Genetica e Malattie Rare in Oftalmologia

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Genetica nelle eredo degenerazioni retiniche

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Genetica e malattia

- **CANCRO**
  - **Malattia genetica**
  - **Alterazioni genetiche limitate alle cellule tumorali**

- **Malattie genetiche ereditarie**
  - **Malattie genetiche**
  - **Alterazione genetica in tutte le cellule dell'organismo. Alcuni tessuti/organi ne risentono**

The Human Genome Project

The (r)evolution in genetics

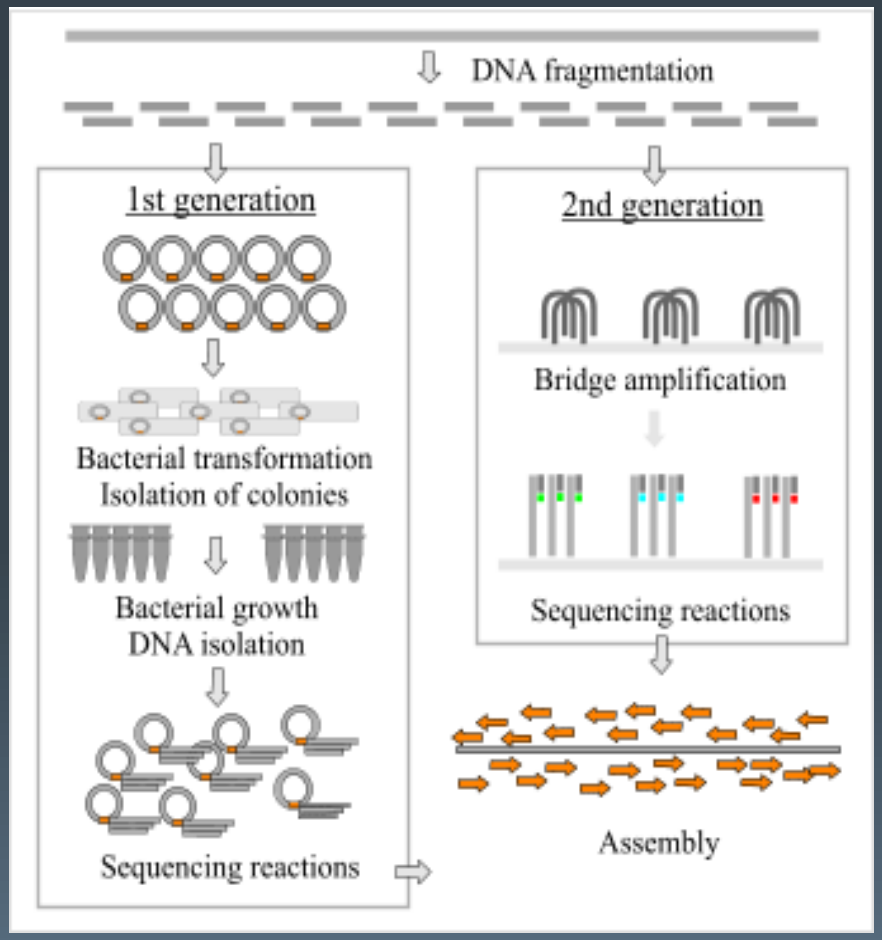
- **The Human Genome**
  - Started in 1990 and completed in 2003
  - The goal was to define and annotate around 25,0000 genes
  - The estimated cost was of $ 2.3B
  - The project led the way to a new horizon in genetic testing

Tecniche molecolari in patologia oculare

- La diagnosi molecolare dei disordini retinici è basata sull'analisi del DNA
- Diversi meodi dispoinibili:
  - Il ***Sanger sequencing*** è il gold-standard nel determinare il gene mutato, ma a causa dell'eterogeneità di questi disordini è costoso e richiede tempi lunghi
  - Alcuni ***kit di microarrays*** in commercio permettono di identificare soltanto i geni conosciuti in base al pattern di ereditarietà
    - Gli ***SNP microarrays*** sono tools utili per l'analisi di linkage
  - Il ***Next-generation sequencing*** (sequenziamento di nuova generazione) permette di identificare nuove mutazioni, oltre a quelle già note, in tempi brevi e a costi ridotti

Next Generation Sequencing

The (r)evolution in Genetics



1995

H. influenzae

1.8Mb, 1 year, ≈ $1M

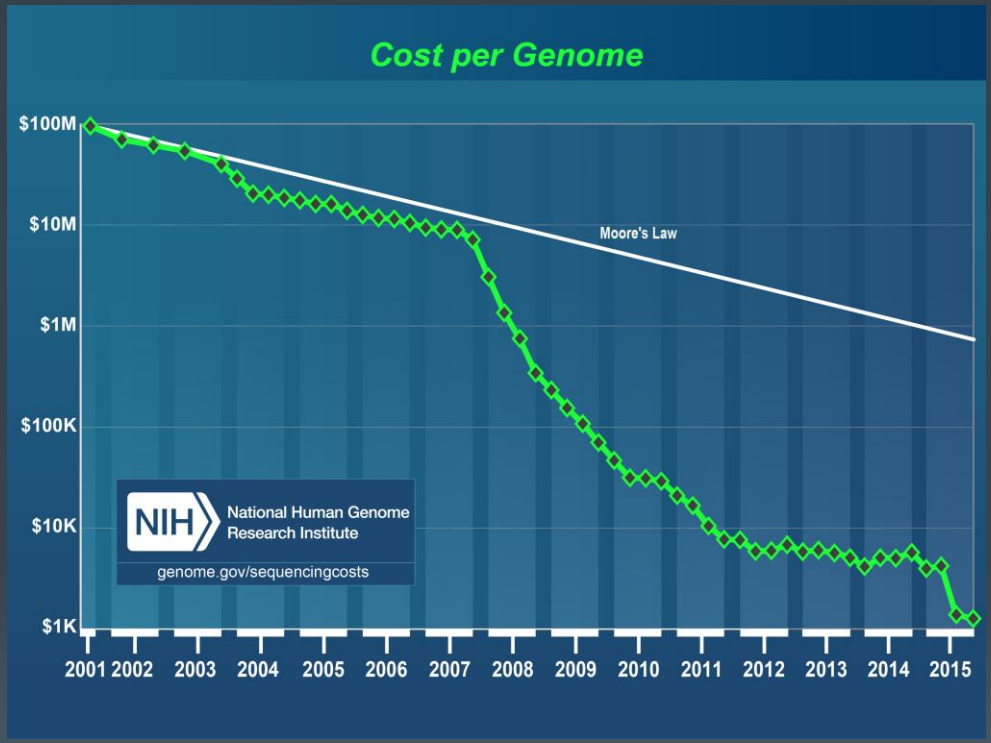
2012

E. coli

5Mb, 1 day, ≈ $80

Cost of Sequencing is expanding the market….

