REPORT

Mutation of Solute Carrier *SLC16A12* Associates with a Syndrome Combining Juvenile Cataract with Microcornea and Renal Glucosuria

Barbara Kloeckener-Gruissem,[1,2,7,*] Kristof Vandekerckhove,[3,7,8] Gudrun Nürnberg,[4,6] John Neidhardt,[1] Christina Zeitz,[1,9] Peter Nürnberg,[4,5] Isaak Schipper,[3] and Wolfgang Berger[1]

Unobstructed vision requires a particular refractive index of the lens, a measure based on the organization of the structural proteins within the differentiated lens cells. To ensure an intact lens structure, homeostasis within the lens cells is indispensable. Alterations of the lens structure result in opacity and lead to cataract. Renal glucosuria is defined by elevated glucose level in the urine without hyperglycemia and without evidence of morphological renal anomalies. In a Swiss family with autosomal dominant juvenile cataract, microcornea, and renal glucosuria, we have identified a nonsense mutation in a member of the carboxylic acid transporter family SLC16. The underlying gene defect in *SLC16A12* resides within a 3 cM region on chromosome 10q23.13 defined by linkage mapping of this phenotype. We found tissue-specific variability of *SLC16A12* transcript levels in control samples, with high expression in the eye and kidney, the two organs affected by this syndrome. This report demonstrates biological relevance of this solute carrier. We hypothesize that SLC16A12 is important for lens and kidney homeostasis and discuss its potential role in age-related cataract.

Lens transparency, a requirement of unobstructed vision, is achieved by ordered events of cell differentiation accompanied by controlled arrangement of proteins, mainly crystallins. Differentiation of the lens cells follows a precise sequence of events.[1] Mitotic activity of a small number of lens epithelial cells (LEC) provides a continuous supply of new cells that, upon signal-induced differentiation, will begin with a cellular elongation process, followed by the breakdown of the nucleus and organelles. Concomitantly, some but not all metabolic activity ceases. Tightly packed, highly elongated cells comprise the several millimeter-thick lens structure. Changes in this structure, composition, or the assembly of the structural proteins, of which crystallines make about 90%, will result in alteration of the refractive index. This increasing opacity of the lens is termed cataract. Defined by age of onset, one distinguishes between congenital (infantile), juvenile, and age-related cataract. The first two, also referred to as childhood cataract, show wide heterogeneity with respect to the genetic and phenotypic aspects.[2] Frequently, mutations that disturb the development of the lens occur in structural lens proteins and will lead to childhood cataract. Among the genetic factors that influence age-related cataract, no genes with mutations have yet been identified. Genes involved in recessively or dominantly inherited cataract encode structural components of the lens cells but also components of the cytoskeleton, of the cell membrane, transcription factors, metabolic proteins, chromatin-modifying protein −4B, and the gene *TMEM114*, encoding a protein with four predicted transmembrane domains but of unknown function.[3–6]

Occasionally, cataract is accompanied by additional symptoms, among them microcornea.[4,5] Of particular interest to this work is a Swiss family with juvenile cataract, associated with microcornea and renal glucosuria.[7] Although renal glucosuria is not considered a disease, affected individuals show characteristic elevation of glucose concentration in the urine, without evidence of other renal tubular defects. The pattern of inheritance has been described as codominant with variable penetrance.[8] In the family described by Vandekerckhove and colleagues,[7] 9 of 12 cataract patients also showed elevated levels of glucose in their urine, in the absence of any other renal or metabolic abnormalities (Figures 1 and 2; Table 1).

