



PCD Genetik

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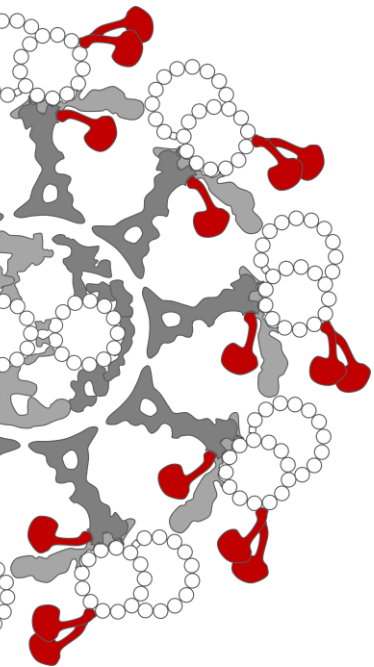
UMR_S933 "Childhood genetic diseases"

Sorbonne Université, Inserm – Prof. Serge Amselem

Hôpital Armand Trousseau, Paris, France



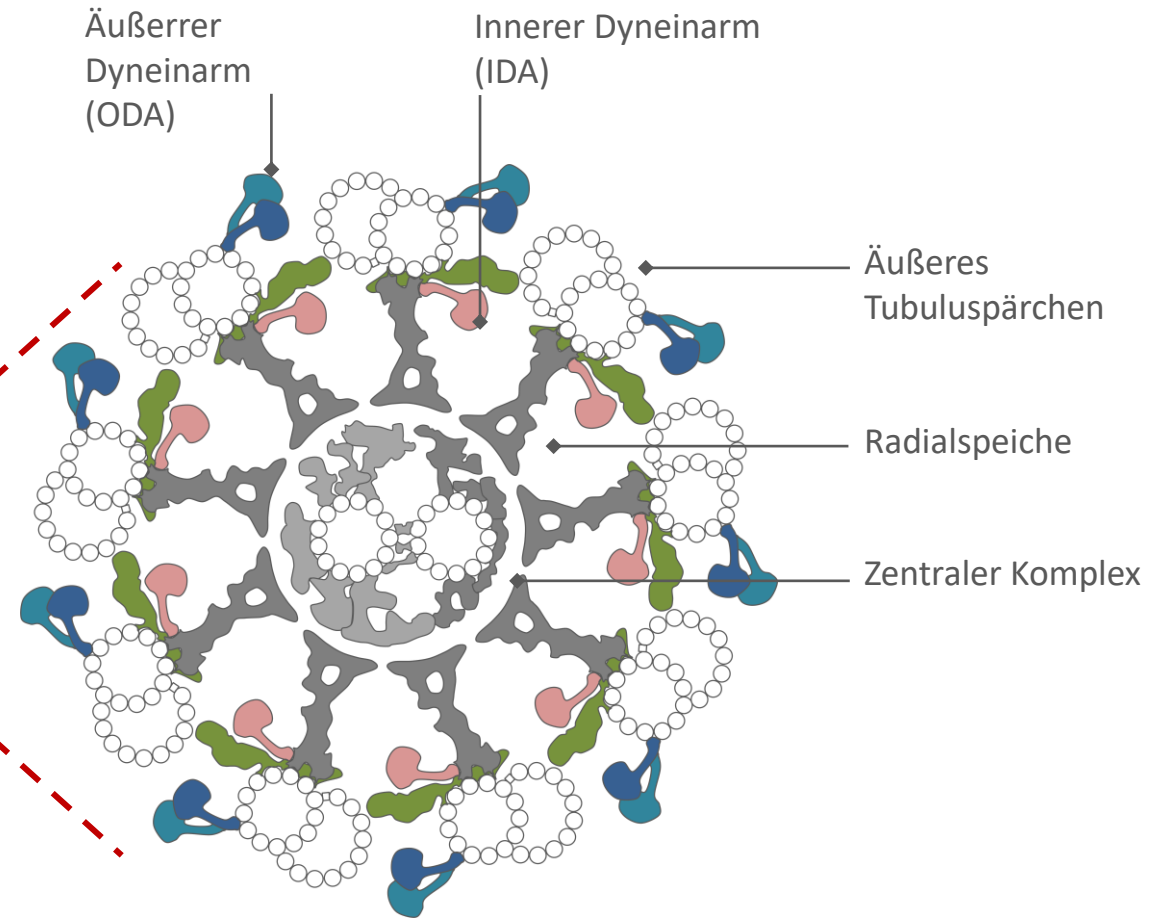
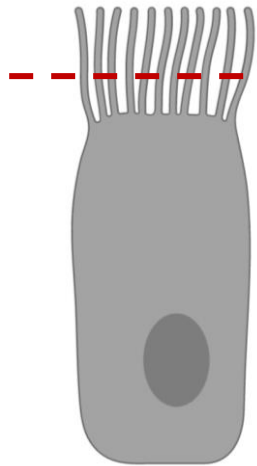
Basics



