A study of candidate genes for day blindness in the standard wire haired dachshund
Anne Caroline Wiik1, Ernst-Otto Ropstad2, Ellen Bjerkås2 and Frode Lingaas*1

Address: 1Department of Basic Sciences and Aquatic Medicine, Division of Genetics, Norwegian School of Veterinary Science, P.O.Box 8146 Dep, 0033 Oslo, Norway and 2Department of Companion Animal Clinical Sciences, Norwegian School of Veterinary Science, P.O.Box 8146 Dep, 0033 Oslo, Norway

Email: Anne Caroline Wiik - annecaroline.wiik@veths.no; Ernst-Otto Ropstad - Ernst-Otto.Ropstad@veths.no; Ellen Bjerkås - ellen.bjerkaas@veths.no; Frode Lingaas* - frode.lingaas@veths.no

* Corresponding author

Abstract

Background: A genetic study was performed to identify candidate genes associated with day blindness in the standard wire haired dachshund. Based on a literature review of diseases in dogs and human with phenotypes similar to day blindness, ten genes were selected and evaluated as potential candidate genes associated with day blindness in the breed.

Results: Three of the genes, CNGB3, CNGA3 and GNAT2, involved in cone degeneration and seven genes and loci, ABCA4, RDH5, CORD8, CORD9, RPGRIP1, GUCY2D and CRX, reported to be involved in cone-rod dystrophies were studied. Polymorphic markers at each of the candidate loci were studied in a family with 36 informative offspring. The study revealed a high frequency of recombinations between the candidate marker alleles and the disease.

Conclusion: Since all of the markers were at the exact position of the candidate loci, and several recombinations were detected for each of the loci, all ten genes were excluded as causal for this canine, early onset cone-rod dystrophy. The described markers may, however, be useful to screen other canine resource families segregating eye diseases for association to the ten genes.

Background

Inherited retinal degenerations form a diverse spectrum of blinding disorders in humans and other mammals, including a large number of dog breeds [1]. Retinal diseases are inherited as monogenic or complex traits. In the last two decades over 130 genes that cause retinal diseases have been identified [2].

Progressive retinal atrophies (PRA) are the most common retinopathies in dogs and constitute a heterogeneous group of phenotypically similar disorders equivalent to retinitis pigmentosa (RP) in man. PRA, like RP, is primarily a disease of rod photoreceptors, while cone function and structure degenerate secondarily. PRA has been identified and studied in more than 100 breeds and distinct loci primarily responsible for each disorder have been identified in at least 22 different breeds [1,3].

The cone dystrophies comprise a phenotypically heterogeneous group of hereditary retinal degenerations characterized by progressive dysfunction of the photopic (cone-mediated) system. The presenting signs include day blind-
ness, loss of colour vision, reduced central visual acuity and preserved peripheral vision [4]. The cone dystrophies are genetically heterogenous and may be sporadic, autosomal dominant, autosomal recessive or X-linked recessive [2].

Canine cone degeneration is phenotypically similar to human achromatopsia [5]. Identified genes associated with human achromatopsia are the phototransducin genes GNAT2 (HSA1) [6], the CNGA3 (HSA2) [7] and the CNGB3 (HSA8) [8] genes.

Autosomal recessive cone degeneration occurs naturally in Alaskan malamute [9] and German shorthaired pointer (GSP) and is due to different mutations in CNGB3 [5,10]. Sporadic cases is seen in a number of other breeds [11,12].

The cone-rod dystrophies (crd) are characterized by a predominant loss of cone function, with relative preservation of rod function [13,14]. The number of genes or loci currently identified for crd in humans is low, compared to those for RP [2]. Identified genes associated with autosomal recessive inherited crd in man include ABCA4 [15,16] and RDH5 [17] in addition to the mapped loci CORD8 [18,19] and CORD9 [20]. ABCA4 and RDH5 are genes involved in the retinoid cycle, the CORD8 and CORD9 loci are yet to be identified. The standard wire haired dachshund (SWHD), the miniature long haired dachshund (MLHD) and the pit bull terrier (PBT) are the only dog breeds to date known to be affected by crd [21-23].

