NIH Public Access
Author Manuscript
Clin Genet. Author manuscript; available in PMC 2014 November 21.

Published in final edited form as:
Clin Genet. 2013 August ; 84(2): 99–101. doi:10.1111/cge.12204.

The golden era of ocular disease gene discovery: Race to the finish

A Swaroop and **PA Sieving**
National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

Within the last decade, technological advances have led to amazing genetic insights into Mendelian and multifactorial ocular diseases. We provide a perspective of the progress in gene discovery and discuss the implications. We believe that the time has come to redefine the goals and begin utilizing the genetic knowledge for clinical management and treatment design. The unbelievable opportunities now exist for those nimble enough to seize them.

Keywords

clinical management; genetics; next-generation sequencing; ocular disease; therapies; vision

Nowhere in the field of medicine is the impact of genetics so evident as in diseases affecting vision and visual function. Vision is the most extensive of all human senses, and complex higher order tasks are largely dependent on the world we see. Loss of sight has devastating personal and social consequences, with tremendous burden on world resources. Investigations of healthy vision and visual disorders have been at the leading edge in genetics and biomedical research, creating major strides in diagnosis, therapy and clinical management. In this issue, eleven leading groups cover a broad spectrum of ocular diseases and discuss the genetic studies from the perspective of both clinicians and scientists.

A touch of history

Genetics of diseases affecting vision is celebrating 30 years of remarkable success. We have come a long way in defining the genetic basis of ocular disease since the linkage of a polymorphic DNA marker L1.28 (by old-fashioned Southern blotting) on the X chromosome to retinitis pigmentosa (RP) (1) and the cytogenetic identification of a genomic deletion encompassing Duchenne muscular dystrophy, chronic granulomatous disease and RP (2). Soon thereafter, two major discoveries rocked the world of molecular genetics with repercussions far beyond – the identification of genes for retinoblastoma (3, 4) and for the G-protein coupled receptors, visual opsins, that underlie vision and variations in color perception (5). The mapping of an autosomal dominant RP locus near rhodopsin and

Corresponding author: Anand Swaroop, National Eye Institute, National Institutes of Health, Bethesda, MD, USA. Tel.: 301-435 5754; fax: 301-480-9917; swaroopa@nei.nih.gov.

Conflict of interest
The authors have no conflict of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

subsequent identification of rhodopsin mutations in 1990 (6, 7) began an extraordinary decade of gene discovery in vision research. Extensive genetic heterogeneity soon became obvious for most clinical entities that were grossly defined based on observed phenotypes. In this issue, three reports (by Daiger et al., pp. 132–141; Liu & Zack, pp. 142–149; and Coussa et al., pp. 150–159) provide an update on Mendelian retinal diseases and associated intricacies.

Visual dysfunction as part of syndromic diseases

While debilitating, loss of vision is not life threatening, and it persists in the human population. In addition, visual dysfunction can be easily recognized by patients and objectively analyzed by clinicians. Hence, it is not surprising that 25–30% of diseases listed in the compendium of human genes and phenotypes (http://www.ncbi.nlm.nih.gov/omim) have a vision-associated term in their clinical descriptions. Previously under-appreciated aberrant visual phenotypes are now being identified in numerous syndromic diseases. Retinal and auditory dysfunctions are observed in Usher syndrome causing deaf-blindness (8). Ciliopathies, a general term used for diseases affecting the primary cilium, include a highly penetrant phenotype of photoreceptor dysfunction, along with varying degree of kidney, brain and hearing defects (9).

The transition from rare and monogenic disease to multifactorial common disorders

Identification of complement factor H (*CFH*) as a susceptibility locus for age-related macular degeneration (AMD) was a watershed event in the genetic studies of complex diseases. Three concurrent pioneering reports in the same issue of *Science* (10–12) and two others (13, 14) provided a huge dose of confidence to frustrated researchers working on common and complex diseases, underscoring the power of human genome project (15) and validating international efforts on the generation of haplotype map (16). Subsequent genome-wide association studies and meta-analysis have now identified and confirmed at least 19 genetic loci that are associated with susceptibility to AMD (17–19). For the first time we have direct clues to probe the biological basis of this devastating ocular disease. We have also begun to elucidate complexities of other common visual dysfunctions, as elaborated in five reports in this issue (Wiggs et al., pp. 167–174; Aldave et al., pp. 109–119; Stambolian, pp. 102–108; Shiels & Hejtmancik, pp. 120–127; and Ratnapriya & Chew, pp. 160–166).