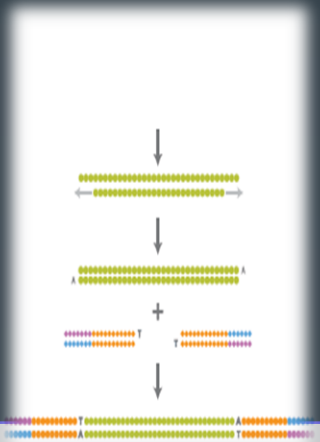
- "..it's a general crash of prices in the industry as a whole. Things are going to continue in this fashion.."
- The Sequencing Landscape is changing… lower cost market end
- Cost per Mb went down 50,000X

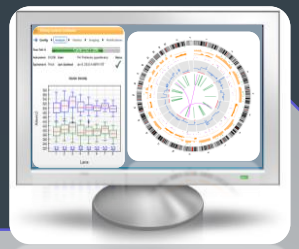


http://www.genome.gov/sequencingcosts/

Next Generation Sequencing

Integrated Workflow Solution

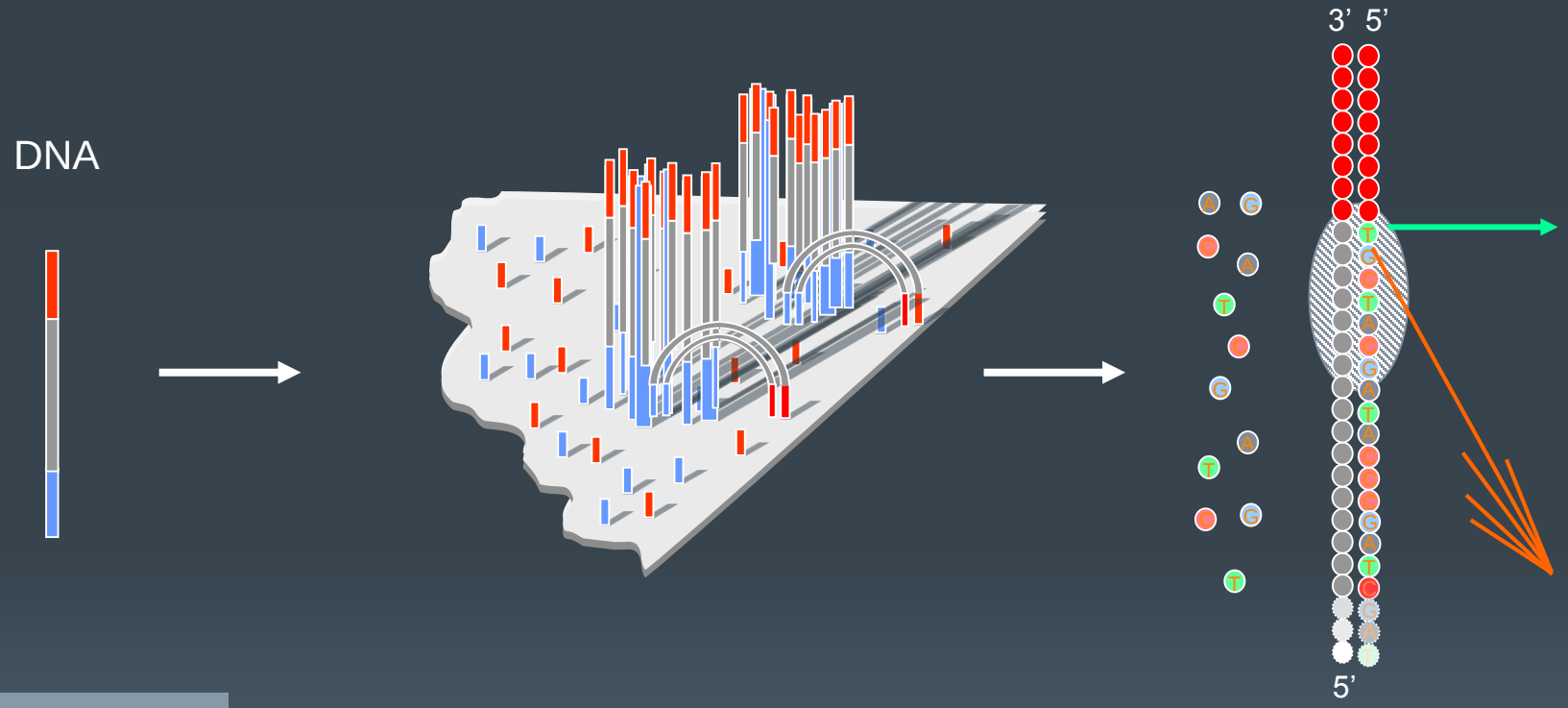




Sample Preparation → **Clustering** → **Sequencing** → **Analysis**

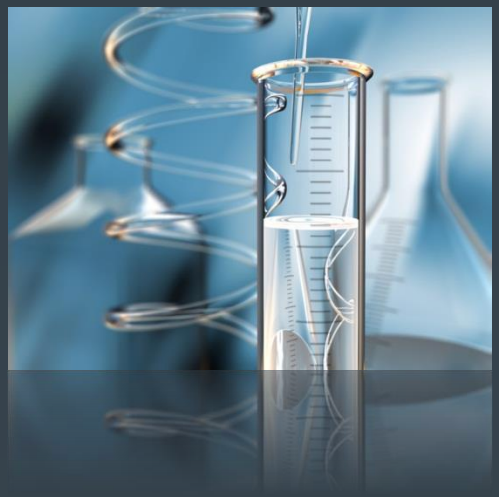
Illumina Sequencing Technology

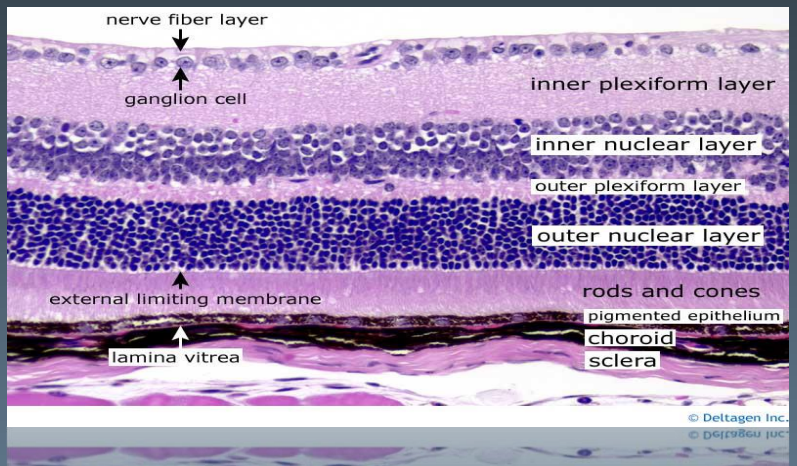
Robust Reversible Terminator Chemistry Foundation