Canine ABCA4 has been studied as a candidate gene for cone-rod degeneration in the pit bull terrier, although no mutations were found [21]. Mutations in the RPGRIP1 gene have been reported to be a cause of Leber congenital amaurosis (LCA) [24,25]. LCA is the earliest and most severe form of all retinal dystrophies responsible for congenital blindness [26]. Mutations causing residual RPGRIP1 activity may lead to phenotypes such as RP or crd, which are less severe than LCA [27]. In 2003, Hameed et al. (2003) [28] showed evidence that some RPGRIP1 gene mutations are associated with recessive cone-rod dystrophy. Recently Mellersh et al. (2006) [22] found a mutation in canine RPGRIP1 associated with autosomal recessive crd in miniature longhaired dachshunds.

A high level of genetic heterogeneity of the disease group is observed and a range of mutations in RPGRIP1, CRX and GUCY2D cause different retinal diseases with different modes of inheritance [14,27-34].

A resource strain of standard wire haired dachshund displaying day blindness was developed to allow characterization of the phenotype and identification of the causal mutation. Electrophotography (ERG) and clinical studies showed that secondary degeneration of the rods appeared during the progression of the disease of the dogs of the colony, indicating a progressive cone-rod dystrophy (crd) [23]. The disease seems to be inherited in an autosomal recessive manner, and diversity in the age of onset and progression of the retinal degeneration within the group of affected dachshunds is observed.

This study was conducted in parallel with clinical studies [35] and genes known to be involved in human cone degeneration, cone dystrophy and cone-rod dystrophy were evaluated as candidate genes for the day blindness in the SWHD (See Table 1).

### Results

An overview of the studied genes and their location is shown in Table 1. Studies of segregation of each of the 10 candidate loci and clinical disease in informative parents and offspring revealed a number of new candidate gene allele-disease phenotype combinations ("recombinants") in the offspring. The segregation of potential candidate gene alleles was studied in inbred offspring from parents

| Candidate | Canine chr | Location | Annotation | Coding for | Disease* |
|-----------|------------|----------|------------|------------|----------|
| CNGB3     | CFA29      | 35896147-35752878 | NC_006611 | cyclic nucleotide gated channel beta 3 | cd |
| CNGA3     | CFA10      | 47377091-47357441 | NC_006592 | cyclic nucleotide gated channel alpha 3 | cd |
| GNAT2     | CFA6       | 45319301-45327681 | NC_006588 | guanine nucleotide binding protein (G protein), alpha transducing activity polypeptide 2 | cd |
| ABCA4     | CFA6       | 58112924-58240779 | NC_006588 | ATP-binding cassette, sub-family A (ABC1), member 4 | crd |
| RDH5      | CFA10      | 3102451-3106432 | NC_006592 | retinol dehydrogenase 5 (11-cis/9-cis) | crd |
| CORD8     | CFA9       | HSA1q12-24 | unknown | unknown | crd |
| CORD9     | CFA9       | HSA1p11 | unknown | unknown | crd |
| RPGRIP1   | CFA15      | 21355638-21394395 | NC_006597 | retinitis pigmentosa GTPase regulator interacting protein 1 | crd |
| GUCY2D    | CFA5       | 35838279-35853509 | NC_006587 | guanylate cyclase 2D, membrane (retina-specific) | crd |
| CRX       | CFA1       | 111135799-111146903 | NC_006585 | cone-rod homeobox | crd |

*cd = cone degeneration and crd = cone-rod-dystrophy
with known disease genotypes. Females where either homozygous affected (= clinical diseased) or carriers (= clinical healthy offspring of affected male). Since the father in these litters usually was homozygous affected, the theoretical phenotype of the offspring would depend on which of the two potential alleles (affected or non-affected) it received from its carrier mother. The most frequently occurring genotype-phenotype combination was counted as the non-recombinants, while any new genotype-phenotype combination, with regard to their parents, was counted as recombinant. Each litter was counted as a separate unit and the recombination frequency were summed over all families. A minimum of 6 recombinants were identified for each of the 10 loci (See Table 2). This excludes all the candidate genes as the cause of mutation causing the disease. The family is illustrated in Figure 1. The genotypes of ABCA4-markers are shown below each individual and show free recombination of ABCA4-variants between affected and unaffected offspring.

