Inherited Eye Disease

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Inherited retinal dystrophies
• clinically heterogeneous
• variable visual loss
• bilateral symmetrical retinal abnormalities
• AD, AR, XL & mitochondrial inheritance
• considerable heterogeneity even within these subtypes

Inherited retinal dystrophies
• phenotypically variable
  • onset
  • rate of progression
  • severity
  • fundus appearance
  • fundus autofluorescence
  • electrophysiology
  • psychophysics

Single gene disorders affecting the retina
Inherited retinal diseases

- stationary versus progressive
- predominant rod vs. cone
- macular vs. periphery
- structural developmental disorders

Disorders

- Retinitis Pigmentosa *
  - progressive rod photoreceptor demise
- Cone dystrophy / Cone-Rod dystrophy
- Achromatopsia *
  - Stationary cone dysfunction
- Congenital night blindness *
  - Stationary rod dysfunction
- Macular Dystrophies
  - Best Disease

Electrophysiology and retinal structure

Standard full-field ERGs

Dark-adapted

Light-adapted
Pattern Electroretinography

- Contrast response reflects macular function
- No significant contribution from the peripheral retina

Inheritance

- Autosomal dominant
- Autosomal recessive
- X-linked recessive
- Mitochondrial (16,569bp)
- X-linked dominant (incontinentia pigmenti, Aicardi)
- Digenic (bi- or triallelic)
  - \( RDS^{+-} \) & \( ROM1^{+-} \) -> RP (Kajiwara, Dryja Science 1994)
  - Bardet-Biedl Syndrome (Katsanis Science 2001)
- Rules
  - If male to male not X-linked
  - If male to anyone not mitochondrial

Number of single gene disorders affecting retinal function

- 46 year old male
- Night blindness since teens
- Mainstream education
- Driving until 20s
- Progressive loss of field
- Family history of vision loss (mother, maternal uncle, maternal grand-father)

http://www.retnet.org
Autosomal Dominant RP

• Rhodopsin gene (RP4) chromosome 3q
• Mutation
  – c.1040c->t
  – p.Pro347Leu

14 year old boy

• Night-blindness
• Fit and well, no medication history
• Acuities 6/6 6/6 (emmetrope)
• Mild restriction of visual field
14 YRS  glaucoma
RP11

- 19q ADRP Vithana et al. (2001) PRPF31
- one of four splicing genes causative of ADRP –
  - PRPF8 – RP13, 17p
  - PRPF3 – RP18, 1q
  - Pim-1 kinase Activating protein – RP9, 7p
- non-penetrance of carriers is due to allele from non-affected parent.

ADRP genes

- rod opsins - RP4 - 3q
- NRL - RP27 14q #
- PRPF8 - RP13 - 17p
- PRPF31 - RP11 - 19q *
- PRPF3 - RP18 - 1q
- PAP1 - RP9 - 7p *
- IMPDH1 - RP10 - 7q
- NR2E3 – 15q #
- RDH12 – 14q #
- TOPORS – RP31 – 9q
- RDS - RP7 - 6p
- ORP1 - RP1 8q *

Red – rod specific expression
Blue – splicing factor
Dark blue – other ubiquitously expressed gene
Green – expressed in both rods and cones, rods more susceptible to mutation
# - other alleles cause recessive disease

http://www.retnet.org
Non-syndromic ARRP genes

- USH2A
- NR2E3
- PDE6A
- PDE6B
- LRAT
- MERTK – central macular hyperfluorescent plaque
- CNGA1
- CNGB1
- CERKL
- RLBP1 – white dots when early, gyrate-like appearance later
- RGR
- RDH12
- SAG
- TULP1
- APL1
- CRB1 – perivascular sparing, retinal thickening and RPE pigment
- GUCY2D – severe, photophobia common, preserved retinal appearance
- RPE65 – absent retinal autofluorescence
- RPGRIP1
- ABCA4 – starts with macular dystrophy
- CYP4V2 – intraretinal crystals
- NR6 – similar to NR2E3 disease
- SPATA7
- CEP290
- LCA5
- EYS
- IDH3B
- PCDH21