Determination of the underlying genetic defect and whether cataract and glucosuria are caused by the same pathogenic alteration was subject of this study. We began with linkage analysis with the Affymetrix GeneChip Human Mapping 10K Array, version 2.0 (Affymetrix, Santa Clara, CA). Nonparametric linkage analysis with all genotypes of a chromosome simultaneously was carried out with MERLIN, and parametric linkage analysis was performed by the program ALLEGRO[9] assuming a disease allele frequency of 0.0001 and autosomal dominant inheritance with full penetrance for cataract. Haplotypes were reconstructed with ALLEGRO and presented graphically

[1]Division of Medical Molecular Genetics and Gene Diagnostics, Institute of Medical Genetics, University Zurich, CH-8603 Schwerzenbach, Switzerland; [2]Department of Biology, ETH, CH-8092 Zurich, Switzerland; [3]Eye Clinic, Kanton Hospital Luzern, CH-6000 Luzern, Switzerland; [4]Cologne Center for Genomics, [5]Institute for Genetics, University of Cologne, DE-50674 Cologne, Germany; [6]RZPD Deutsches Ressourcenzentrum für Genomforschung GmbH, DE-14509 Berlin, Germany
[7]These authors contributed equally to this work.
[8]Present address: Eye Clinic, Inselspital, CH-3010 Bern, Switzerland.
[9]Present address: Laboratoire de Physiopathologie Cellulaire et Moléculaire de la Rétine, Inserm U592, Institut de la Vision, Université Pierre et Marie Curie Paris 6, FR-75012 Paris, France.
*Correspondence: kloeckener@medgen.unizh.ch
DOI 10.1016/j.ajhg.2007.12.013.

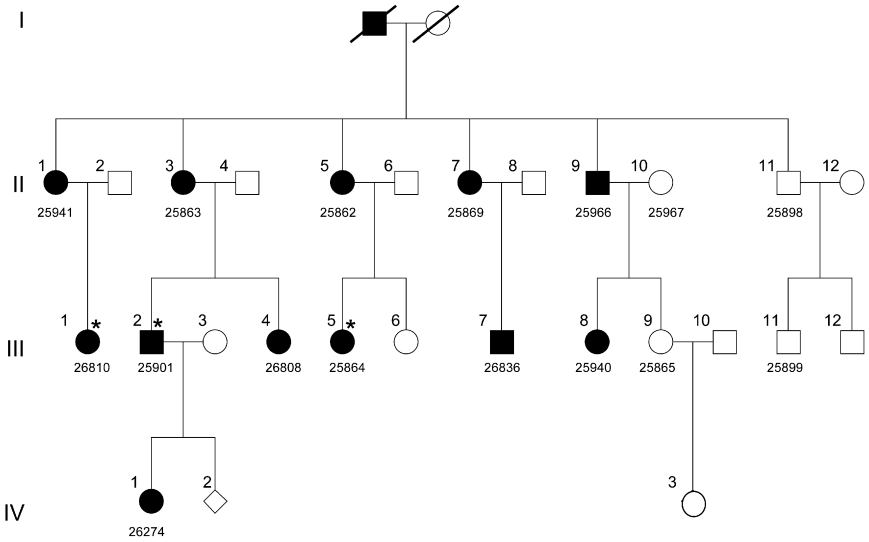

Figure 1. Pedigree of Swiss Family Segregating Juvenile Cataract with Microcornea and Glucosuria
Modified after Vandekerckhove et al.[7] Filled symbols represent affected status for all three phenotypes, with three exceptions indicated by star; III-1 and III-2 are negative and III-5 is borderline for glucosuria (Table 1). Five-digit laboratory identification numbers (given below pedigree symbols) were assigned prior to DNA extraction. Family members IV-2 and IV-3 were not tested for any of the three phenotypes.

with HaploPainter.[10] Results predicted that the disease-causing mutation for the juvenile cataract and microcornea maps to an interval on chromosome 10q23.31 (Figure 3) of 3 cM, spanning between the SNP markers rs701826 and rs2254391 (Figure 4). For the glucosuria phenotype, no significant LOD score was obtained (data not shown), probably resulting from incomplete penetrance. Calculations of 50% penetrance for affected patients revealed a LOD score slightly above 2 on a region of chromosome 10, which overlaps with the 3 cM interval for cataract. These findings suggest that more affected family members are required to obtain a significant LOD score for glucosuria.

