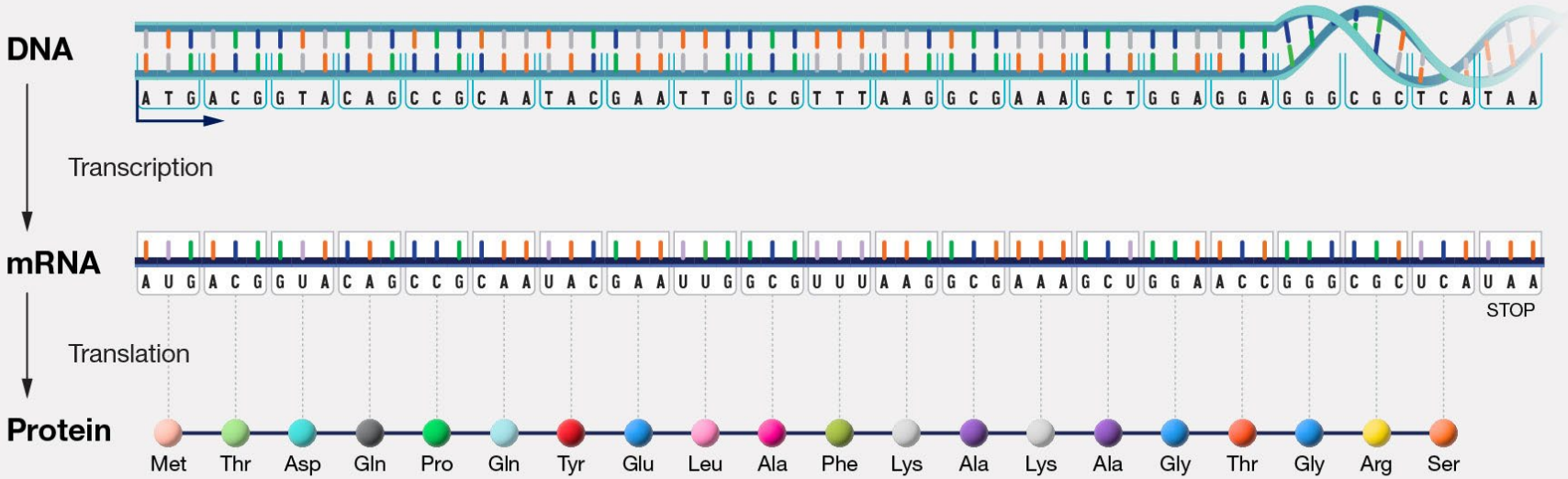
10
11
12
13
14
15
16
17
18
19
20
21
22
X Y
or
X X

Genes

- Are segments of DNA that encode a protein
- Have a designated “address” on the human chromosomes
- Are transcribed in messenger RNA
- Messenger RNA is then translated into protein