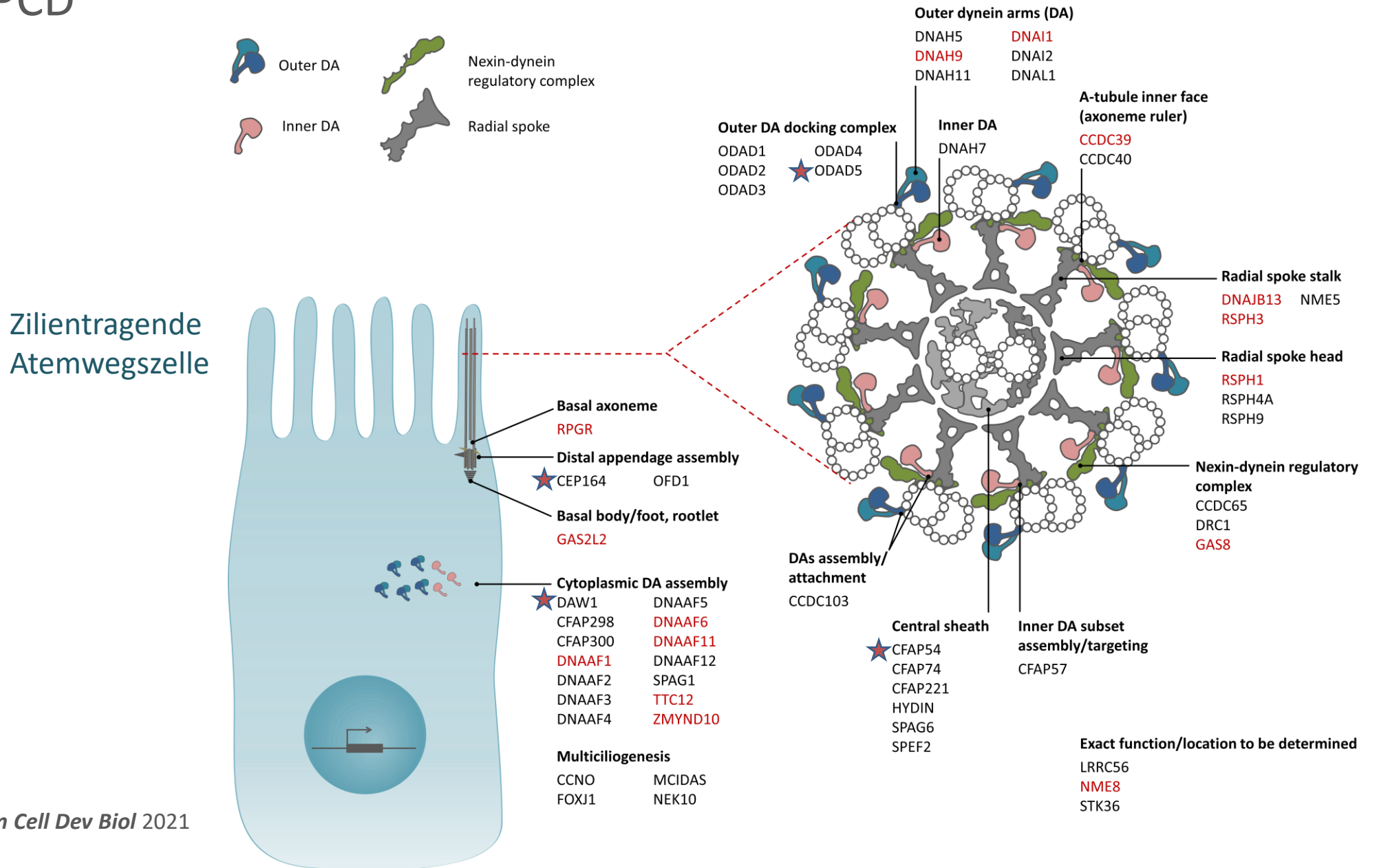
Axoneme von Zilien und Flagellen

Atemwege
Eileiter
Samenleiter

Spermien



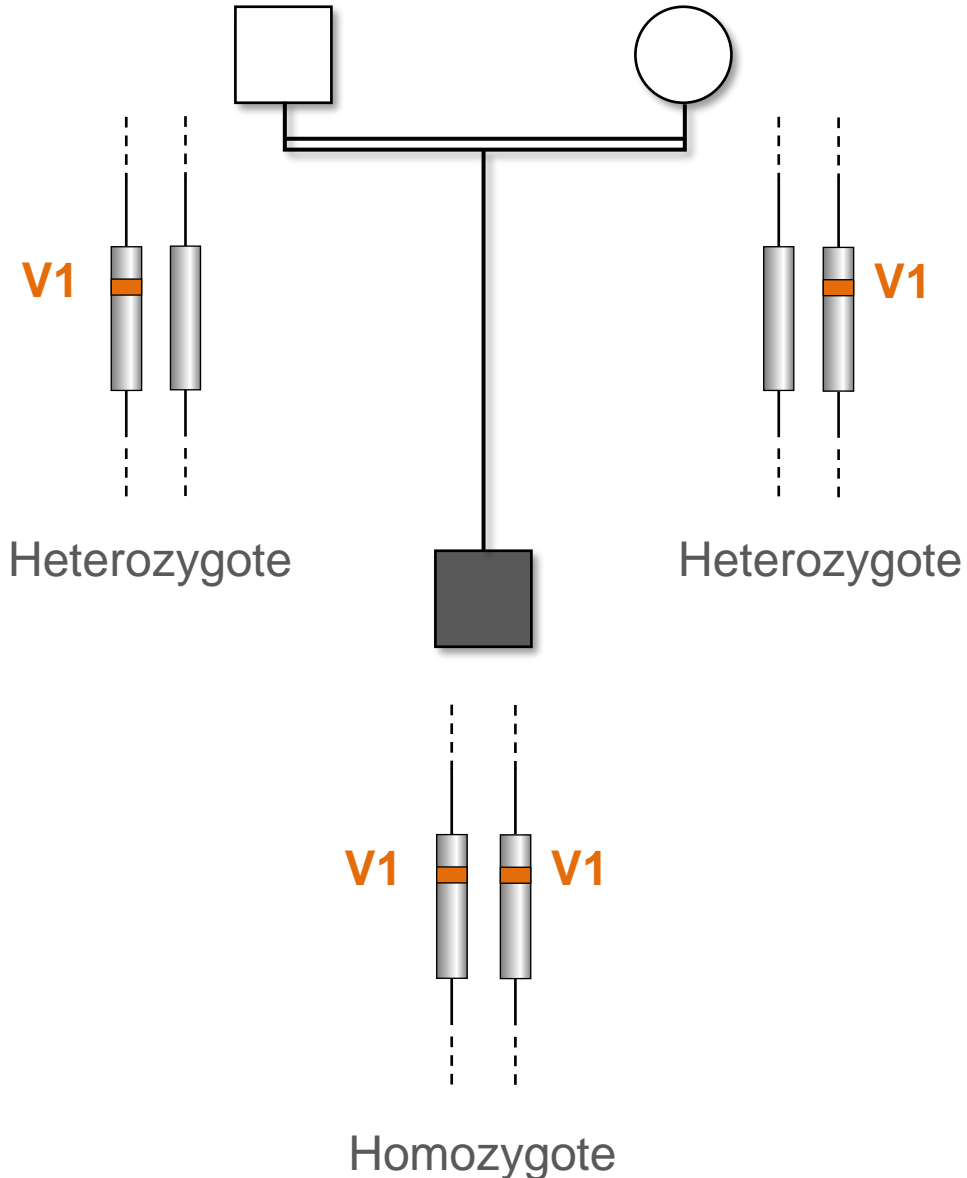
Gene der PCD



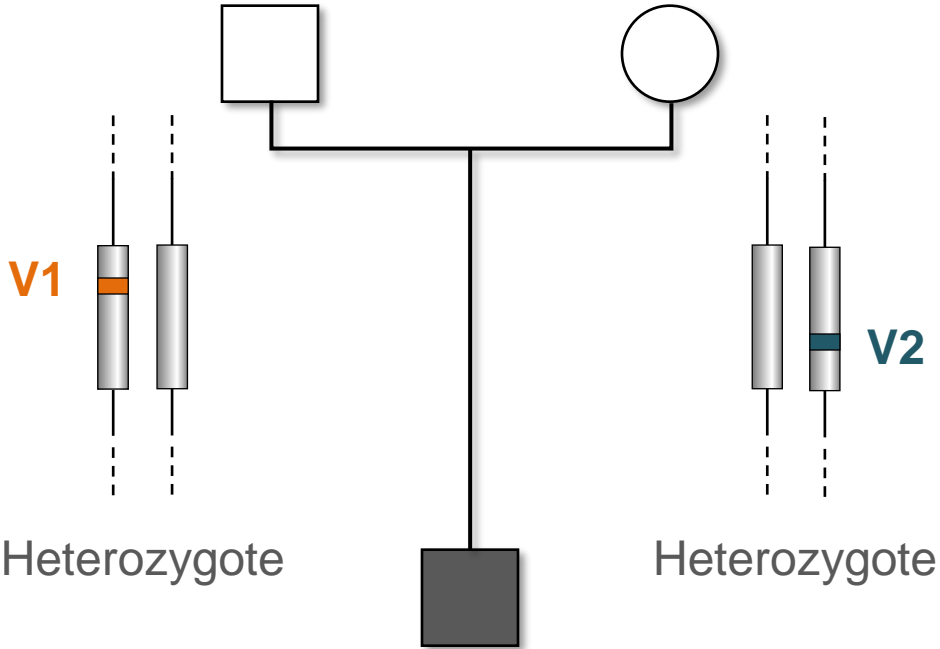
Aus Legendre et al. *Semin Cell Dev Biol* 2021