The NCBI map viewer (Build 36.2, August 2007) displayed 31 genes and 3 phenotypes (selection shown in Table 2) within the linkage interval on chromosome 10q23.31. Among the phenotypes, none seemed obviously related to cataract. Distal to this linkage interval maps the homeobox gene *PITX3* (MIM 602669). Mutations in this gene are known to cause the dominant form of congenital cataract and anterior segment mesenchymal dysgenesis (ASMD).[11,12] We performed sequence analysis in the DNA of one affected patient (II-1) without finding a mutation (data not shown; primer sequences are available upon request).

Considering the function of each of the 31 genes within the linkage interval, we reasoned that *FAS* and *SLC16A12* were potential candidate genes. *FAS* (MIM 134637), encoding the tumor necrosis factor receptor super family

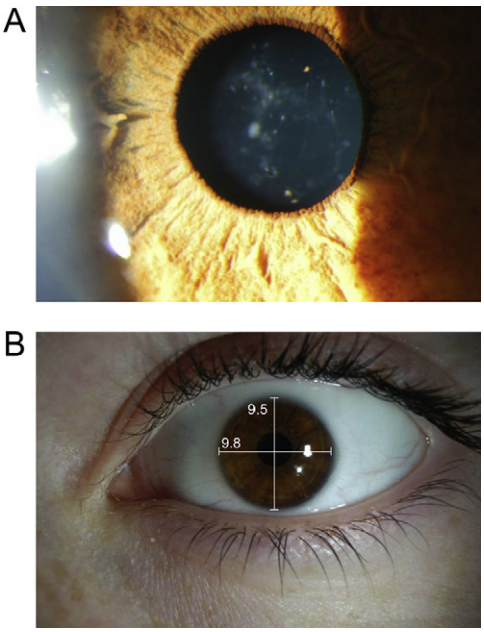

Figure 2. Cataract and Microcornea Phenotype of Patient III-5
Preoperative cortico-nuclear cataract in right eye is shown in (A) and microcornea (9.8 × 9.5 mm) in (B).

Table 1. Summary of Clinical Data

Pedigree ID	Cataract	Microcornea	Glucosuria
II-1	+	+	+
II-3	+	+	+
II-5	+	+	+
II-7	+	+	+[a]
II-9	+	+	+
II-11	-	-	-
III-1	+	+	-[a]
III-2	+	+	-
III-4	+	+	+
III-5	+	+	+/−[b]
III-7	+	+	+
III-8	+	+	+
III-9	-	-	+[c]
III-11	-	-	-

Pedigree identification numbers are taken from Figure 1. Presence/absence of cataract, microcornea, and renal glucosuria is given as +/−. Assignment of microcornea was given if values were below 11.0 mm. Glucosuria was evaluated as positive (+) if glucose concentration was above 0.8 mmol/L.
[a] Glucose values were generally obtained from postprandial samples except for patients II-7 and III-1.
[b] Test performed during pregnancy.
[c] Borderline value.