♀ 32 y

Difficulty seeing detail
- Better seeing in the dark (?better than others)
- colour discrimination poor
- wears tinted spectacles
- ‘no worse’ over lifetime

• No family history, parents are first cousins
• VA: BE: 6/60, nystagmus, HRR/Ishihara test plates only
Molecular Genetics

**CNGA3** (2q11) : cone $\alpha$-subunit of the cGMP-gated (CNG) cation channel

**CNGB3** (8q21-q22) : cone $\beta$-subunit of the CNG cation channel

**GNAT2** (1p13) : cone $\alpha$-subunit of transducin

Chromosome 14 (isodisomy) **CNGB3**

**PDE6C** (10q24) : cone $\alpha$-subunit of cGMP-phosphodiesterase (PDE)

Inherited macular dystrophies

- progressive central visual loss
- clinically heterogeneous
- variable severity
- bilateral symmetrical macular abnormalities
- AD, AR, XL & mitochondrial inheritance
- dysfunction not always limited to macula
Stargardt disease

- AR retinal dystrophy
- macular atrophy
- white flecks at level of RPE
- abnormal autofluorescent material in RPE
- lipofuscin accumulation in RPE
- abnormal pattern ERG
- normal / ↓ cone / ↓ cone-rod ffERG

Age 14
VA 6/60 6/36
10 year brother
VA 6/18  6/18

**ABCA4 gene**
- Locus 1p21
- 50 exons
- highly polymorphic
- expressed in rod and cone photoreceptors
- encodes ABC transporter protein involved in removing all-trans retinal from OS discs

Allikmets et al Nat Genet 1997;17:8269-81

**AF imaging in STGD disease**

**ABCA4 mutations and retinal disease**

- normal
- null
- missense
- AMD

- RP/CORD
- STGD
- STGD
- null
A2E formation in RPE
A2E is major fluorophore of lipofuscin

Stargardt disease
Associated with accumulation of A2E in RPE
High levels of A2E:
- damages cell membranes
- affects lysosomal function
- results in release of pro-apoptotic proteins from mitochondria

Therapy in mouse model
Slow visual cycle:
- limit light exposure
- isotretinoin (13-cis retinoic acid)
Stargardt disease

- primary abnormality is in photoreceptors
- defective ATP dependent transport mechanism
- leads to accumulation of A2E and lipofuscin in RPE
- secondary photoreceptor atrophy

Therapeutic agents may be targeted at the ATP dependent transport mechanism, slowing visual cycle or A2E formation

Subject OS

- age 5
- nyctalopia from birth
- Light staring from 2/52
- Squint at 6/12
- Poor vision noted from 10/12
- Decreased VF from 1 yr
- No nystagmus
RPE65
... is a candidate for gene therapy

Lancelot: 2001


Gene therapy in patients with RPE65 mutations 2008

Maguire et al – NEJM May 2008
Bainbridge et al - NEJM May 2008
Cideciyan et al – PNAS Sept 2008

RPE65 trials – comparisons

- Subjective improvement in dark vision, 1 – 2 weeks, in two studies
- Improved visual function in 7/9 patients.
- ERG, retinal structure (AF OCT) unchanged
- One significant complication – macular hole (Maguire et al)

Visually-guided mobility:
Subject #3; 6 months following surgery

Subject 3
Right (study) Eye
4 lux Illumination
Gene therapy future

- RPE65
  - Longer follow up
  - Younger patients
- RPE disease
  - MERTK, BEST1, REP1, LRAT, CYP4V2, RLBP1
- Photoreceptor disease
- Dominant disease (knock-down replacement strategy)
- Assessing efficacy in a timely fashion is a significant challenge

Inherited Retinal Dystrophies

- wide heterogeneity
- therapy may be possible in progressive disorders
- novel therapies will be directed at patients with known genotype
- knowledge of disease mechanisms will dictate therapeutic approaches
- disorders must be well characterised
- natural history must be known