Vom Team adaptiert

Rezessive Erkrankungen

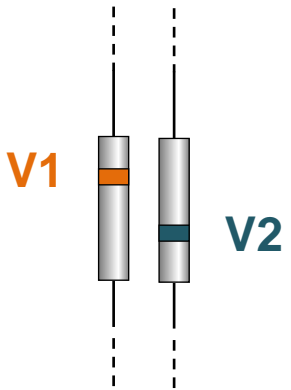


Rezessive Erkrankungen



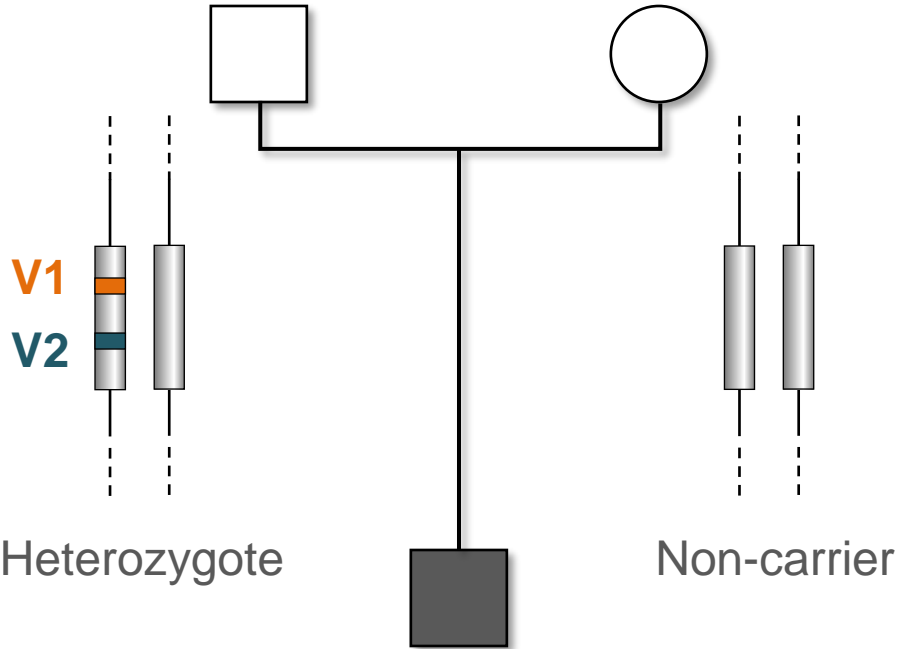
Heterozygote

Heterozygote



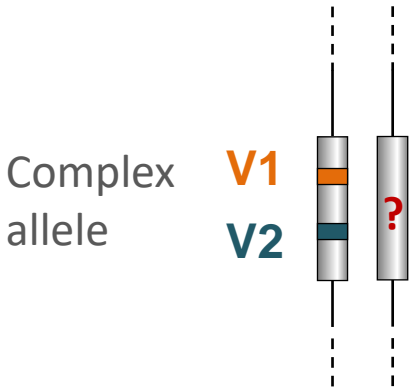
Compound heterozygote