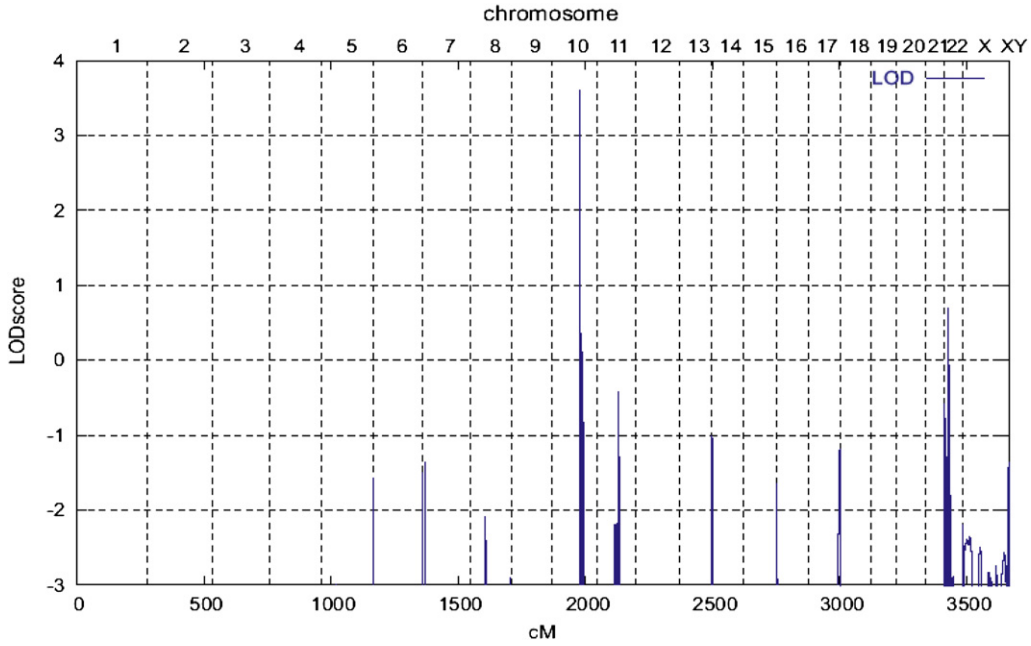

Figure 3. LOD Scores across the Genome for the Phenotype of Cataract with Microcornea
Chromosome number and genetic distances in cM (centi Morgan) is horizontally displayed; LOD score is given along the vertical axis.

member 6, could play a role during differentiation of lens cells.[13] DNA sequence analysis did not reveal a coding region mutation, but upstream of the transcription unit we detected a deletion of six thymidin residues. This alteration was also found in unaffected family members, so it was excluded as disease causing. In addition, a deletion of seven thymidin residues at the same site has been reported as SNP rs3074157.

Metabolic requirements of the lens cells can be accommodated by establishing a transport system for small molecules. The gene encoding the solute carrier SLC16A12 (ENSG00000152779, NCBI GeneID 387700) belongs to a family of 14 monocarboxylate transporters.[14] All members display an average size of 40–50 kDa and are characterized by 12 transmembrane domains (TMDs). Besides DNA sequence and gene annotation for *SLC16A12*, no information on its genetic and biochemical properties was available. We sequenced the five coding exons (3 to 8) including approximately 50–100 base pairs of their respective flanking introns and UTR regions (primer information in Table 3) and found a heterozygous mutation in exon 6: c.643C→T, which is predicted to lead to a premature termination codon p.Q215X (Figure 5). This mutation was found in all 12 cataract patients of the Swiss family whereas the three unaffected individuals (II-11, III-9, and III-11) did not carry this alteration. It was also absent in 370 normal alleles, two of which were from an unrelated spouse of the family (II-10) (Figure 1). Thus, we considered *SLC16A12* as the gene associated with the development of this cataract.

Knowledge of the expression pattern of *SLC16A12* would aid in understanding its effect on cataract with microcornea and glucosuria. For that purpose, we performed RT-PCR experiments based on established procedures[15] with RNA from several organs, including the two affected structures, lens and kidney (Figure 6). In general, the solute carrier was detected in retina, brain, lung, kidney, liver, and testis, although at remarkably different levels. We compared the amount of *SLC16A12* transcripts with that of the endogenous control transcripts from *RNA polymerase II* gene, and we estimated that the solute carrier seemed most highly expressed in kidney, followed by retina, lung, and testis and very weakly in brain and liver (Figure 6B). The expected RT-PCR fragment was not detected in blood cells (data not shown). In addition, we assayed *SLC16A12* transcripts isolated from human retina, retinal pigment epithelial cells (RPE), and lens of a 47-year-old eye donor lacking any signs of cataract and confirmed the expression pattern we had seen from purchased RNA (Figures 6B and 6C). Importantly, *SLC16A12* transcripts were also detected in the human lens (Figure 6C). Because only a very small portion of the lens, namely the lens epithelial cells (LECs), may be transcriptionally active, we concluded that expression of *SLC16A12* in the LECs must be relatively high. Our RT-PCR data show that *SLC16A12* expression is regulated in a cell/tissue-specific manner. These observations concur with the reported expression pattern of other SLC16 family members, which can be either ubiquitous or tissue specific.[14,16] Tissue-specific regulation of *SLC16A12* expression is further supported by the lack of additional manifesting symptoms in the Swiss family.