NGS
& patologia oculare

- Conoscere la patogenesi delle malattie
- Diagnosi
- Prognosi
- Terapia mirata





Audo et al. Orphanet Journal of Rare Diseases 2012, 7:8
http://www.ojrd.com/content/7/1/8

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Development and application of a next-generation-sequencing (NGS) approach to detect known and novel gene defects underlying retinal diseases

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GENETICS IN MEDICINE | ORIGINAL RESEARCH ARTICLE

Next-generation sequencing in health-care delivery: lessons from the functional analysis of rhodopsin

Wayne I.L. Davies MA, PhD Susan M. Downes FRCOphth, MD Josephine K. Fu BSc Morag E. Shanks PhD Richard R. Copley BA, DPhil Stefano Lise PhD Simon C. Ramsden PhD Graeme C. M. Black FRCOphth, DPhil Kate Gibson BSc Russell G. Foster BSc, PhD Mark W. Hankins PhD Andrea H. Németh FRCP, DPhil

RESEARCH ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

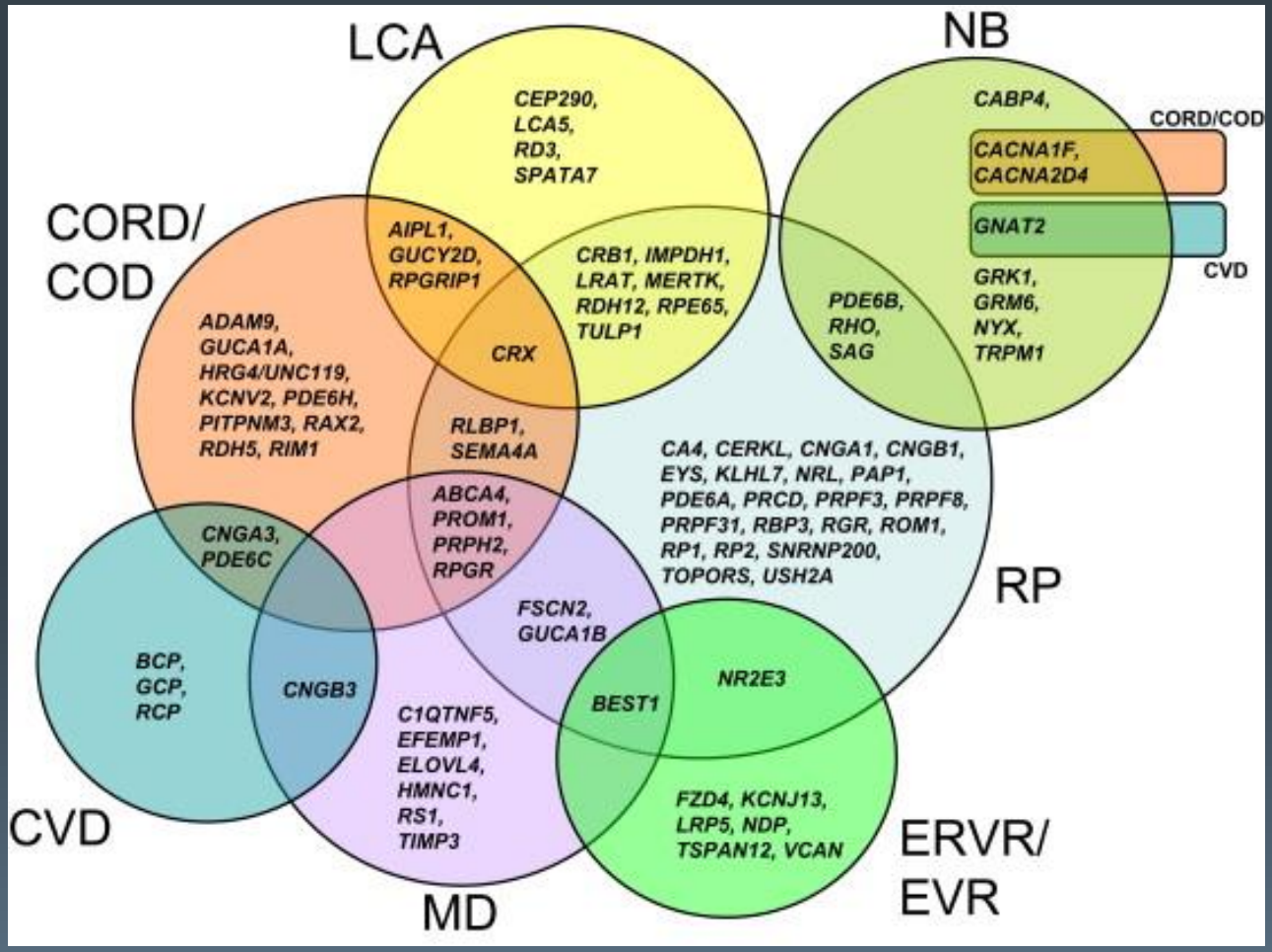
Next-Generation Genetic Testing for Retinitis Pigmentosa

Kornelia Neveling,[1,4] Rob W.J. Collin,[1–3] Christian Gilissen,[1,3,4] Ramon A.C. van Huet,[2] Linda Visser,[5] Michael P. Kwint,[1] Sabine J. Gijsen,[1] Marijke N. Zonneveld,[1] Nienke Wieskamp,[1] Joep de Ligt,[1,3,4] Anna M. Siemiatkowska,[1] Lies H. Hoefsloot,[1,4] Michael F. Buckley,[1] Ulrich Kellner,[6] Kari E. Brenham,[7] Anneke I. den Hollander,[1–4] Alexander Hoischen,[1,3,4] Carel Hoyng,[2,4] B. Jeroen Klevering,[2,4] L. Ingeborgh van den Born,[5] Joris A. Veltman,[1,3,4†] Frans P.M. Cremers,[1,3†] and Hans Scheffer[1,4†*]