## Discussion

The large number of retinal genes or loci have been identified and presented at the RetNet™ web page [2], facilitates a candidate gene approach in the study of canine retinal diseases. Human genes with mutations giving similar phenotypes and inheritance patterns to the one found in the affected SWHDs were selected as candidate genes. The preliminary clinical diagnoses for the affected SWHDs suggested that the disease was comparable with human cone degeneration, hence the inclusion of CNGB3, CNGA3 and GNAT2, which are associated primarily with cone degeneration. In the initial phase of the study the family material was not sufficient for segregation studies and we therefore sequenced the coding parts of these three genes. No mutations where identified in any of the three genes (methods and results not shown). Continued electrophysiological and clinical studies of the affected dachshunds were conducted in parallel with the genetic studies and revealed secondary continuing degeneration of the rods, indicating a progressive cone-rod dystrophy (crd) [23]. Seven genes reported to be associated with autosomal recessive cone-rod dystrophies (crd) [2], ABCA4, RDH5, CORD8, CORD9, RPGRIP1, CRX and GUCY2D were therefore included in the study.

It is important to be aware of the fact that the disease-allele/haplotype present in all dogs in the family arises from inbreeding on one single affected founder (Figure 1). The informative markers were selected at the exact position of the candidate genes, most of them less than approximately 0.1 Mb distance. A distance of 0.1 Mb compares to a genetic distance of ~0.1 cM, or 1 recombination per 1000 offspring. The minimum number of detected recombinations in our family (1 recombination per 36 informative offspring) would compare to a recombination frequency/genetic distance of ~2.8 cM or a physical distance of ~2.8 Mb. We would not expect any recombinants if a mutation in any of the candidate genes caused this disease with a simple recessive inheritance. Our results show a minimum of 6 recombinations (GNAT2; 31 informative offspring) or more than 19.3 Mb distance (Table 2), excluding all the candidate genes as the site of the mutation causing the disease. However, even though the specific candidate genes can be excluded as the cause of the disease because of the high number of recombinations, the chromosomal regions are not necessarily excluded. The clinical findings defining the diseases as a cone-rod dystrophy rather than cone degeneration also support the exclusion of CNGB3, CNGA3 and GNAT2. The candidate loci CORD8 and CORD9 are not yet mapped and the genes remain to be identified, but the markers typed for these loci are located within 2.8 Mb of the gene and several recombinations exclude these loci as well.

It might be considered likely that crd in MLDH and SWDH was caused by the same mutation, since these two breeds have in part the same genetic background. There are, however, obvious differences in the clinical phenotypes of the disease in the two breeds. One of the most characteristic clinical findings in the SWDH is pinpoint-sized pupils, observed in 60% of the 8-week old, crd-affected puppies. Older crd-affected dogs displayed dilated pupils and delayed pupillary light reflexes (PLRs)

| Locus   | no. of informative offspring | no. of recombinant offspring | Recombination frequency | LOD score |
|---------|------------------------------|------------------------------|-------------------------|-----------|
| CNGB3   | 34                           | 11                           | 0.32                    | 0.940     |
| CNGA3   | 20                           | 7                            | 0.35                    | 0.397     |
| GNAT2   | 31                           | 6                            | 0.19                    | 2.717     |
| ABCA4   | 34                           | 11                           | 0.32                    | 0.940     |
| RDH5    | 34                           | 11                           | 0.32                    | 0.940     |
| CORD8   | 25                           | 10                           | 0.40                    | 0.219     |
| CORD9   | 18                           | 5                            | 0.28                    | 0.800     |
| CRX     | 24                           | 8                            | 0.33                    | 0.590     |
| GUCY2D  | 23                           | 7                            | 0.30                    | 0.786     |
when stimulated with a focal light source [23]. This is in contrast to the clinical signs of PBT and MLHD, which include dilated pupils at 7–8 weeks of age for PBT and normal PLRs at 25 weeks of age for MLHD, respectively [21,34]. The differences in clinical signs between the MLHD and the SWHD, support the finding of free recombination between RPGRIP1 and the disease in the SWHD. This shows that this disease in the SWHDs is a unique animal model for cone-rod dystrophy.

The development of animal models of ocular disease represents an invaluable resource for testing and evaluating treatment strategies relevant to both human and canine disease. Attempts at restoring vision in dogs and human by gene therapy have been made, providing optimism regarding potential for recovery of functional vision [36-41]. Uncovering the genetic basis of the cone-rod dystrophy in the SWHD may contribute to finding new gene therapy treatments.