This report provides the first evidence (to our knowledge) for the physiological function of SLC16A12. In combination with the knowledge of the transport function of other SLC16 isoforms, a prediction of molecular activity

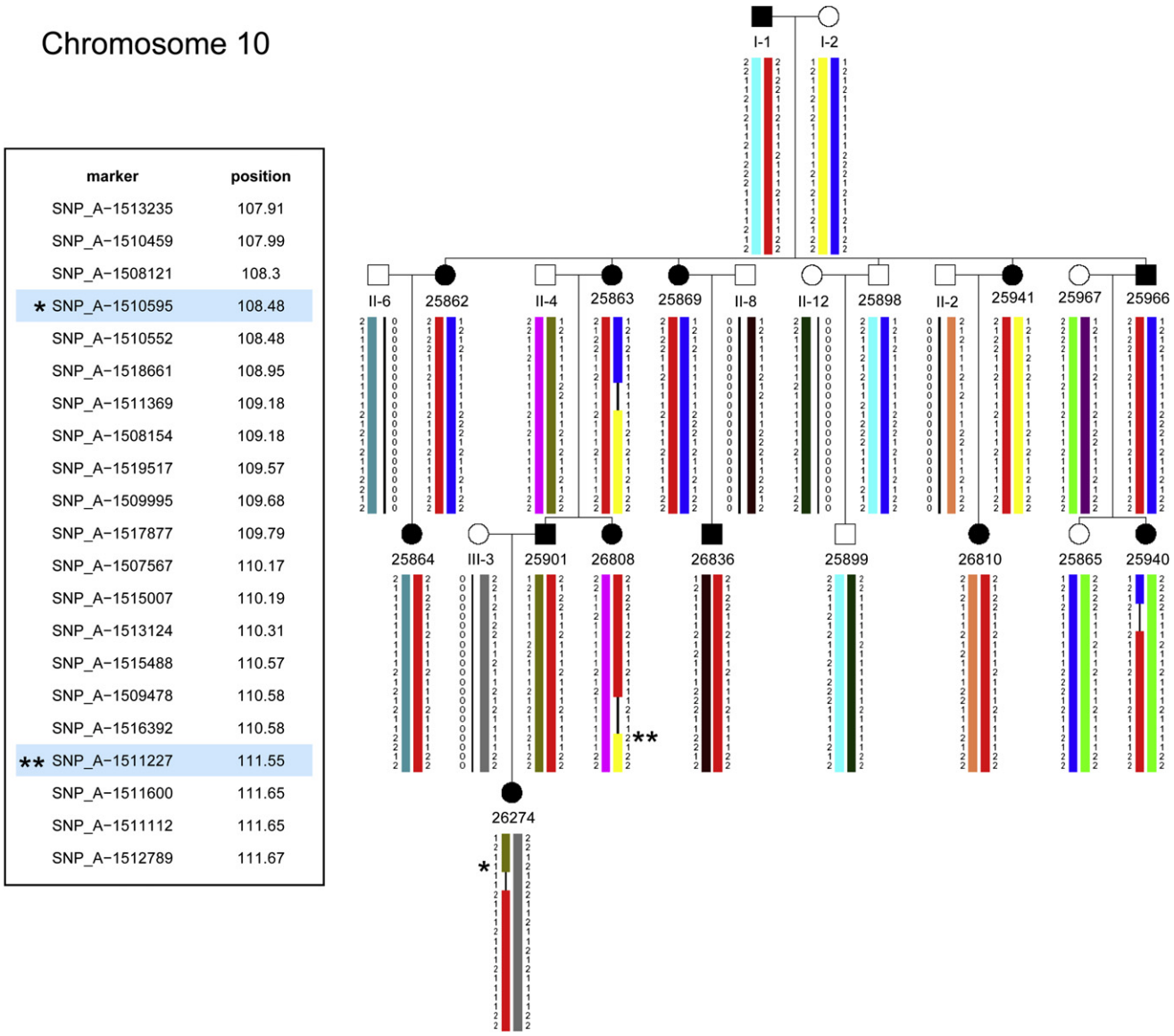

Figure 4. Haplotypes for the Cataract-Linked Region on Chromosome 10

Recombinations in patients 26808 (III-4) and 26274 (IV-1) define a critical interval of 2.6 Mega bases (Mb) delimited by markers SNP_A_1510595 (rs701826) (*) and SNP_A_1511227 (rs2254391) (**) at positions 108.48 and 111.55 cM, respectively. Disease chromosome in red.