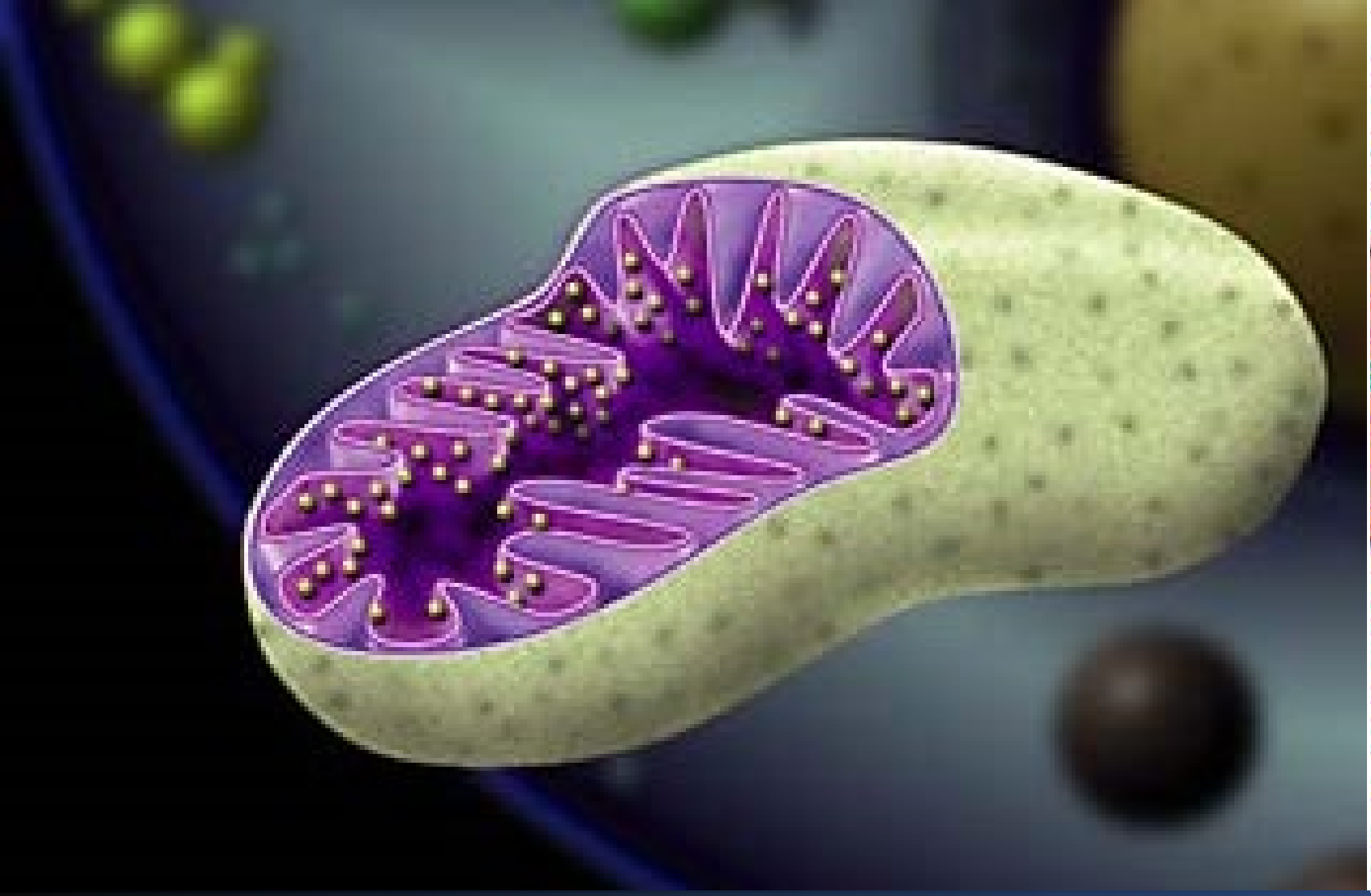

DNA
A T G A C G G T A C A G C C G C A A T A C G A A T T G G C G T T T A A G G C G A A A G C T G G A G G A G G G C G C T C A T A A
Transcription
mRNA
A U G A C G G U A C A G C C G C A A U A C G A A U U G G C G U U U A A G G C G A A A G C U G G A A C C G G G C G C U C A U A A
STOP
Translation
Protein
Met Thr Asp Gln Pro Gln Tyr Glu Leu Ala Phe Lys Ala Lys Ala Gly Thr Gly Arg Ser