The advent of next-generation sequencing

Next-generation sequencing platforms have revolutionized the field of biology and medicine (20, 21). Clinically relevant genetic diagnosis and treatment designs are now conceivable using tiny amounts of nucleic acids or even a single cell (22–25). Whole exome sequencing is rapidly being used around the globe to find genetic defects in small families or simplex patients (26). The analytics remain extremely challenging and represent one of the research forefronts. With declining cost and high efficiency methodology, whole genome sequencing is no longer out of reach. These studies are expected to yield new insights into the role of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

variants from multi-gene contributions and modifiers for otherwise monogenic traits and will help clarify the severity range between affected individuals even within a single family.

What follows?

At 30, the field of ocular genetics is mature and consolidating what has been learned. It is now time to apply this knowledge for the benefit of patients. Two articles (by Blain et al., pp. 190–197 and by Branham & Yashar, pp. 183–189) discuss the power of genetics in counseling patients and families. In addition, genetic grouping of patients is an effective biological adjunct to clinical phenotyping in the selection of patients for appropriate therapies, as discussed by Jacobson et al. (pp. 175–182) in this issue.

Despite major strides, the challenges remain for complete translation of gene discovery data to clinical settings. In vision disorders, like others, the clinical findings do not always correlate with identified genetic defects. This is likely due to extensive genetic diversity in humans as many alleles while silent on their own may modify the impact of other mutations. Thus, one must be cautious in interpreting the genetic data for clinical management. The next frontier in clinical genetics will involve the incorporation of patient-specific genetic information into interaction networks and cellular pathways.

Rational treatment design

Gene discovery for visual dysfunctions has provided powerful new avenues for gene-based therapies, founded on the understanding of basic biology. Three independent groups have successfully performed the gene therapy for Leber congenital amaurosis caused by mutations in *RPE65* (27–29). However, disease biology rapidly invokes secondary biological complexities, and we must not be lulled into considering gene therapy a complete cure with reversion to a fully normal state; some issues will require additional scrutiny (30, 31). The current complexity of disease causing genes, each with many unique mutations, ultimately will succumb to rapid and tailored interventions beyond current technologies. Meanwhile, the complexity of clinical phenotypes is already giving way to disease insights at the cellular and systems level that yield opportunity for rational treatment design.

Final thoughts

The primary contribution of genetics is the evolution of the concept of medical disease. Retinal and macular degeneration, cone–rod dystrophies, cataract, and corneal dystrophies are now being recognized based on the underlying gene or genetic defect. The clinicians and surgeons examining the patients are becoming aware of the genetic underpinnings and biological process(es) that cause the disease, assisting in better counseling, clinical management and treatment strategies.

References

1. Bhattacharya SS, Wright AF, Clayton JF, et al. Close genetic linkage between X-linked retinitis pigmentosa and a restriction fragment length polymorphism identified by recombinant DNA probe L1.28. Nature. 1984; 309:253–255. [PubMed: 6325945]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