The present work has excluded a number of genes as a cause of crd in the SWHD. Research in human and animals continuously identifies new genes that may be associated with crd. In addition to continued studies of a few specific candidate genes, future research will focus on a whole genome scan by linkage studies with polymorphic markers [42] or by SNP-array typing [43]. The development of the canine genotyping array of ~27000 SNPs show that genome-wide association mapping of mendelian traits in dog breeds can be achieved with only ~20 dogs [44]. The use of SNP array technology, followed by fine mapping based on microsatellites and regional gene studies may be the best method to elucidate which gene is involved in this disease.

**Conclusion**

The genes involved in cone degeneration, CNGB3, CNGA3 and GNAT2, and the genes involved in cone-rod dystrophy, ABCA4, RDH5, Cord8, Cord9, RPGRIP1, GUCY2D and CRX, were all excluded from being involved in the cone-rod dystrophy described in this family of SWHD. The study provides a number of genetic markers for use in other studies. Further work, based on a whole genome association study will be performed to identify the mutation involved in the disease.

![Figure 1](http://www.biomedcentral.com/1746-6148/4/23)

**Figure 1**

The informative resource family, consisting of offspring from a single affected male. The numbers below each individual represent ABCA4 genotypes, and clearly shows the free recombination of marker-alleles compared to disease in the family.
Methods

Animals
Day blindness was diagnosed in two wire haired dachshund littermates, one male and one female, in a litter of four. The parents were phenotypically normal. The male was bred to two unrelated crossbred dogs with no history of previous eye disease and the dogs in the F1 generation were unaffected. A purpose-bred colony was established through back-crossing the male with his daughters, producing both affected and unaffected offspring. The retinal changes were always bilaterally symmetrical and the initial onset was observed from 10 months to 3 years of age. A complete retinal atrophy was evident within the age of 5–6 years.

Clinical diagnosis
To evaluate vision, all dogs were subjected to behavioral testing (maze test), examination of pupillary light reflexes (PLRs), indirect ophthalmoscopy and bilateral full-field electroretinography (ERG). Light microscopy, electron microscopy and immunohistochemistry were carried out in 22 selected cases at ages 5–304 weeks, in order to confirm the diagnoses [23].

All procedures used in this study adhered to the guidelines of the Norwegian Animal Research Authority (Forsøksdyrutfall) and to the Association for Research in Vision and Ophthalmology's "Statement for the use of Animals in Ophthalmic Vision and Research".

Samples
Blood samples were collected into EDTA-coated tubes from all the related dogs in the day blind colony and from two non-affected, unrelated dogs. Genomic DNA was isolated from the blood samples using DNeasy Tissue kit (Qiagen, GmbH, Germany).

The collected DNA samples were subjected to candidate gene screening. All the ten loci were typed by polymorphic markers at these loci in five informative dachshund families comprising 43 dogs -7 parents and 36 offspring (Figure 1), to detect recombinants between each of the loci and the disease.

Study of marker-disease segregation in the resource family
Genotyping of CNGB3 was done with two closely linked markers, FH2772 [45] and c29.002 [46], embracing the

Table 3: Primers for amplification of the microsatellites at the exact position of the candidate gene loci