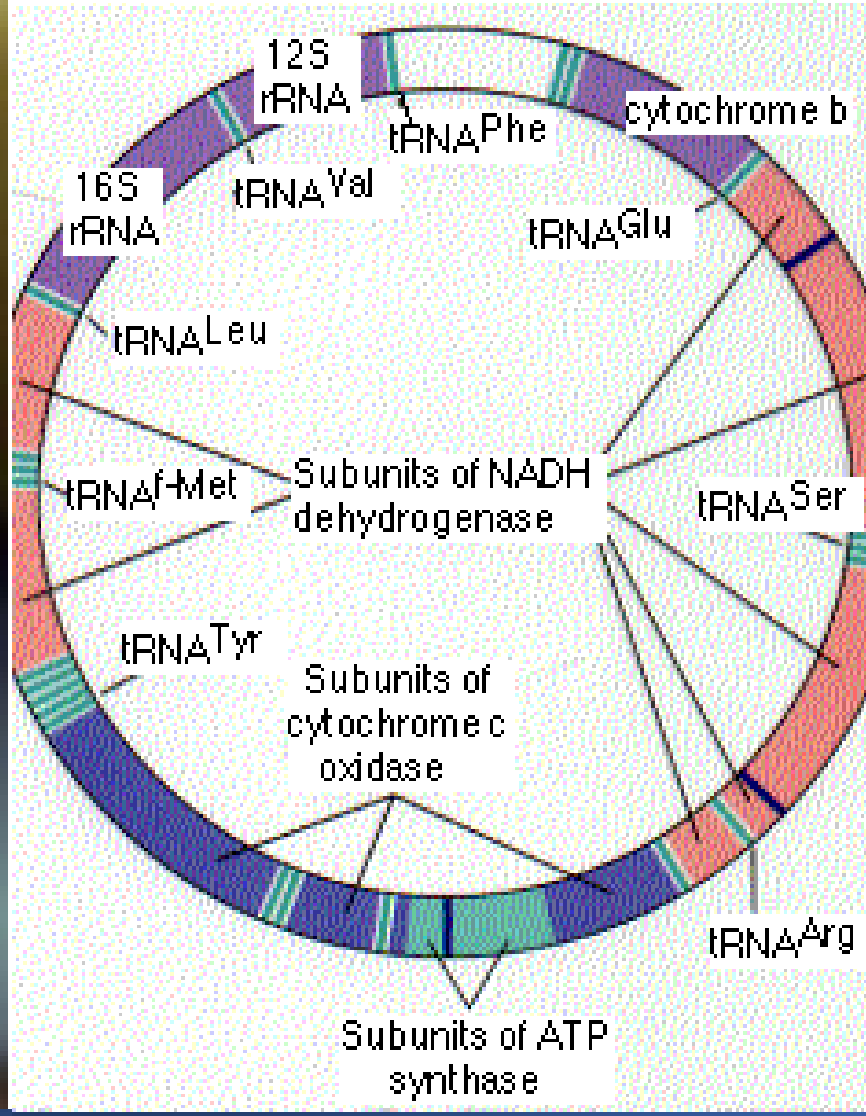
Mendelian Patterns in Human Inheritance

Autosomal Dominant

Autosomal Recessive

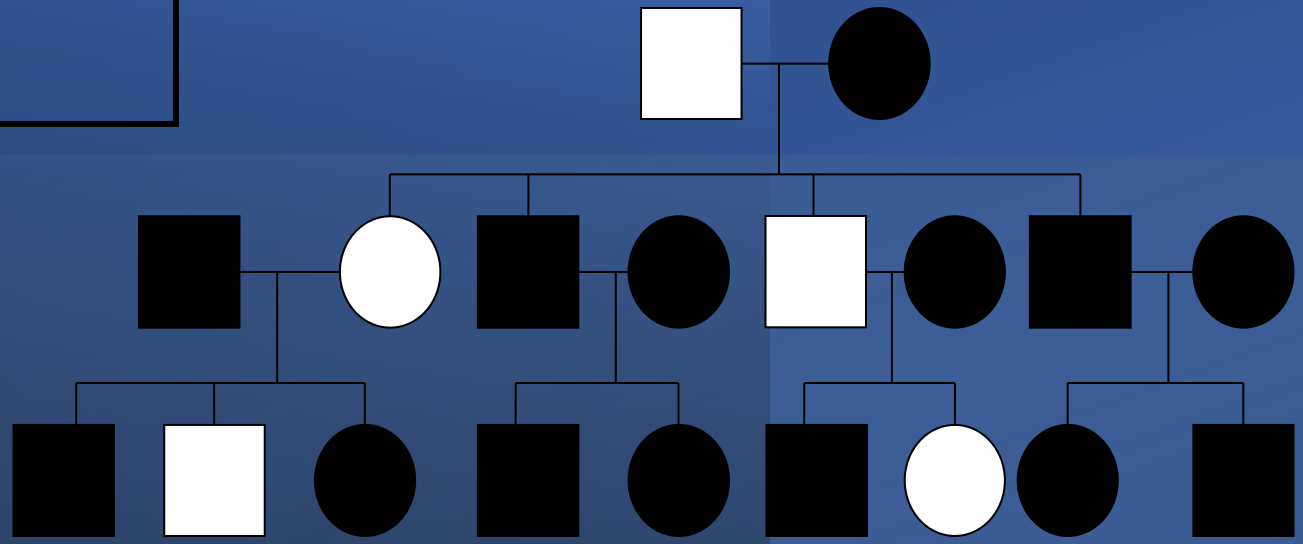
X-linked





Mitochondrial Genome

Autosomal Dominant Inheritance



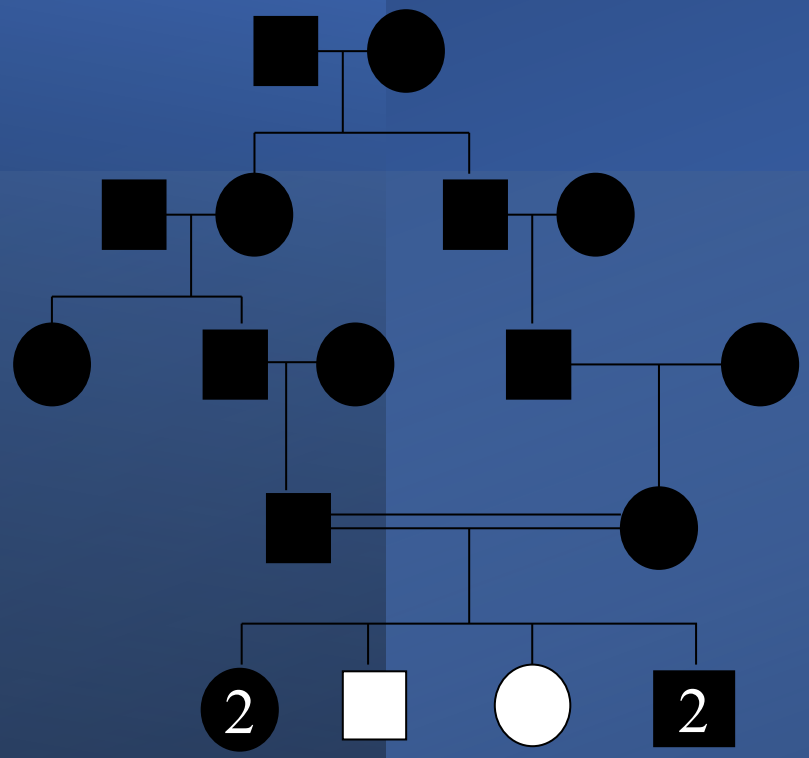
- Vertical transmission – typically, the phenotype appears in every generation
- Approximately equal numbers of males and females are affected
- Male to male transmission is present
- Affected parent has 50% chance of transmitting the trait to each offspring