or



Heterozygote

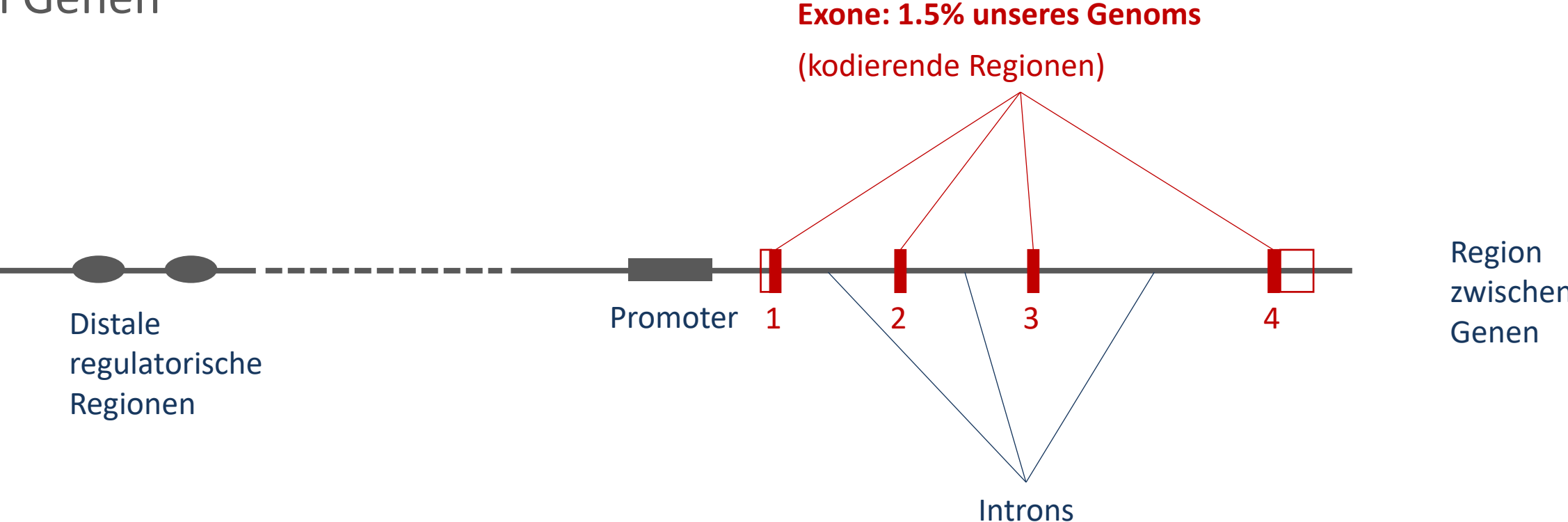
Non-carrier



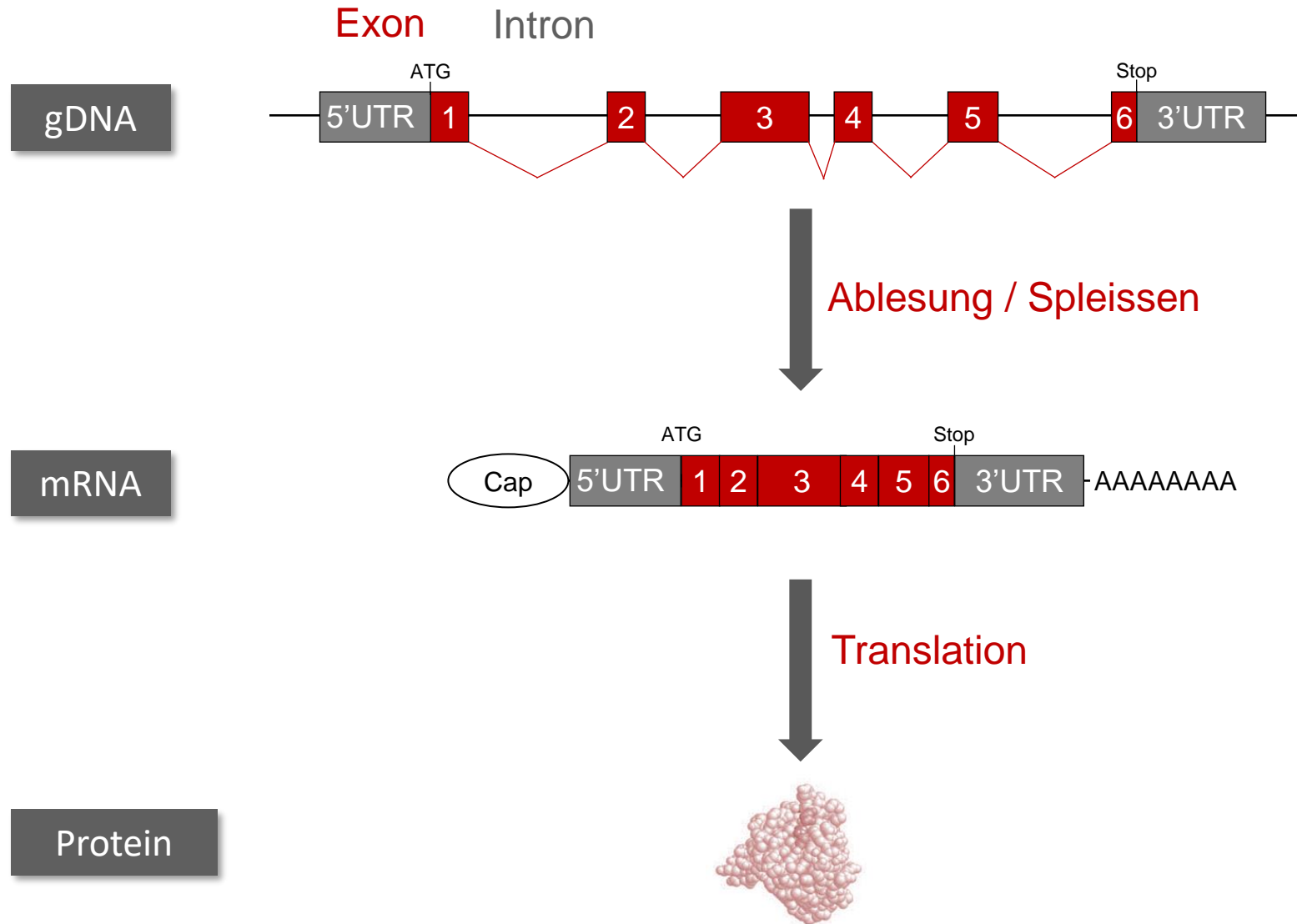
Complex allele

Heterozygote

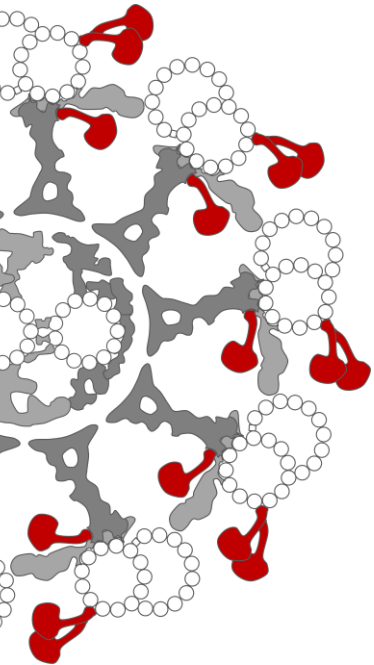
Allgemeine Struktur von Genen



Vom Gen zum Eiweiß (Protein)