| Microsatellite | Forward primer (5’-3’) | Reverse primer (5’-3’) | Size of PCR-product (bp) | Nucleotide repeat | Location (bp) | Accession number |
|----------------|------------------------|------------------------|-------------------------|------------------|---------------|-----------------|
| CNGB3-FH2772   | CCCAAAGCACAATCCTAA TTT | GGAGTCTGCTTCTCCCT TTC | 168                     | di               | Chr29:35405042-35405217 | UniSTS 263646 |
| CNGB3-C29.002  | TATTAATTCCAGTACC ACCC | AGGCCAGGACGACTTC C | 208                     | di               | Chr29:36423257-36423471 | UniSTS 262830 |
| CNGA3-GT19     | CTCCTCCTCCCTCCTCCTC TAG | CCAGGGGAGCTTTC TACA A | 337                     | 3                   | Chr10:47307640-47307977 | BV729091 |
| CNGA3-GT20     | GCAAGCAGTCCGATTTTTTTA TTA | TCGCCGTTGGACTGCA CTC | 304                     | di               | Chr10:47283009-47283313 | BV729076 |
| GNT2-GAAA16    | CCCATTCTTGTCTTTAAGT CT | GACTGGTCTCCTCACCCA T | 350                     | tetra            | Chr6:45194834-45195184 | BV729077 |
| GNT2-CTT22     | CTTCTGGATTTCTCCCTA TGA | GCCCAAATTCTCAATCTC C | 273                     | tri              | Chr6:45461591-45461864 | BV729078 |
| ABCA4-FH2370   | CGTGAATAAATTGCTAGA TGGG | GGGAGTTTGGACAGTGGG AGA | 238                     | tetra            | Chr6:58046419-58046656 | BV729079 |
| RDH5-TAGA10    | GAAGATGAGCTAGTGA TGAAGA | GCTGAAATGAGAAGCTGT GAC | 286                     |               | Chr10:3068645-3068931 | BV729080 |
| RDH5-GAAA16    | CTCCTGGTTGAGAGTCTC AGT | AGCCAGATGCGAAGCTG GAT | 209                     |               | Chr10:30002063-3002276 | BV729081 |
| CORD8-FMOS-GAAA12 | CCCAAGTTGGGTTTTC AAGG | CCCCTCCCTCTCTCTTCTT CC | 204                     | tetra            | Chr9:60070458-60070662 | BV729082 |
| CORD8-FMOS-TTITA10 | CCAAGTTGGGTTTTC AAGG | CCCCTCCCTCTCTCTTCTT CC | 175                     |                | Chr9:60665430-60665480 | BV729083 |
| CORD9-RP1-ATm22 | CTCCTGGTACAAGAGTGC ACGA | GGTCTTGGAGAAGGAGA GCTG | 296                     |               | Chr29:9128657-9128953 | BV729084 |
| CORD9-RP1-TTTC21m | CTCCTGGTACCTGCTTCTC GAC | AGTCAATGGAGCCTGCA ACT | 410                     |               | Chr29:9011174-9011583 | BV729085 |
| RPGRIP1-GAAA26  | TGGTACCTGTTCCAAAGT TGGTTT | AGTTACGAGCGGGAGA GACA TGG | 475                     |                | Chr15:21287275-21287750 | BV729086 |
| GUCY2D-TTTC15  | ACAATGGGACATCTGT TGA | TTCCTGCTCTGCTGTG TCT | 405                     |                | Chr5:35459311-35459716 | BV729089 |
| GUCY2D-GAAA17  | CTCCTCCCTTCTCCCTA CCT | TCATTACCTGCTCCAG CAGT | 444                     |                | Chr5:35514793-35515246 | BV729090 |
| CRX-GAAA15m    | TGCTGTCACATTTTCTA CCT | AGAAGTGGCAGAGCACA GGT | 438                     |                | Chr1:111096908-111097346 | BV729087 |
| CRX-GT21       | ACCAGAAGCAAGGAGCAG ATG | TCAGGGTTGGAGTCTCTT AGG | 427                     | di              | Chr1:111076912-111077339 | BV729088 |
gene (530 Kb and 350 Kb distance respectively). Markers for genotyping of CNGA3, GNAT2 ABCA4, RDH5, CRX, GUCY2D and RPRGRIP1 were identified by searching a sequence of about 200,000 bp, including the gene(s) (gene +/− ~100,000 bp), for various microsatellite motives. FH2370, a marker closely linked to ABCA4 [46] was also genotyped. For the loci CORD5 and CORD9, 200,000 basepairs surrounding genes at the site of the two loci, respectively FM05 and RP1, were used to identify polymorphic markers. Tetra- and dinucleotide repeat microsatellites with more than ten and nineteen repeats, respectively, were selected. Primers for amplification of selected microsatellites were designed using primer3 [47] (See Table 3). One primer in each pair was labelled with fluorescein for automated detection in an automated fragment analyzer, ABI3100 Genetic Analyser.

PCR amplification reactions were performed using 83 μM of each primer in a 15 μl reaction containing 1.5 μl DNA prepared as described above, 1x PCR buffer containing 1.5 mM MgCl₂, 83 μM each of dATP, dCTP, dGTP and dTTP, and 0.33 units Taq DNA polymerase (Qiagen).

After an initial denaturation at 95°C for 2 min and 30 sec, samples were amplified for 28 cycles at 95°C for 30 sec, 58°C for 40 sec and 72°C for 50 sec, followed by a final extension of 72°C for 5 min and 30 sec. The sizes of the alleles were estimated with an automated sequencer (ABI PRISM™ 3100 Genetic Analyzer, Applied Biosystems, Foster City, CA, U.S.A.) with software for fragment analysis.

Authors' contributions
FL and EB jointly conceived of the study. ACW carried out most of the practical molecular part of the study supervised by FL. ACW drafted the manuscript in collaboration with FL, EOR and EB. All authors read and approved the final manuscript.