Adapted from The Pedigree: A Basic Guide, by Jorgenson, Yoder and Shapiro

Autosomal Recessive Inheritance

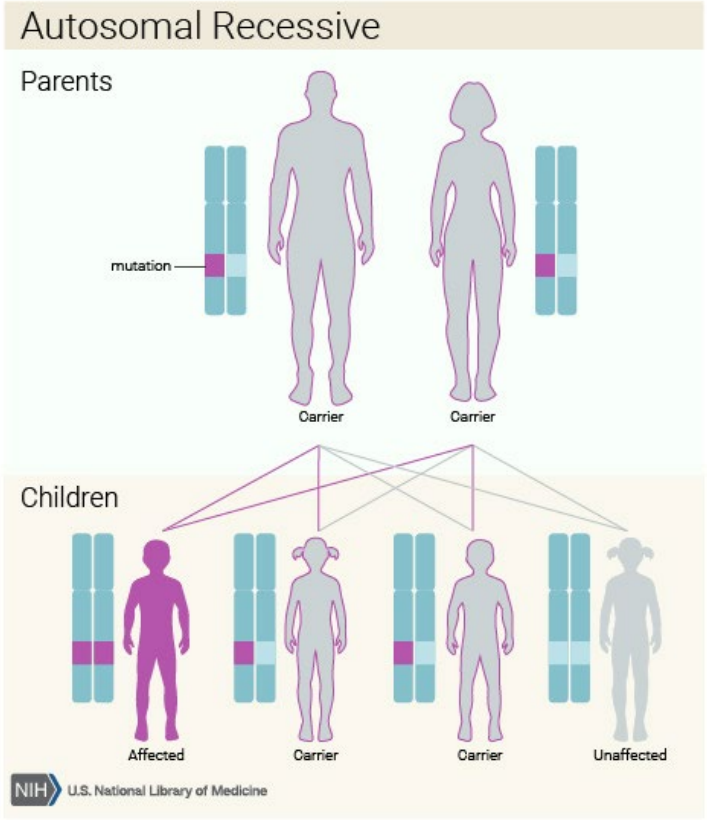
- Horizontal pattern in pedigrees
- # of Males ~ # of Females
- Consanguinity is increased among families with recessive disorders
- Offspring of two heterozygous parents
  - 25% risk of being affected
  - 50% risk of being a carrier
  - 25% risk of being a non-carrier

  2/3 of unaffected offspring are carriers



Adapted from The Pedigree: A Basic Guide, by Jorgenson, Yoder and Shapiro

Alström Syndrome is Inherited as an Autosomal Recessive Condition



Alström Syndrome is Caused by Variants in the ALMS1 Gene

- ALMS1 is on the short arm of chromosome 2
- The product of the gene plays a role in many functions, including:
  - energy metabolism homeostasis
  - cell differentiation
  - ciliary signaling pathways
  - cell cycle control
  - intracellular trafficking (movement of molecules between cells

Mutations in *ALMS1* cause obesity, type 2 diabetes and neurosensory degeneration in Alström syndrome

Gayle B. Collin[1], Jan D. Marshall[1], Akihiro Ikeda[1], W. Venus So[2], Isabelle Russell-Eggitt[3], Pietro Maffei[4], Sebastian Beck[5], Cornelius F. Boerkoel[6], Nicola Sicolo[4], Mitchell Martin[2], Patsy M. Nishina[1] & Jürgen K. Naggert[1]

Published online: 8 April 2002, DOI: 10.1038/ng867

The ALMS1 Gene

Molecular Findings in Alström Syndrome: 2007

- 250 individuals from 206 unrelated families
- “Hot spots” for variation were seen in exon 16, exon 10 and exon 8
- Most common pathogenic variant was a 1 bp deletion (12 %)
- Variants in exon 16 seemed to cause a more severe phenotype
- Variants in exon 8 were associated with absent, mild or delayed kidney involvement

Marshall et al. (2007)

OPEN ACCESS

Original research

Genotype–phenotype associations in Alström syndrome: a systematic review and meta-analysis

Brais Bea-Mascato [1,2] Diana Valverde[1,2]