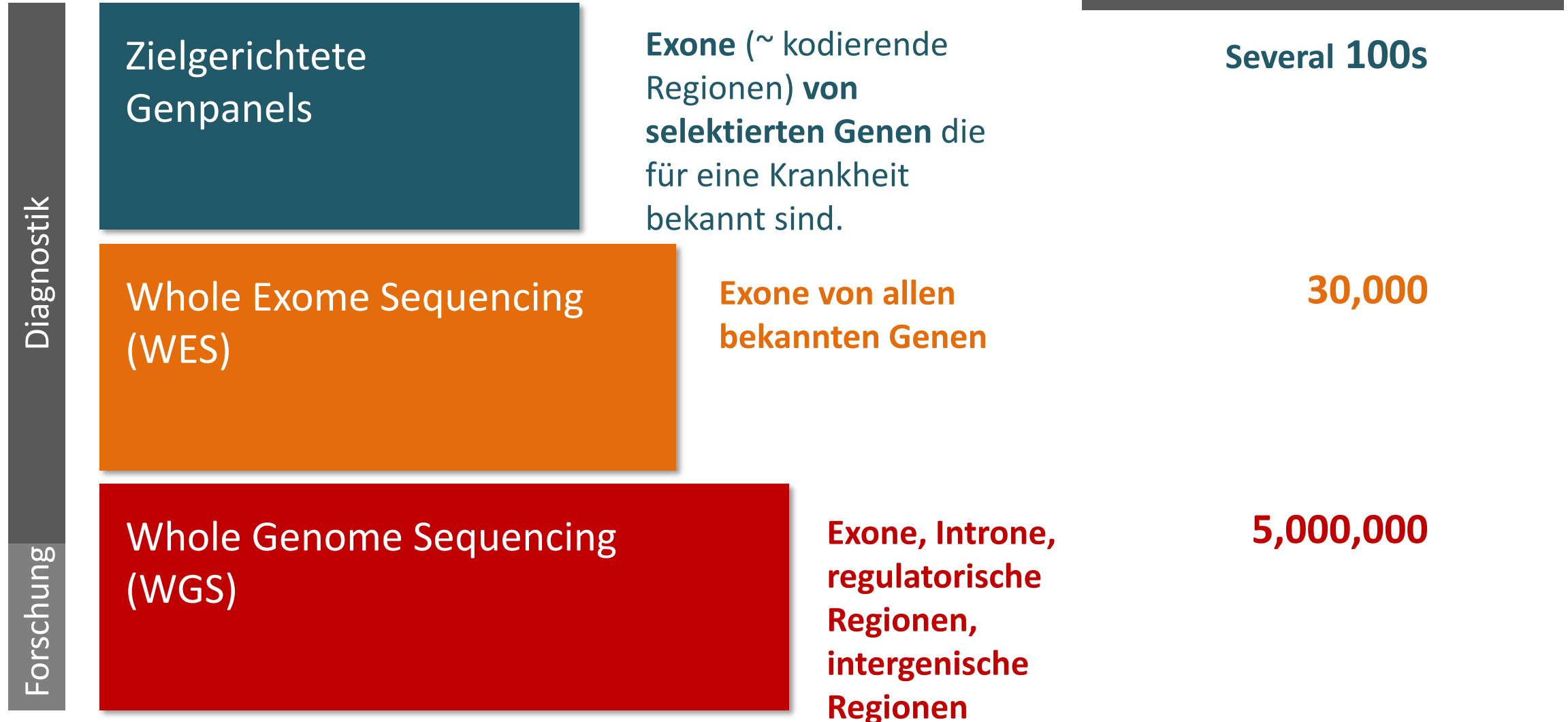


Unsere Genome sind vielfältig



Next-Generation Sequencing (NGS)

Anzahl der Variationen
pro Person



Exomesequenzierung = Alle Exone eines Patienten

1 Patient

Exom-
analyse

30,000 Variationen / Referenzgenom

3,000 seltene oder nicht
beschriebene in der allgemeinen
Bevölkerung

300 potentiell krankmachend

100 synonyme Varianten

300 « missense »

7 « nonsense »

5 Spleissvarianten

1 Leserahmenverschiebung

10-100 = Krankheitsverursachende Varianten

Variation classification

Class 5

Pathologisch

Genetische Beratung

Class 4

Wahrscheinlich Pathologisch

Class 3

Unklare Bedeutung (VUS)

Keine genetische
Beratung

Class 2

Wahrscheinlich gutartig

Class 1

gutartig

Das Finden der relevanten pathogenen Varianten unter hunderten Varianten.

Pathogene Variante in einem relevanten Gen

An illustration of a dense, dark green jungle scene. Various animals like a sloth, a monkey, and a jaguar are visible among the trees. Multiple grey arrows point from text labels to different parts of the scene.

Eine heterozygote vielleicht pathogene Variante in einem relevanten Gen.

Eine heterozygote VUS in einem relevanten Gen

Eine heterozygote pathogene Variante in einem relevanten Gen

2 VUS in einem guten Kandidatengen

Eine heterozygote pathogene Variante in einem Gen mit unbekannter Funktion

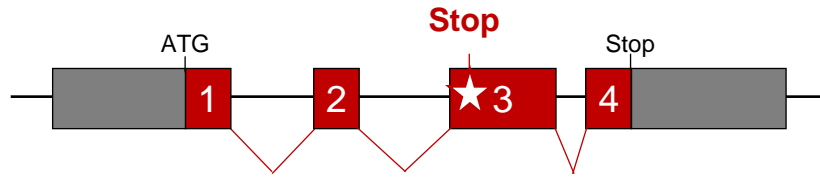
2 VUS in einem anderen Atemwegserkrankungs gen

Eine heterozygote pathogene Mutation in einem umstrittenen Gen

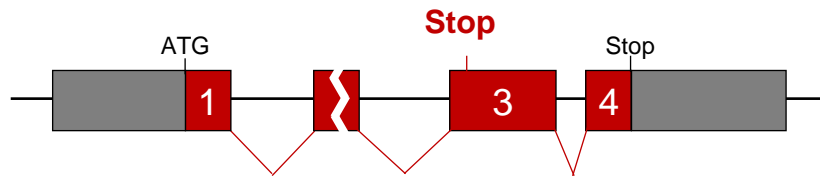
Eine heterozygote, potentiell pathogene Variante in einem guten Kandidatengen