2. Francke U, Ochs HD, de Martinville B, et al. Minor Xp21 chromosome deletion in a male associated with expression of Duchenne muscular dystrophy, chronic granulomatous disease, retinitis pigmentosa, and McLeod syndrome. Am J Hum Genet. 1985; 37:250–267. [PubMed: 4039107]
3. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature. 1986; 323:643–646. [PubMed: 2877398]
4. Lee WH, Bookstein R, Hong F, Young LJ, Shew JY, Lee EY. Human retinoblastoma susceptibility gene: cloning, identification, and sequence. Science. 1987; 235:1394–1399. [PubMed: 3823889]
5. Nathans J, Thomas D, Hogness DS. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. Science. 1986; 232:193–202. [PubMed: 2937147]
6. Blanton SH, Cottingham AW, Giesenschlag N, Heckenlively JR, Humphries P, Daiger SP. Further evidence of exclusion of linkage between type II autosomal dominant retinitis pigmentosa (ADRP) and D3S47 on 3q. Genomics. 1990; 8:179–181. [PubMed: 2081594]
7. Dryja TP, McGee TL, Reichel E, et al. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature. 1990; 343:364–366. [PubMed: 2137202]
8. Friedman TB, Schultz JM, Ahmed ZM, Tsilou ET, Brewer CC. Usher syndrome: hearing loss with vision loss. Adv Otorhinolaryngol. 2011; 70:56–65. [PubMed: 21358186]
9. Novarino G, Akizu N, Gleeson JG. Modeling human disease in humans: the ciliopathies. Cell. 2011; 147:70–79. [PubMed: 21962508]
10. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science. 2005; 308:385–389. [PubMed: 15761122]
11. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005; 308:419–421. [PubMed: 15761120]
12. Edwards AO, Ritter R 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science. 2005; 308:421–424. [PubMed: 15761121]
13. Zareparsi S, Branham KE, Li M, et al. Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. Am J Hum Genet. 2005; 77:149–153. [PubMed: 15895326]
14. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci USA. 2005; 102:7227–7232. [PubMed: 15870199]
15. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. JAMA. 2001; 285:540–544. [PubMed: 11176855]
16. International HapMap Consortium. The International HapMap Project. Nature. 2003; 426:789–796. [PubMed: 14685227]
17. Chen W, Stambolian D, Edwards AO, et al. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. Proc Natl Acad Sci USA. 2010; 107:7401–7406. [PubMed: 20385819]
18. AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. Nat Genet. 2013; 45:433–439. [PubMed: 23455636]
19. Neale BM, Fagerness J, Reynolds R, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). Proc Natl Acad Sci USA. 2010; 107:7395–7400. [PubMed: 20385826]
20. Mardis ER. Next-generation sequencing platforms. Annu Rev Anal Chem. 2013 Apr 1. [Epub ahead of print]. PMID: 23560931.
21. Metzker ML. Sequencing technologies – the next generation. Nat Rev Genet. 2010; 11:31–46. [PubMed: 19997069]
22. Hawkins RD, Hon GC, Ren B. Next-generation genomics: an integrative approach. Nat Rev Genet. 2010; 11:476–486. [PubMed: 20531367]
23. Gargis AS, Kalman L, Berry MW, et al. Assuring the quality of next-generation sequencing in clinical laboratory practice. Nat Biotechnol. 2012; 30:1033–1036. [PubMed: 23138292]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

24. Wong KM, Hudson TJ, McPherson JD. Unraveling the genetics of cancer: genome sequencing and beyond. Annu Rev Genomics Hum Genet. 2011; 12:407–430. [PubMed: 21639794]

25. Katsanis SH, Katsanis N. Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013; 14:415–426. [PubMed: 23681062]

26. Cooper GM, Shendure J. Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data. Nat Rev Genet. 2011; 12:628–640. [PubMed: 21850043]

27. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med. 2008; 358:2240–2248. [PubMed: 18441370]

28. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med. 2008; 358:2231–2239. [PubMed: 18441371]

29. Hauswirth WW, Aleman TS, Kaushal S, et al. Treatment of Leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial. Hum Gene Ther. 2008; 19:979–990. [PubMed: 18774912]

30. Jacobson SG, Cideciyan AV, Ratnakaram R, et al. Gene therapy for Leber congenital amaurosis caused by RPE65 mutations: safety and efficacy in 15 children and adults followed up to 3 years. Arch Ophthalmol. 2012; 130:9–24. [PubMed: 21911650]

31. Cideciyan AV, Jacobson SG, Beltran WA, et al. Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement. Proc Natl Acad Sci USA. 2013; 110:E517–E525. [PubMed: 23341635]