Malattie retiniche ereditarie

- Eterogeneità clinica: elevato numero di geni mutati correlati
- >150 geni responsabili sono stati identificati (http://sph.uth.tmc.edu/Retnet/home.htm)
- Mutazioni non identificate in elevato numero di pazienti

Mutazioni e disordini retinici ereditari



RP: Retinitis Pigmentosa
LCA: Leber Congenital Amaurosis
NB: Night Blindness
CORD/COD:Cone rod and cone Dystrophies
CVD:Colour Vision Defects
MD: Macular Degeneration
ERVR/EVR: Erosive and exudative vitreoretinophaties

Distrofie Retiniche (DR)

- Malattie degenerative della retina, molto eterogenee
- 1/4.000 individui
- Oltre 120-150 geni coinvolti: mutazioni alterano funzioni visive
- Stessa mutazione/gene: diverse malattie!!
- *Rod-dominated diseases, cone-dominated diseases* and *generalised retinal degenerations*
- Sindromiche o no
- Tutte le modalità di trasmissione (Dominante, Recessiva, X-linked….)

Cecità notturna congenita stazionaria (CSNB)

- CSNB è una forma non progressiva di cecità notturna (nictalopia)
  - I pazienti hanno difficoltà a vedere con intensità luminosa relativamente basse.
- Difetto completo a livello del bastoncello od incompleto a livello di cono e bastoncello
- 11 geni sono stati identificati nei pazienti con CSNB, con ruoli in:
  - Funzione del canale del calcio: *CACNA1F, CACNA2D4 e TRPM1*
  - Legame di calcio: *CABP4*
  - Funzioni del recettore del glutammato: *GRM6*
  - Cascata di fototransduzione: *GNAT1, GRK1, PDE6B, SAG e RHO*
- La forma incompleta di CSNB (CSNB2) legata a cromosoma X è causata da una rottura del gene *CACNA1F*, che codifica la subunità α1F dei canali di calcio

Genes˜	Inheritance*	Phenotype
GNAT1, PDE6B, RHO	Dominant	Night blindness
CABP4, CACNA2D4	Recessive	Incomplete night blindness
GRM6, TRPM1	Recessive	Night blindness
SAG, GRK1	Recessive	Oguchi disease
CACNA1F	X-Linked	Incomplete night blindness (CSNB2)
NYX	X-Linked	Night blindness (CSNB1)

Distrofie progressive dei coni e dei coni-bastoncelli (COD e CORD)

- L'insorgenza di COD e CORD avviene di solito durante l'infanzia o l'adolescenza.
- Di solito coinvolgimento di un fotorecettore (COD) seguito eventualmente dal secondo (CORD).
- Il coinvolgimento aggiuntivo del bastoncello porta ad un aumento della gravità con la maggior parte dei malati che hanno raggiunto la cecità legale all'età di 40 anni
- Oltre 30 geni descritti con le mutazioni causate da malattie
- Le cause molecolari possono essere identificate in circa:
  - Il 20% della dominanza autosomica
  - 74% di X-linked
  - 23-25% di autosomica recessiva
- Le mutazioni che coinvolgono ABCA4 sono più comuni nei casi di CORD rispetto alla coorte di COD (76% vs 63%)

Gene~	Inheritance*	Potential function
GUCA1A	Dominant	Phototransduction
GUCY2D	Dominant	Phototransduction
PDE6C	Recessive	Phototransduction
PDE6H	Recessive	Phototransduction
CNGB3	Recessive	Phototransduction
PRPH2	Dominant	Phototransduction
ABCA4	Recessive	Retinal Metabolism
RDH5	Recessive	Retinal metabolism
CRX	Dominant	Transcription factor
RAX2	Recessive	Transcription
RPGRIP1	Recessive	Interacts with RPGR
ADAM9	Recessive	Cell/matrix interaction
AIPL1	Dominant	Transport, protein trafficking
TTLL5	Recessive	Cilia function
CACNA1F	X-Linked	Calcium channel
CACNA2D4	Recessive	Ion channel
HRG4	Dominant	Neurotransmitter release
KCNV2	Recessive	Ion channel subunit
RIMS1	Dominant	Neurotransmitter release
PITPNM3	Dominant	Transport
SEMA4A	Dominant & recessive	Axon guidance
CERKL	Recessive	Cell signalling
RPGR	Dominant & recessive	Intraflagellar transport
PROM1	Dominant	Cellular structure
CDHR1	Recessive	Cellular structure
C21orf2	Recessive	Unknown
C8orf37	Recessive	Unknown
CNNM4	Recessive	Unknown
RAB28	Recessive	Unknown

Acromatopsia

- Le forme stazionarie della distrofia conica possono esistere in due forme in cui l'achromatopsia completa o incompleta comporta la perdita di ogni percezione del colore o la percezione di un solo colore specifico.
- Tritanopia o visione blu difettosa è un fenotipo autosomico dominante causato da mutazioni nel gene *OPN1SW* (codifica l'opsina sensibile alle onde corte che rileva la luce blu)
- I geni associati all'acromatopsia completa autosomica recessiva comprendono *CNGA3, CNGB3, GNAT2, PDE6C* e *PDE6H*.
- Il solo *CNGB3* è responsabile fino al 50% dei casi
- *CNGA3* e *CNGB3* codificano le subunità α e β di canali cGMP-gated situati nel fotorecettore (cono), che sono coinvolti in passaggi chiave della fototrasduzione.

DR non sindromiche generalizzate

- DR che comportano il degrado simultaneo delle funzioni dei 2 fotorecettori (bastoncelli e coni) sono definite DR generalizzate. La maggior parte dei casi presenta un deterioramento della visione progressivo e spesso grave. Esistono sia forme sindromiche che non sindromiche.

Coroideremia

- L'unica forma X-linked è la choroideremia, causata da mutazioni del gene *CHM*
- *CHM* codifica REP-1, una sottounità della proteina rab1 rewsponsabile del traffico intracellulare e del trasporto intracellulare di proteine e organelli
- Gli studi che utilizzano strumenti genomici per ottenere la diagnosi molecolare si stanno dimostrando utili nel perfezionamentodella diagnosi clinica.