Typen der pathogenen Varianten

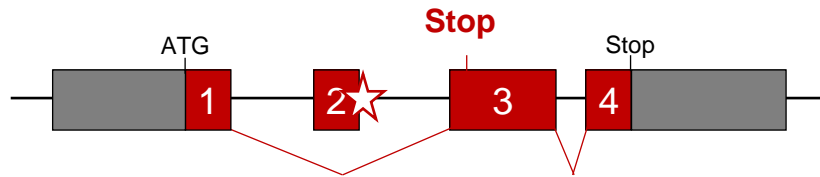
Nonsense



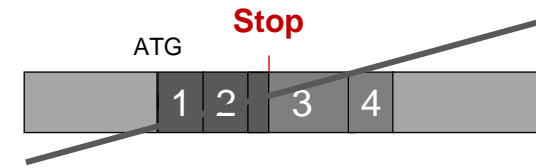
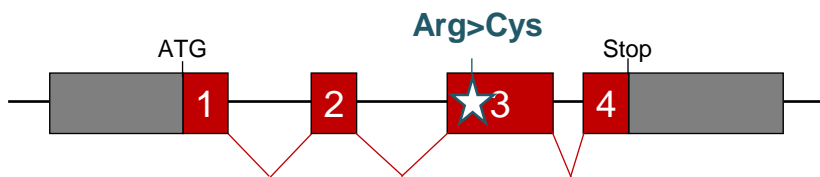
Leseraster



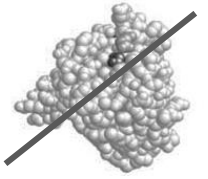
Spleiss



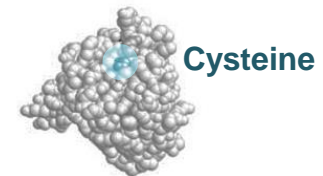
Missense



Nonsense-vermittelter
mRNA Abbau



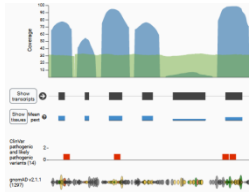
Kein Protein



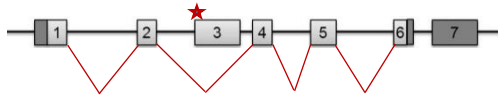
Protein mit einer
Aminosäureveränderung

Die Beurteilung einer missense Variante

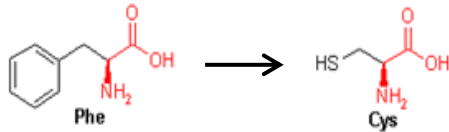
Frequenz in 'Kontrollen' Datenbanken?



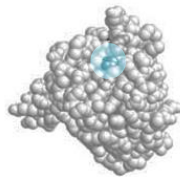
Spleissen?



Typ?



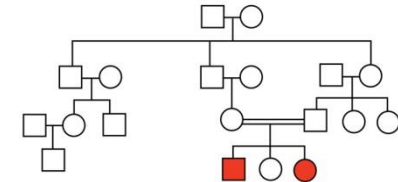
Lokalisation?



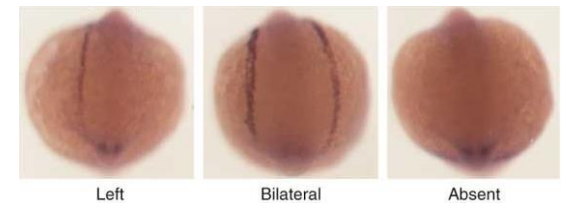
Konservierung?

Homo_sapiens	ITILVALRRLHCPRNYVHTQLF
Canis_lupus	IAILVALRRLHCPRNYIHTQLF
Mus_musculus	IAILVALRRLHCPRNYIHTQLF
Rattus_norvegicus	IAILVALRRLHCPRNYIHTQLF
Gallus_gallus	VTVLMFRLHCPRNYIHIQLF
Danio_rerio	VLILLFRRLHCTPRNYIHMQLF
	:*: :*:*:*:*:*:*

Genetische Untersuchung der Familie



Funktionelle Studien (Forschung)



Merveille et al. *Nat Genet* 2011

gnomAD Kontrollpopulationsdatenbank

DNAH5

p.Arg4429Gln

wahrscheinlich
gutartig!

Population Frequencies

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
▶ East Asian	785	19948	15	0.03935
▶ South Asian	486	30616	10	0.01587
▶ Other	20	7216	0	0.002772
▶ Latino/Admixed American	6	35440	0	0.0001693
▶ African/African-American	3	24964	0	0.0001202
▶ European (non-Finnish)	9	129046	0	0.00006974
▶ Ashkenazi Jewish	0	10366	0	0.000
▶ European (Finnish)	0	25112	0	0.000

7.5%
heterozygote
Träger!

1/650
homozygot!

UCSC Genbrowser: In 100 Wirbeltieren konserviert

4429

DNAH5

p.Arg4429Gln

Likely benign !

Species	Conservation	Residue	Amino Acid
Human	D	R	Arg
Chimp	D	R	
Gorilla	D	R	
Orangutan	D	R	
Gibbon	D	R	
Rhesus	D	R	
Crab-eating_macaque	D	R	
Marmoset	D	R	
Squirrel_monkey	D	R	
Bushbaby	E	R	
Chinese_tree_shrew	D	R	
Squirrel	D	R	
Lesser_Egyptian_jerboa	D	R	
Prairie_vole	D	R	
Chinese_hamster	D	R	
Golden_hamster	D	R	
Mouse	D	R	
Naked_mole-rat	D	R	
Guinea_pig	D	R	
Chinchilla	D	R	
Brush-tailed_rat	D	R	
Rabbit	D	R	
Pika	D	R	
Pig	D	R	
Alpaca	D	R	
Bactrian_camel	D	R	
→ Dolphin	D	Q	Gln
→ Killer_whale	D	Q	
Tibetan_antelope	D	R	
Sheep	D	R	
Domestic_goat	D	R	
Horse	D	R	
White_rhinoceros	N	R	