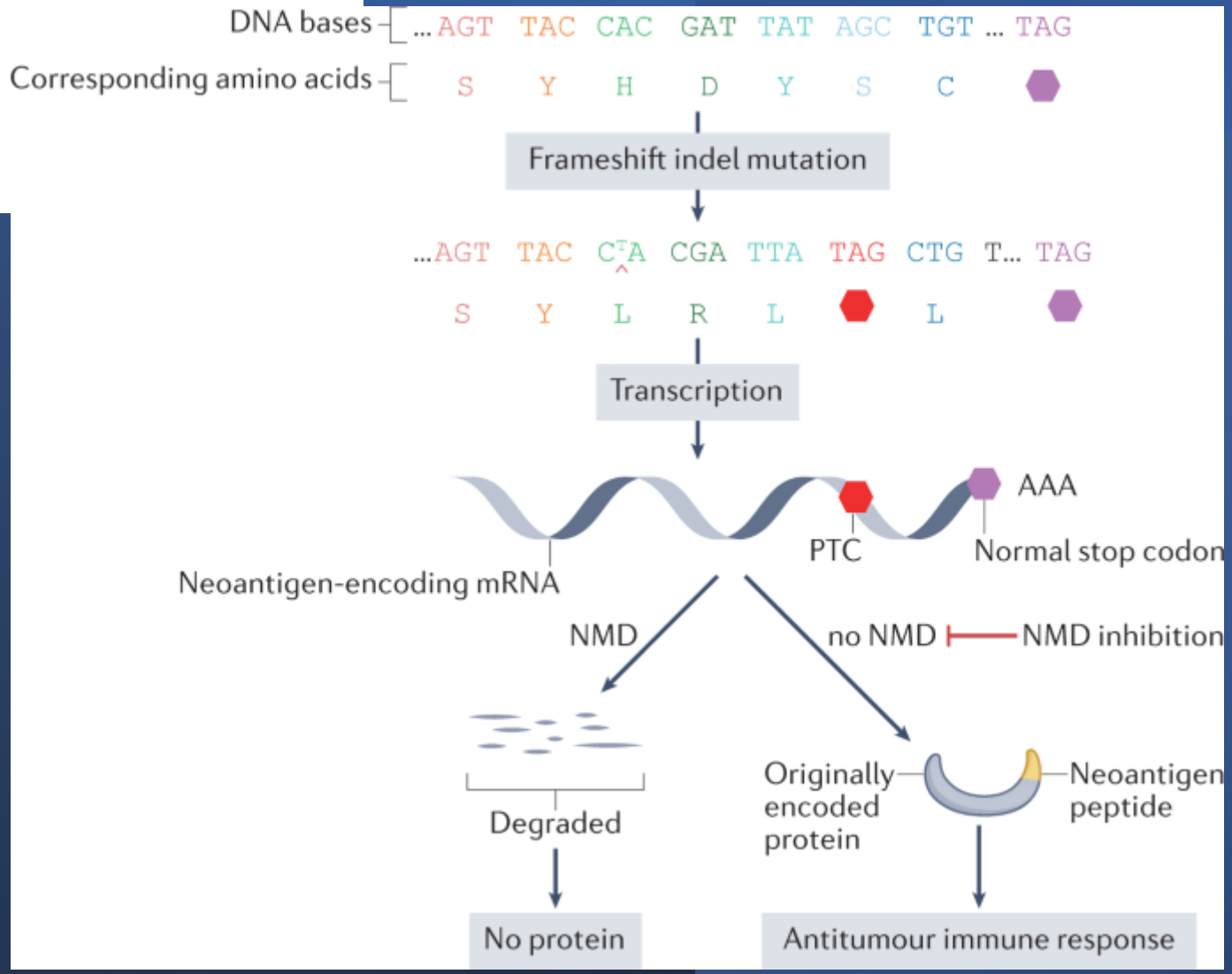
- Most of the variants associated with Alström Syndrome cause complete loss of function of the ALMS1 protein
- Most of the disease-causing variants are found in exons 8, 10 and 16 of the ALMS1 gene
- Pathogenic variants in exon 10 were associated with a higher prevalence of liver disease
- Variants causing truncation of the mRNA before exon 9 or after exon 14 were associated with lower severity scores

Review Article | Published: 27 May 2022

Nonsense-mediated RNA decay: an emerging modulator of malignancy

Kun Tan, Dwayne G. Stupack & Miles F. Wilkinson

Nature Reviews Cancer **22**, 437–451 (2022) | Cite this article



Genotype-Phenotype Correlations

- Most of the disease-causing variants are found in exons 8, 10 and 16 of the ALMS1 gene
- Pathogenic variants in exon 10 were associated with a higher prevalence of liver disease
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Bea-Mascato and Valverde, 2023

Differences among us: Why??

Differing biologic consequences of different pathogenic variants

Gene-gene interactions

Gene-environment interactions


Thank you for
your attention!