Amaurosi Congenita di Leber (LCA)

- La DR generalizzata non sindromica più comune è la LCA.
- L'inizio della LCA è precoce: gli individui colpiti che sviluppano sintomi entro il primo anno di vita.
- Oltre 20 geni associati a LCA: quasi tutti seguono un pattern di ereditarietà autosomica recessiva.

Gene	Inheritance*	Potential function	Estimated frequency
GUCY2D	Recessive	Phototransduction	6-21%
RDH12	Recessive	Phototransduction	~4%
LRAT	Recessive	Retinal metabolism	<1%
RPE65	Recessive	Visual cycle	3-16%
RD3	Recessive	Splicing	Rare
CRX	Dominant & Recessive	Transcription factor	~3%
OTX2	Dominant	Transcription factor	Rare
CRB1	Recessive	Tissue development and maintenance	10%
TULP1	Recessive	Tissue development & maintenance	1-2%
IMPDH1	Dominant	Regulates cell growth	Rare
GDF6	Recessive	Growth factor	Unknown
CABP4	Recessive	Cell signalling	Unknown
AIPL1	Recessive	Transport, protein trafficking	4-8%
CEP290	Recessive	Centrosomal & ciliary protein	<30%
IQCB1	Recessive	Interacts with RPGR & connecting cilia	Unknown
LCA5	Recessive	Centrosome protein with ciliary function	1-7%
NMNAT1	Recessive	Photoreceptor maintenance	5%
RPGRIP1	Recessive	Interacts with RPGR	~5%
KCNJ13	Recessive	Potassium channel	Unknown
DTHD1	Recessive	Unknown	Unknown
SPATA7	Recessive	Unknown	2%

Analisi NGS in pazienti affetti da distrofia retinica: esperienza UNIBO

- PI: Sergio Z. Scalinci, UNIBO
- Genetic report: Giulia De Falco, Queen Mary University, London
- Genetic testing: PPP, UNIBO-IEMEST

- 40 patients
- Different retinal disorders

Disease Category	Mapped and Identified Genes
Leber congenital amaurosis, autosomal dominant	CRX, IMPDH1, OTX2
Leber congenital amaurosis, autosomal recessive	AIPL1, CABP4, CEP290, CRB1, CRX, DTHD1, GDF6, GUCY2D, IQCB1, KCNJ13, LCA5, LRAT, NMNAT1, RD3, RDH12, RPE65, RPGRIP1, SPATA7, TULP1
Macular degeneration, autosomal dominant	BEST1, C1QTNF5, EFEMP1, ELOVL4, FSCN2, GUCA1B, HMCN1, IMPG1, PROM1, PRPH2, RP1L1, TIMP3
Macular degeneration, autosomal recessive	ABCA4, CFH, IMPG1
Macular degeneration, X-linked	RPGR
Ocular-retinal developmental disease, autosomal dominant	VCAN
Optic atrophy, autosomal dominant	MFN2, NR2F1, OPA1
Optic atrophy, autosomal recessive	TMEM126A
Optic atrophy, X-linked	TIMM8A
Retinitis pigmentosa, autosomal dominant	BEST1, CA4, CRX, FSCN2, GUCA1B, IMPDH1, KLHL7, NR2E3, NRL, PRPF3, PRPF4, PRPF6, PRPF8, PRPF31, PRPH2, RDH12, RHO, ROM1, RP1, RP9, RPE65, SEMA4A, SNRNP200, TOPORS
Retinitis pigmentosa, autosomal recessive	ABCA4, ARL2BP, BEST1, C2orf71, C8orf37, CERKL, CLRN1, CNGA1, CNGB1, CRB1, DHDDS, DHX38, EMC1, EYS, FAM161A, GPR125, IDH3B, IMPG2, KIAA1549, KIZ, LRAT, MAK, MERTK, MVK, NEK2, NR2E3, NRL, PDE6A, PDE6B, PDE6G, PRCD, PROM1, RBP3, RGR, RHO, RLBP1, RP1, RPE65, SAG, SLC7A14, SPATA7, TTC8, TULP1, USH2A, ZNF513
Retinitis pigmentosa, X-linked	OFD1, RP2, RPGR
Syndromic/systemic diseases with retinopathy, autosomal dominant	ABCC6, ATXN7, COL11A1, COL2A1, JAG1, KCNJ13, KIF11, MFN2, OPA3, PAX2, TREX1, VCAN
Syndromic/systemic diseases with retinopathy, autosomal recessive	ABCC6, ABHD12, ACBD5, ADAMTS18, AHI1, ALMS1, CC2D2A, CEP164, CEP290, CLN3, COL9A1, CSPP1, FLVCR1, GNPTG, HARS, IFT140, INPP5E, INVS, IQCB1, LRP5, MKS1, MTTP, NPHP1, NPHP3, NPHP4, OPA3, PANK2, PCYT1A, PEX1, PEX7, PHYH, PXMP3, RPGRIP1L, SDCCAG8, TMEM237, TTPA, TUB, WDPCP, WDR19, WFS1, ZNF423
Syndromic/systemic diseases with retinopathy, X-linked	OFD1, TIMM8A
Usher syndrome, autosomal recessive	ABHD12, CDH23, CIB2, CLRN1, DFNB31, GPR98, HARS, MYO7A, PCDH15, USH1C, USH1G, USH2A

Prospettive Terapeutiche?

Prospettive terapeutiche basate sulla diagnosi genetica

- La Terapia cellulare sostitutiva (trapianto di fotorecettori derivati da cellule staminali o precursori RPE nella retina) è stata applicata con successo a diversi modelli di roditori di degenerazione della retina ed è attualmente in sperimentazione clinica umana per il trattamento della degenerazione maculare legata all'età e la malattia di Stargardt
- La Gene Augmentation Therapy per i pazienti con amaurosi congenita di Leber sembra sicura, anche se l'effetto sulla funzione visiva è stato deludente: la degenerazione della retina progredisce nonostante la buona espressione genica
  - Tale approccio ha impedito o arrestato con successo la degenerazione della retina nei modelli murini e canini di deficit di *RPGR* e di un modello di topo knockout *RP2*