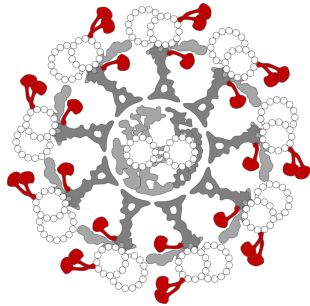
Variable klinische Zeichen

Phenotyp/Genotyp Korrelation

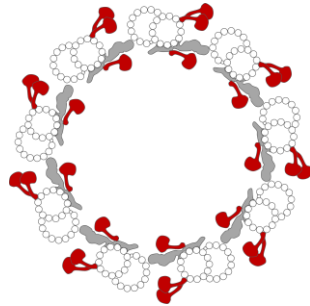
Primäre, ziliäre Dyskinesie

Dyneinarm Gene

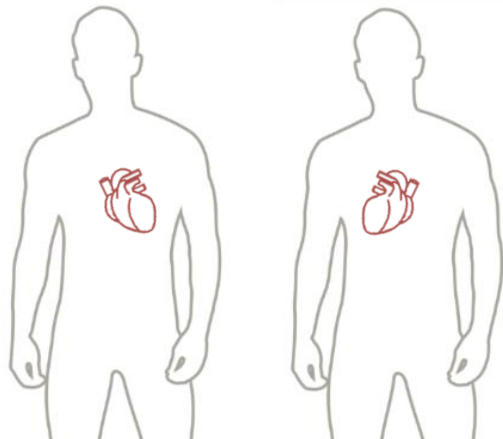
Atemwegszilie



Nodalzilie

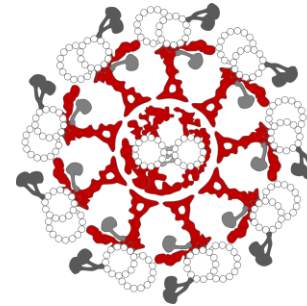


Situs inversus: 50%

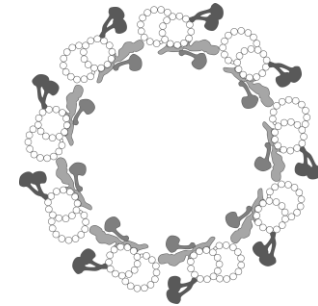


Zentralkomplex / Radialspeichen / DRC Gene

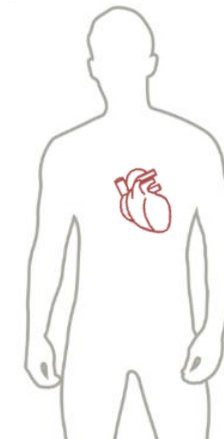
Atemwegszilie



Nodalzilie



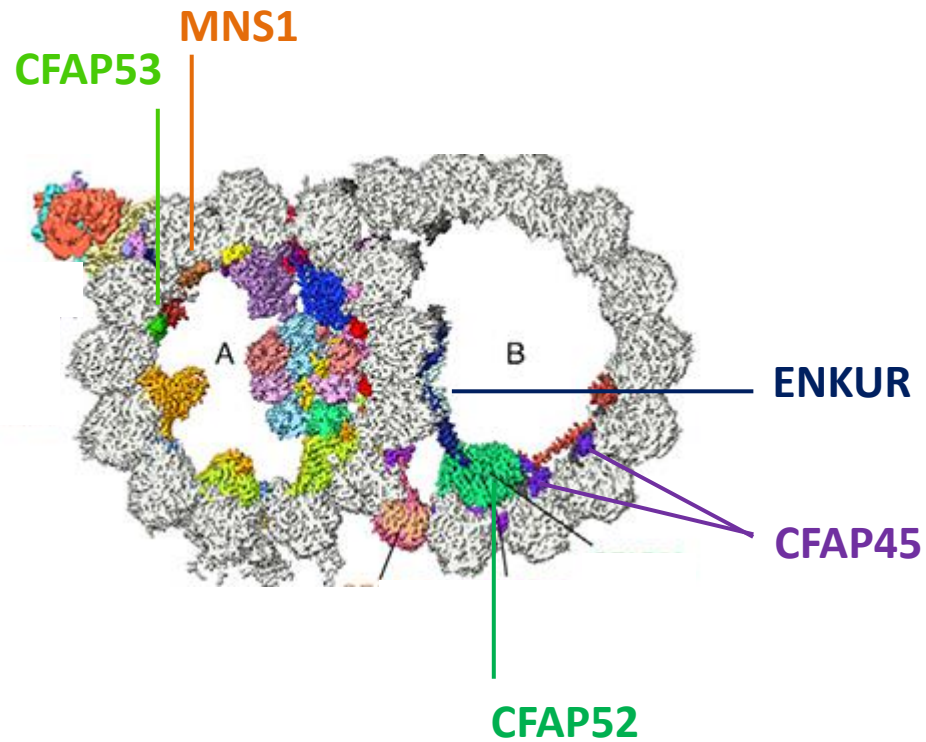
Keine *Situs*anomalien



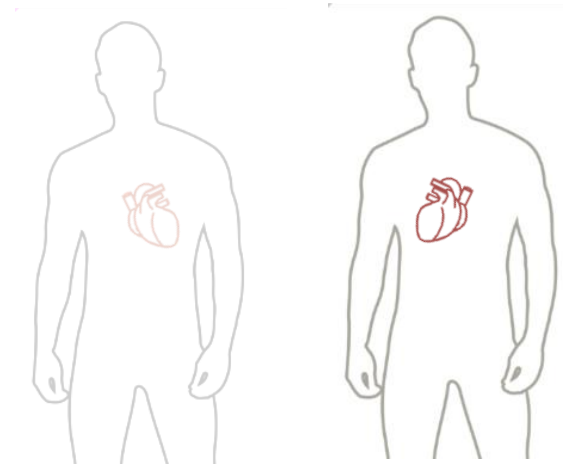
Phenotyp/Genotypkorrelation

Isolierter *Situs inversus*

Mikrotubule innere Proteine (MIPs)



Situs inversus ohne Lungenerkrankung





From Gui et al. *Cell* 2021 (Brown lab)

Primäre ziliäre Dyskinesie & Fruchtbarkeit

Fertilitätstatus der PCD Patienten nach ihrem PCD Genotyp

Ein großer Anteil der männlichen und weiblichen PCD Patienten sind fertile.