is possible. These transporters are highly conserved throughout evolution and can be found in prokaryotes as well as eukaryotes, from yeast to mammals. They can transport lactate, aromatic amino acids, short-chain fatty acids, butyrate, ketones, or thyroid hormone in a proton-dependent or -independent fashion.[14] Subcellular localization of some family members in the eye and also kidney points to highly specific tasks of molecular transport.[17,18] Although neither the localization in the lens or kidney nor substrate specificity of this transporter is known, we speculate that its reduction would interfere with homeostasis. In the lens, solutes need to move from the cortical lens epithelial cells to the inner fiber cells. In the kidney, solutes also need to move between tubular cells and blood.

Prediction of membrane topology[19] revealed a 536 amino acid protein containing 12 transmembrane domains (TMDs) with both termini located intracellularly. Whereas the large intracellular loop and both termini show high variability in their amino acid sequence among the different SLC16 family members, highest conservation is found in the first and fifth TMD.[14] The p.Q215X mutation in SLC16A12 is located within the large cytoplasmic loop near the fourth TMD (Figure 7), predicted to result in a truncated protein with severely impaired or completely absent transport function. The premature termination codon might cause mRNA decay of the mutant allele, possibly by the mechanism of nonsense-mediated decay,[20] but a dominant-negative effect or gain of function of the

Table 2. Phenotype and Loci that Map to the Linkage Interval on Chromosome 10

Symbol	Description	MIM	Position
	Phenotypes		
TNFRSF6	*tumor necrosis factor receptor superfamily, member 6*	134637	10q24.1
LIPA	*Wolman disease, liposomal acid lipase deficiency*	278000	10q24-q25
SCZD11	*schizophrenia susceptibility locus*	608078	10q22.3
	Loci	MIM or Ensembl	GeneID
LIPF	lipase, gastric	601980	8513
LIPK	lipase, family member K	ENSG00000204021	643414
LIPN	member N	ENSG00000204020	643418
LIPM	member M	ENSG00000173239	340654
ANKRD22	ankyrin repeat domain 22	ENSG00000152766	118932
STAMBPL1	STAM binding protein-like 1	ENSG00000138134	57559
ACTA2	actin, alpha 2, smooth muscle,	ENSG00000107796	59
FAS	Fas (TNF receptor superfamily, member 6)	134637	355
CH25H	cholesterol 25-hydroxylase	604551	9023
LIPA	lipase A, (Wolman disease)	278000	3988
IFIT2	interferon-induced protein with tetratricopeptide repeats 2	147040	3433
IFIT3	repeats 3	604650	3437
IFIT1L	repeats 1-like	ENSG00000204010	439996
IFIT1	repeats 1	147690	3434
IFIT5	repeats 5	ENSG00000152778	24138
SLC16A12	solute carrier family 16, member 12 (monocarboxylic acid transporter 12)	ENSG00000152779	387700
MIRN107	microRNA 107		406901
PANK1	pantothenate kinase 1	606160	53354
MPHOSPH1	M-phase phosphoprotein 1	605498	9585
HTR7	5-hydroxytryptamine (serotonin) receptor 7 (adenylate cyclase-coupled)	182137	3363
RPP30	ribonuclease P/MRP 30kDa subunit	606115	10556
ANKRD1	ankyrin repeat domain 1 (cardiac muscle)	609599	27063
NUDT9P1	nudix (nucleoside diphosphate linked moiety X)-type motif 9 pseudogene 1		119369
PCGF5	polycomb group ring finger 5	ENSG00000180628	84333
HECTD2	HECT domain containing 2	ENSG00000165338	143279
PPP1R3C	protein phosphatase 1, regulatory (inhibitor) subunit 3C	602999	5507
TNKS2	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase 2	607128	80351