Therapeutic perspectives based on genetic diagnosis

Table 5 Examples of therapies applied in the retinal dystrophies

Approach	Context	Strategy summary
Gene therapy	Human clinical trial	*RPE65* delivered by Adeno-associated Virus (AAV)
	Mouse model	*CHM* delivered by Adeno-associated Virus (AAV)
	Human clinical trial	*CHM* delivered by Adeno-associated Virus (AAV)
	In vitro model	*CEP290* delivered by Lentivirus vector
	Rat model	*MERTK* delivered by Adeno-associated Virus (AAV)
	Mouse model	CRB1 and *CRB2* delivered by Adeno-associated Virus (AAV)
Cell replacement	Rat model	Human RPC transplantation restores mature rat retina cells
	Mouse model	Adult mouse iPSC differentiate into photoreceptors
	Mouse model	RPCs differentiate and integrate into functional photoreceptors
	Mouse model	RPCs differentiate into photoreceptors
Retinal implants	Clinical trials	Argus II Retinal Prosthesis System

Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial

Robert E MacLaren, Markus Groppe, Alun R Barnard, Charles L Cottriall, Tanya Tolmachova, Len Seymour, K Reed Clark, Matthew J During, Frans P M Cremers, Graeme C M Black, Andrew J Lotery, Susan M Downes, Andrew R Webster, Miguel C Seabra

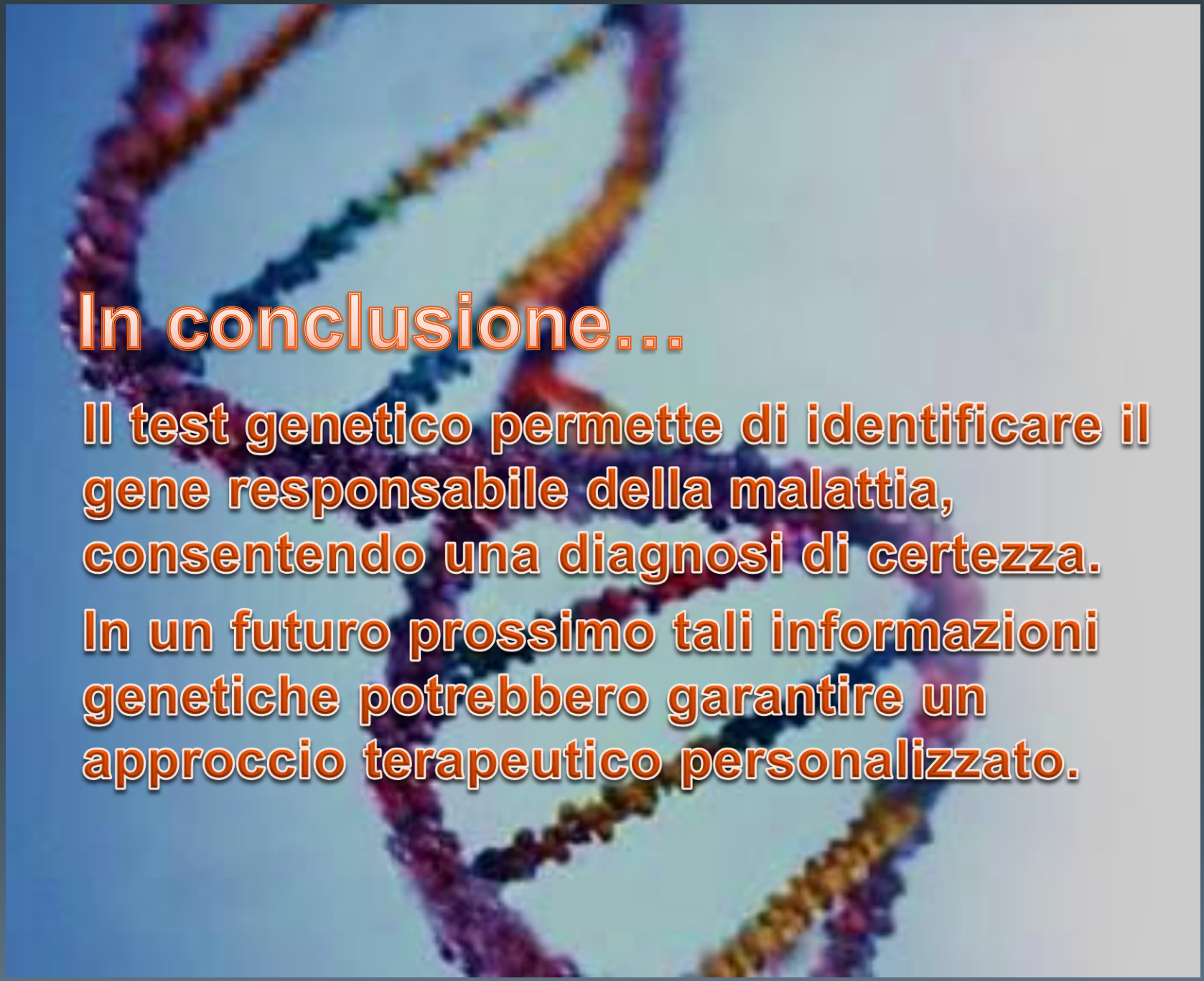
Summary

Background Choroideremia is an X-linked recessive disease that leads to blindness due to mutations in the *CHM* gene, which encodes the Rab escort protein 1 (REP1). We assessed the effects of retinal gene therapy with an adeno-associated viral (AAV) vector encoding REP1 (AAV.REP1) in patients with this disease.

Methods In a multicentre clinical trial, six male patients (aged 35–63 years) with choroideremia were administered AAV.REP1 ($0 \cdot 6–1 \cdot 0 \times 10^{10}$ genome particles, subfoveal injection). Visual function tests included best corrected visual acuity, microperimetry, and retinal sensitivity tests for comparison of baseline values with 6 months after surgery. This study is registered with ClinicalTrials.gov, number NCT01461213.

Findings Despite undergoing retinal detachment, which normally reduces vision, two patients with advanced choroideremia who had low baseline best corrected visual acuity gained 21 letters and 11 letters (more than two and four lines of vision). Four other patients with near normal best corrected visual acuity at baseline recovered to within one to three letters. Mean gain in visual acuity overall was 3·8 letters (SE 4·1). Maximal sensitivity measured with dark-adapted microperimetry increased in the treated eyes from 23·0 dB (SE 1·1) at baseline to 25·3 dB (1·3) after treatment (increase 2·3 dB [95% CI 0·8–3·8]). In all patients, over the 6 months, the increase in retinal sensitivity in the treated eyes (mean 1·7 [SE 1·0]) was correlated with the vector dose administered per mm^2 of surviving retina (r=0·82, p=0·04). By contrast, small non-significant reductions (p>0·05) were noted in the control eyes in both maximal sensitivity (–0·8 dB [1·5]) and mean sensitivity (–1·6 dB [0·9]). One patient in whom the vector was not administered to the fovea re-established variable eccentric fixation that included the ectopic island of surviving retinal pigment epithelium that had been exposed to vector.