Vanaken et al. *Eur Respir J* 2017

	 49 ♂		 36 ♀	
	Fertile (n=12)	Infertile (n=37)	Fertile (n=14)	Infertile (n=22)
<i>DNAJB13</i>	0	1	0	0
<i>HYDIN</i>	1	1	0	4
<i>RSPH1</i>	0	1	1	2
<i>RSPH3</i>	0	1	0	1
<i>RSPH4A</i>	3	0	0	0
<i>RSPH9</i>	0	0	1	1
<i>CCDC39</i>	0	7	0	1
<i>CCDC40</i>	1	8	0	1
<i>GAS8</i>	0	1	0	0
<i>DNAH5</i>	3	1	2	1
<i>DNAI1</i>	0	3	2	0
<i>NME8</i>	0	0	0	1
<i>DYX1C1</i>	0	2	0	0
<i>DNAAF1</i>	0	1	0	3
<i>LRRC6</i>	0	4	0	2
<i>RPGR</i>	1	0	0	0
<i>SPAG1</i>	0	1	0	0
<i>ZMYND10</i>	0	1	0	0
<i>DNAH11</i>	3	4	7	3
<i>CCNO</i>	0	0	1	1
<i>MCIDAS</i>	0	0	0	1



Gert Vanaken

Multizilierte Atemwegszellen & Spermienzellen

Coll. Aminata Touré *Physiology and physiopathology of sperm cells*, Université de Grenoble

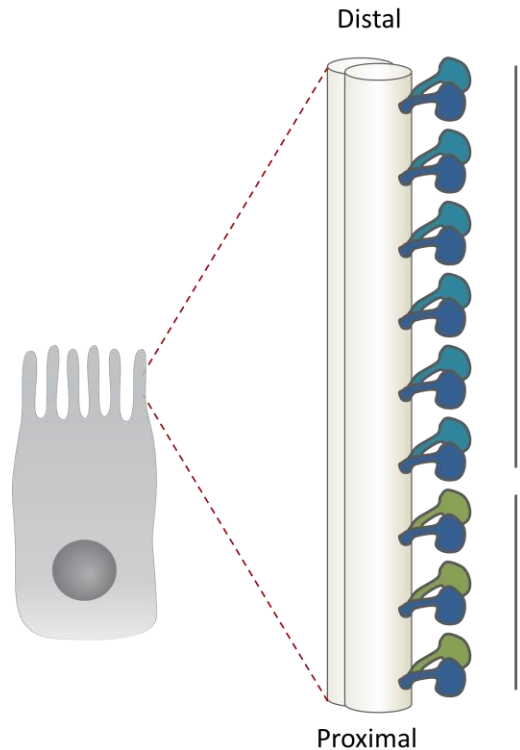


Lucie Thomas

DNAH17: verursacht isolierte männliche Infertilität

Unterschiedliche Zusammensetzung der schweren Kette des Dyneinarms zwischen Atemwegs- und Spermienzellen.

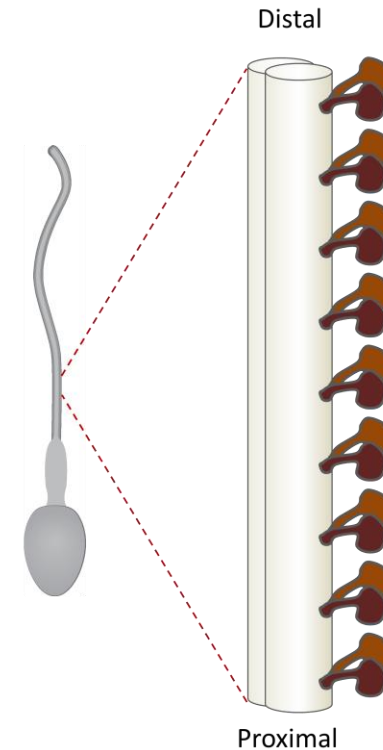
Atemwegs- und multizilierte Zellen



Type 2 ODA
DNAH5 / DNAH9

Type 1 ODA
DNAH5 / DNAH11

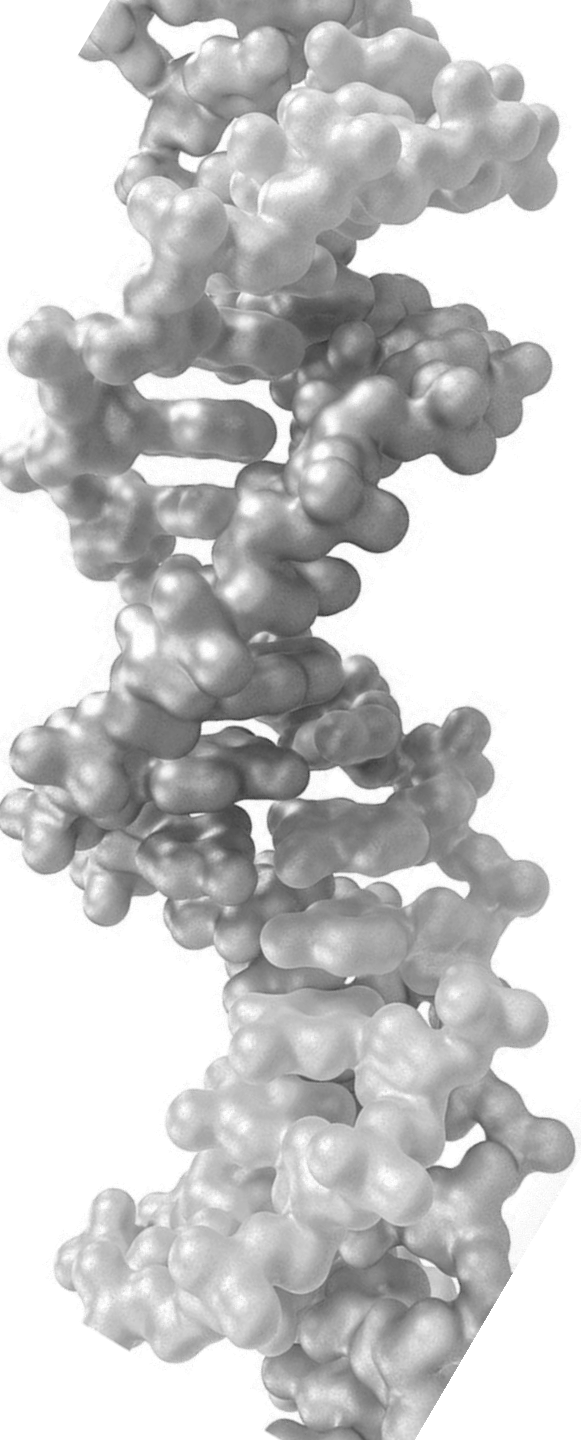
Spermienzellen



DNAH8 / DNAH17

Whitfield et al. *Am J Hum Genet* 2019

From Legendre et al. *Semin Cell Dev Biol* 2021



Zusammenfassung

- 30 000 Varianten im Exom
- Wir alle tragen pathogene Varianten (~10-100)
- Die klinischen Symptome und die Ziliendefekte hängen von den spezifischen Genen ab

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<https://geneticdiseases-lab.fr>

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Patients
& ADCP advocacy group