References
1. Kijas JW, Miller BJ, Pearce-Kelling SE, Aguirre GD, Acland GM: Canine models of ocular disease: outcross breedings define a dominant disorder present in the English mastiff and bull mastiff dog breeds. J Hered 2003, 94:27-30.
2. RetNet™ Retinal Information Network 2007 [http://www.sph.uth.tmc.edu/Retnet/]
3. Narfstrom K, Petersen-Jones S: Diseases of the canine ocular fundus. Blackwell publishing; 2006.
4. Sharpe LT, Stockman A, Jagle H, Nathans J: Color vision: from genes to perception. Edited by: edited by Karl R.Gegenfurtner LTS. Cambridge, Cambridge University Press; 1999:3-52.
5. Sidjanin DJ, Lowe JK, McBeelee JH, Milne BS, Shipp TM, Sargan DR, Aguirre GD, Acland GM, Ostender EA: Canine CNGB3 mutations establish cone degeneration as orthologous to the human achromatopsia locus ACHM3. Hum Mol Genet 2002, 11:1823-1832.
6. Aligania IA, Forshew T, Johnson S, Michalides M, Johnson CA, Trembath RC, Hunt DM, Moore AT, Maher ER: Mapping of a novel locus for achromatopsia (ACHM4) to 1p and identification of a germline mutation in the alpha subunit of cone transducin (GNAT2). J Med Genet 2002, 39:656-660.
7. Kohl S, Marx T, Giddings I, Jagle H, Jacobson SG, Apfelstedt-Sylla E, Zrenner E, Sharpe LT, Wissinger B: Total colourblindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. Nat Genet 1998, 19:257-259.
8. Kohl S, Baumann B, Broghammer M, Jagle H, Sieving P, Kellner U, Speigel R, Anastasi M, Zrenner E, Sharpe LT, Wissinger B: Mutations in the CNGB3 gene encoding the beta-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. Hum Mol Genet 2000, 9:2107-2116.
9. Rubin LF, Bourns TK, Lord LH: Hemeralopia in dogs; heredity of hemeralopia in Alaskan Malamutes. Am J Vet Res 1967, 28:355-357.
10. Seddon JM, Hampson EC, Smith RI, Hughes IP: Genetic heterogeneity of day blindness in Alaskan Malamutes. Annm Genet 2006, 37:407-410.
11. Hurn SD, Hardman C, Stanley RG: Day-blindness in three dogs: clinical and electroretinographic findings. Vet Ophthalmol 2003, 6:127-130.
12. Aligianis IA, Forshew T, Johnson S, Michaelides M, Johnson CA, Trembath RC, Vrabec T, Hussles M, Donoso L, Small KW: Identification of GUCY2D gene mutations in CORD5 families and evidence of incomplete penetrance. Hum Mutat 2003, 21:170-171.
13. Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, Peiffer A, Zabriskie NA, Li Y, Hutchinson A, Dean M, Lupsik JR, Leppert M: Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science 1997, 277:1805-1807.
14. Udar N, Yelchitsa S, Chalukuya M, Yellore V, Nuisinowitz S, Silva-Garcia R, VRabe T, Hussles M, Donoso L, Small KW: Identification of GUCY2D gene mutations in CORD5 families and evidence of incomplete penetrance. Hum Mutat 2003, 21:170-171.
15. Allikmets R, Singh N, Seddon JM, Lewis RA, Bernstein PS, Peiffer A, Zabriskie NA, Li Y, Hutchinson A, Dean M, Lupsik JR: A photoreceptor cell-specific ATB-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet 1997, 15:226-246.
16. Yamamoto H, Simon A, Eriksson U, Berson EL, Dryja TP: Mutations in the gene encoding 11-cis retinol dehydrogenase cause delayed adaptation and fundus albipunctatus. Nat Genet 1999, 22:188-191.
17. Ismail M, Abid A, Ansawar K, Qasim MS, Khalid S: Refinement of the locus for autosomal recessive cone-rod dystrophy (CORD8) linked to chromosome 1q-24 in a Pakistani family and exclusion of candidate genes. J Hum Genet 2006, 51:827-831.
18. Khalid S, Hameed A, Ismail M, Anwar K, Leroy BP, Melville SQ, Payne AM, Bhattacharya SS: Novel locus for autosomal recessive cone-rod dystrophy CORD8 mapping to chromosome 1q-24. Invest Ophthalmol Vis Sci 2000, 41:3709-3712.
19. Danciger M, Hendrickson J, Lyon J, Toomes C, McHale JC, Fishman GA, Inglehearn CF, Jacobson SG, Farber DB: CORD9 a new locus for arCD: mapping to 8p11, estimation of frequency, evaluation of a candidate gene. Invest Ophthalmol Vis Sci, 2001, 42:2458-2465.
20. Kijas JW, Zangerl B, Miller B, Nelson J, Kirkness EF, Aguirre GD, Acland GM: Cloning of the canine ABCA4 gene and evaluation in canine cone-rod dystrophies and progressive retinal atrophies. Mol Vis 2004, 10:223-232.
21. Mellersh CS, Boursnell ME, Pettitt L, Ryder EJ, Holmes NG, Graftham D, Forman OP, Sampson J, Barnett KC, Blanton S, Binns MM, Vaudin M: Canine RPRGRIP1 mutation establishes cone-rod dystrophy in miniature longhaired dachshunds as a homologue of human Leber congenital amaurosis. Genomics 2006, 88:293-301.
22. Kopstad EO, Bjerkas E, Nafsetrom EF, Kuemper EM, Bhattacharya SS: Novel locus for autosomal recessive cone-rod dystrophy CORD8 mapping to chromosome 1q-24. Invest Ophthalmol Vis Sci 2000, 41:3709-3712.
23. Dryja TP, Adams SM, Grimsby JL, Mcgee TL, Hong DH, Li T, Andreaussen S, Berson EL: Null RPRGRIP1 alleles in patients with Leber congenital amaurosis. Am J Hum Genet 2001, 68:1295-1298.
24. Gerber S, Perrault I, Hanein S, Barbet F, Ducroq D, Ghazi I, Martin-Coignard D, Leowski C, Hoffmeyr T, Dufier JL, Munich A, Kaplan J, Rozet JM: Complete exon-intron structure of the RPRGR-interacting protein (RPRGRIP1) gene allows the identification of
mutations underlying Leber congenital amaurosis. Eur J Hum Genet 2001, 9:561-571.