Interpretation The initial results of this retinal gene therapy trial are consistent with improved rod and cone function that overcome any negative effects of retinal detachment. These findings lend support to further assessment of gene therapy in the treatment of choroideremia and other diseases, such as age-related macular degeneration, for which intervention should ideally be applied before the onset of retinal thinning.



In conclusione…

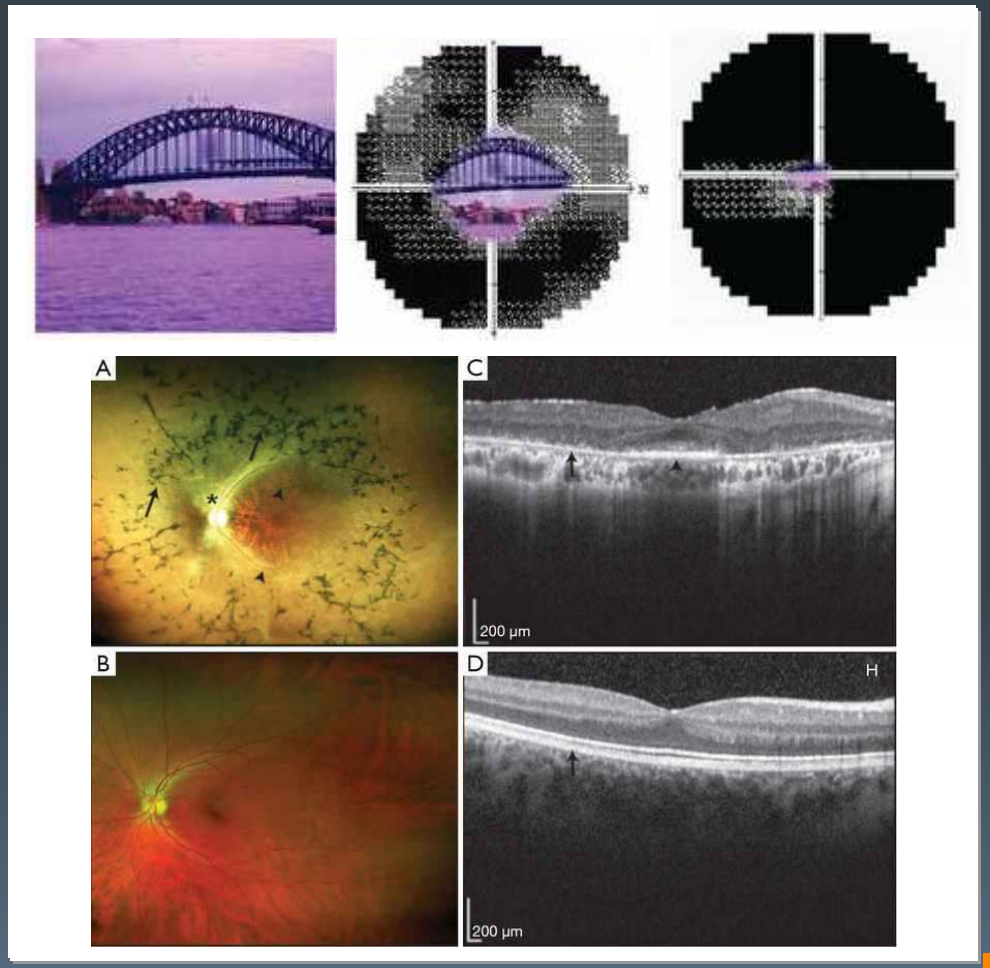
Il test genetico permette di identificare il gene responsabile della malattia, consentendo una diagnosi di certezza.

In un futuro prossimo tali informazioni genetiche potrebbero garantire un approccio terapeutico personalizzato.

GRAZIE!

Retinitis pigmentosa (RP)

- RP is a progressive non-syndromic rod-cone disease and has high levels of clinical and genetic heterogeneity.
  - Locus and allelic heterogeneity, incomplete penetrance and variable expression and penetrance all observed
- Early onset (juvenile RP) vs. adult or late onset RP
- Progressive deterioration of the ability to see in dim light (night blindness)
- Loss of peripheral vision (tunnel vision)
- Complete blindness
- Affected photoreceptors undergo apoptosis, which is evident with the thinning of the outer nuclear layer and pigmented deposits or lesions present in the diseased retina



Retinitis pigmentosa (RP) - Genetics

- Over 60 disease genes are reported to associate with RP
- Functions of the encoded proteins can be grouped into five categories:
  - phototransduction;
  - retinal metabolism;
  - RNA splicing;
  - tissue development and maintenance;
  - cellular structure.
- Modes of inheritance vary with
  - 15-20% autosomal dominant,
  - 5-20% autosomal recessive,
  - 5-15% X-linked,
  - simplex or unknown inheritance observed in 40-50% of cases
- Even with the latest genetic diagnostic techniques, including NGS, molecular diagnosis is only achieved in approximately 50% of tested RP patients

Retinitis pigmentosa (RP) – Genetics II

- Mutations in the gene *RHO,* encoding rhodopsin which is critical in phototransduction, are a leading cause of RP
- Mutations in this gene are seen in ~20-30% of autosomal dominant RP
  - Recessive forms of inheritance are suggested to still confer a phenotype in the heterozygous state, however it is milder or with onset later in life
- The severity of the phenotype appears to depend on the location of the mutation in the protein
- Intrafamilial variation is also noted among patients indicating the likely presence of genetic modifiers and/or environmental factors contributing to the phenotype

- Other RP disease genes implicated in the phototransduction process have an expected frequency of less than 2-5% of patients
  - *RDH12, GUCA1B , PDE6A , PDE6B , CNGA1, CNGB1*

Retinitis pigmentosa (RP) – Genetics III

- Mutations in RP disease-causing genes that encode proteins associated with retinal metabolism generally follow an autosomal recessive inheritance pattern
  - *ABCA4* , *LRAT* , *RBP3* , RGE, *RPE65*

- Genes encoding splicing factors have also been implicated in the expression of an RP phenotype and all follow an autosomal dominant inheritance pattern.
  - *PRPF31*, *PRPF8*, *PRPF3*, *PAP1*, *SNRNP200* and *PRPF6*
  - (eg affect *RHO* splicing)