From the NCBI map viewer (Build 36.2, August 2007), we selected 27 annotated genes, and all phenotypes located to the affected region on chromosome 10q23.31 are shown. For identification, MIM code, Ensembl code, and/or GeneID (NCBI) is given.

truncated protein can not be excluded. Consequently, reduced amounts of the normal allele in the patients could account for a gradual, progressive nature of the cataract. The resulting deficiency in transportation of metabolites in the lens could lead to alteration of structural components of the fiber cells and the refractive index, contributing to the development of cataract. Similarly, defective transport in the kidney could lead to excessive accumulation of glucose in the urine, making SLC16A12, directly or indirectly, involved in glucose transport. Because the causes of glucosuria can be heterogeneous, other factors, singly or in combination with deficient SLC transporter activity, could result in the highly variable phene of glucosuria.

Although several arguments have been presented that support a model in which cataract and glucosuria are caused by the same mutation, we can not rule out that

Table 3. Primer Information

Gene - Exon - Direction	Sequence	Purpose
SLC16A12 ex3f	gtctgccccagtctagtattca	genomic sequencing
SLC16A12 ex3r	cggaaatacacacaccacca	genomic sequencing
SLC16A12 ex4f	ccctgtggtggttgaacact	genomic sequencing
SLC16A12 ex4r	tggctttggctgaagatagg	genomic sequencing
SLC16A12 ex5f	tctattccaaccctgctgct	genomic sequencing
SLC16A12 ex5r	ccagctctgtttaactgctagg	genomic sequencing
SLC16A12 ex6af	gaatgactggtgaggggaga	genomic sequencing
SLC16A12 ex6ar	aacagaacggagacggctaa	genomic sequencing
SLC16A12 ex6bf	cggggagccttactcattct	genomic sequencing
SLC16A12 ex6br	agtaccagcaagggagatgc	genomic sequencing
SLC16A12 ex7f	cacaatgggaaagccatctc	genomic sequencing
SLC16A12 ex7r	atggttttgggggctcttat	genomic sequencing
SLC16A12 ex8f	caaagttacaattggtggtgct	genomic sequencing
SLC16A12 ex8r	agttatgagcacaaatcccaaa	genomic sequencing
SLC16A12exon3f	caggaagtcactggacagca	RT-PCR
SLC16A12exon5r	caggaagtcactggacagca	RT-PCR
SLC16A12exon4_5f	gtgtgaccatgctctgtgct	RT-PCR
SLC16A12exon6r	aagacaaagcccccaagaat	RT-PCR
RPII_cDNA_N20_F	tgtggagatcttcacggtgct	RT-PCR
RPII_cDNA_N234_R	cataagcacgtccaccgtttc	RT-PCR

The name of primers contains information about the gene (*SLC16A12* or *POLR2A*, exon, and direction, forward [f,F] or reverse [r,R]). The sequence of primers points 5′ to 3′.

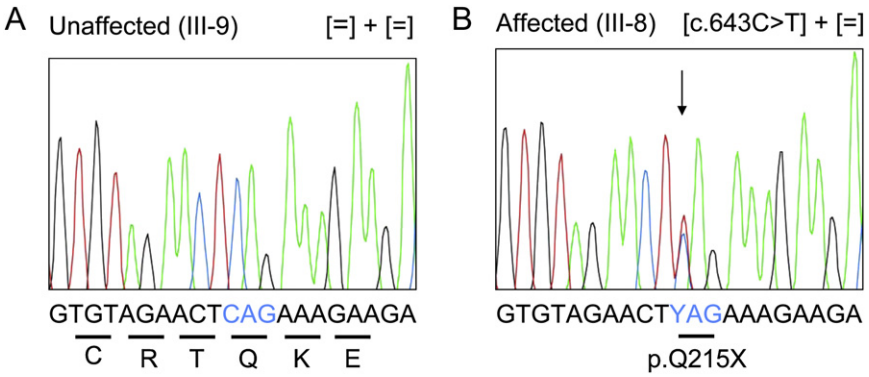

Figure 5. Mutation Screening in *SCL16A12*

Electropherogram shows the mutation in exon 6 within the context of 21 nucleotides. Shown are both the DNA sequence of the unaffected individual III-9 (A) and the heterozygous change of C→T (Y) in the affected individual III- 8 (B). The genotypes are given in brackets. Translation codons are underlined and amino acid identity is written below with single letter code.