26. Acland GM, Aguirre GD, Jacobson SG, McInnes RR, Zack DJ, Stone EM: The genetics of Leber congenital amaurosis. Hum Mol Genet 1998, 7:657-660.

27. Cremers FP, van den Hurk JA, den Hollander AJ: Molecular genetics of Leber congenital amaurosis. Hum Mol Genet 2002, 11:1169-1176.

28. Hameed A, Abid A, Aziz A, Ismail M, Mehdii SQ, Khalig S: Evidence of RPRGPI gene mutations associated with recessive cone-rod dystrophy. J Med Genet 2003, 40:616-619.

29. Freund CL, Gregory-Evans CY, Furukawa T, Papaioannou M, Looser J, Ploder L, Bellingham J, Ng D, Herbrick JA, Duncan A, Scherer SW, Tero K, Scanga D, Ostrander EA, Jacobson SG, Cepko CL, Bhattacharya SS, McNitt RE: Cone-rod dystrophy due to mutations in a novel photoreceptor-specific homeobox gene (CRX) essential for maintenance of the photoreceptor. Cell 1997, 91:543-553.

30. Swain PK, Chen S, Wang QL, Miles CD, Sheffield VC, Jacobson SG, McNitt RE, Dacki JM, Stowe EM: De novo mutations in the CRX homeobox gene associated with Leber congenital amaurosis. Nat Genet 1998, 18:311-312.

31. Sohocki MM, Sullivan LS, Mintz-Hittner HA, Birch D, Heckenlively JR, Freund CL, McNitt RE, Daiger SP: A range of clinical phenotypes associated with mutations in CRX, a photoreceptor transcription-factor gene. Am J Hum Genet 1998, 63:1307-1315.

32. Swain PK, Chen S, Wang QL, Scratchell JM, Coats CL, Brady KD, Fisher-Hall E, Bellingham J, McNitt RE, Comstock KE, Keller ET, Mesirov JP, von EH, Kampe Q, Heddhammer A, Marbella R, Marquiss WR, Ostrander EA, Ponting CP, Galibert F: Chro- somosome-specific single-locus FISH probes allow anchorage mapping of mendelian traits in dogs through genome-wide association. Nat Genet 2001, 28:1321-1328.