Retinitis pigmentosa (RP) – Genetics III

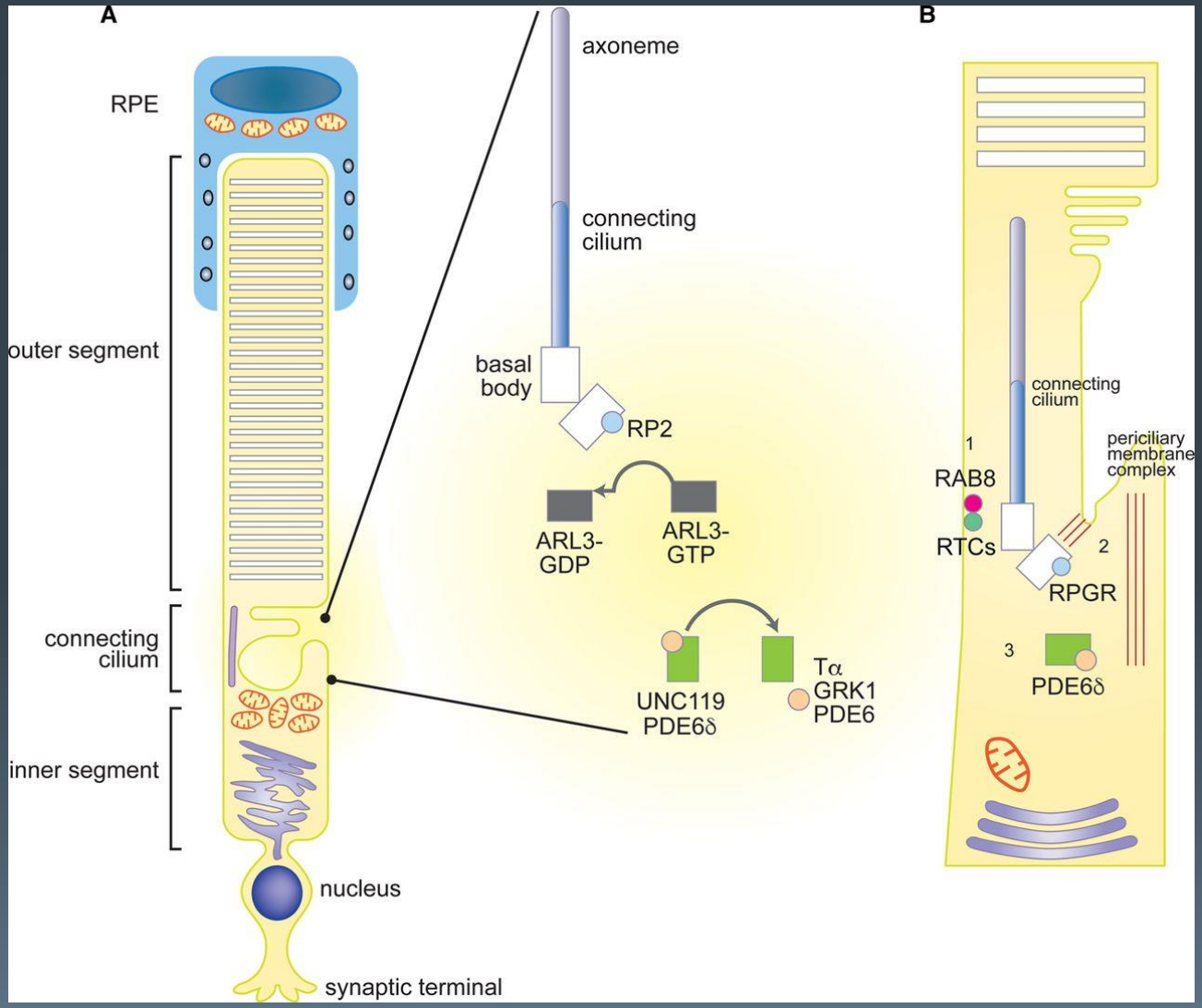
- Retinal tissue development, differentiation and maintenance is critical for proper photoreceptor function
  - *RP1*, *NR2E3*, *CRX*, *NRL*, *SEMA4A*, *FAM161A*, *TULP1*, *RP2*, *CRB1* and *IMPDH1*
  - *CRX*, *NRL* and *NR2E3* → retinal neurogenesis

- Mutations in genes encoding proteins involved in cellular structure
  - Associated with autosomal recessive RP include: *PROM1*, *MAK*, *IMPG2*, *DHDDS*, *CLRN1*, and *USH2A*
  - Aassociated with autosomal dominant RP include: *FSCN2*, *ROM1* and *PRPH2*

Disease mechanisms of X-linked retinitis pigmentosa due to RP2 and RPGR mutations.

- Photoreceptor degeneration is the prominent characteristic of retinitis pigmentosa (RP)
- Abnormalities in many pathways can cause photoreceptor degeneration:
  - Defective protein transport through the connecting cilium, the structure that connects the biosynthetic inner segment with the photosensitive outer segment of the photoreceptors.
- The majority of patients with X-linked RP have mutations in the retinitis pigmentosa GTPase regulator (*RPGR*) or *RP2* genes,
  - Both components of the connecting cilium

Suggested roles for RP2 and RPGR in the photoreceptor



RPGR/XLRP

- *RPGR*/XLRP causes a severe retinal degeneration, leaving patients blind from a young age.
- Within the gene, however, differing patient *RPGR* mutations cause notable phenotypic variability.
  - worsening disease being documented as the mutation approaches the N-terminal end of *RPGR*
- While the vast majority of *RPGR* patients (95%) develop classic RP, cone dystrophy, cone-rod dystrophy, atrophic macular degeneration and systemic ciliopathies have all been documented
- Ddizygotic twins were shown to be discordant for RPGR/XLRP disease severity. Environmental factors and stochastic developmental influences may affect disease progression
  - SNPs in IQCB1 and RPGRIP1L affecting retinal function

RP2

- Human *RP2* mutations cause a severe, atypical form of RP with early macular involvement leading to central visual loss
- Macular atrophy has been seen as the predominant feature in some case studies
- Clinical studies suggest that *RP2/XLRP* patients have a faster loss of central visual acuity than those with *RPGR* mutations, despite comparable visual field loss and electroretinographic disease progression
- *RP2/XLRP* patients are myopic
- The onset of nyctalopia appears similar between the two genotypes
  - Rod degeneration is the prominent feature of *RP2* disease but…
  - Early cone involvement