the two diseases may segregate independently. In case of an unlinked locus for glucosuria, examples of potential candidates include the chaperone protein CD147, which facilitates subcellular sorting of SLC16 members[17] or proteins involved in glucose transportation, i.e., *GLUT* proteins[21] or *SLC5A2*.[8]

Age-related cataract, which is the most common cause for avoidable blindness worldwide, is known to be dependent on both environmental risk factors and genetic factors. A twin study on the cortical type of age-related cataract implies the action of dominant genes to account for genetic heritability of about 50%.[22,23] The progressive course of juvenile cataract described here, resulting most likely from defective transport of small molecules, suggests the potential role of the SLC16A12 transporter in age-related cataracts as well. Depending on the type and location of mutations within the SLC16A12 transporter, more or less severe forms of cataract would be expected, which may also vary in the time of onset. We propose that mutations in a solute carrier such as SLC16A12 could lead to the age-related form of cataract. Knowledge of the substrate may open new venues for nonsurgical treatment.

Taken together, we show for the first time (to our knowledge) the biological relevance of the solute carrier SLC16A12 and suggest a function in the establishment and/or maintenance of homeostasis in the lens and probably also in the kidney.

Acknowledgments

We would like to thank the family for participation in this study; Jaya Balakrishnan, Esther Glaus, and Philippe Reuge (Berger laboratory) for DNA preparations; C. Becker (Nürnberg laboratory) for expert technical assistance in providing the SNP genotype data from Affymetrix microarrays; Gabor Matyas (Berger laboratory) for providing the RNA II Polymerase primers for RT-PCR experiments and for invaluable support with DNA sequencing; and Adrian Knoepfel (Berger laboratory) for sequencing of the *FAS* promoter. We are also grateful for the donation of the human eyes from the eye bank at the University of Zurich. This work was funded in part by the German Federal Ministry of Sciences and Education through the National Genome Research Network (grant 01GR0416 to P.N.) and by a scientific grant from the eye clinic of the Kanton Hospital Luzern, Switzerland.

Received: October 15, 2007
Revised: December 4, 2007
Accepted: December 19, 2007
Published online: February 14, 2008

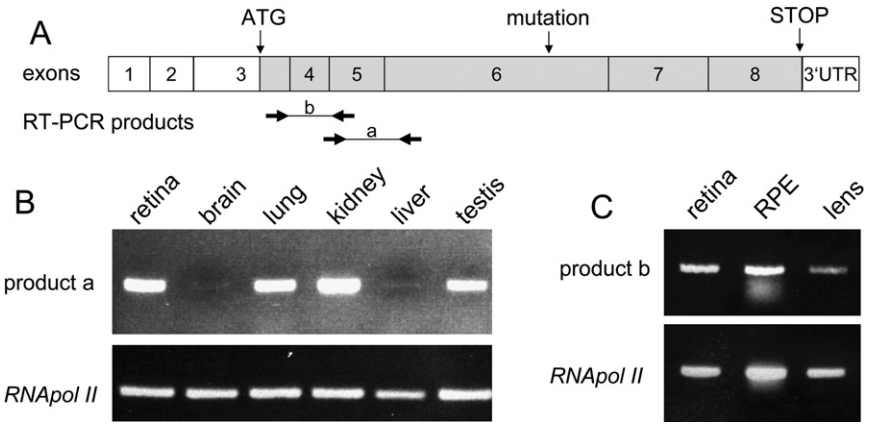

Figure 6. Expression Studies of *SLC16A12*

(A) Schematic representation of exons. Protein coding regions are displayed in darker shade. Translation initiates within exon 3 (vertical arrow, ATG) and terminates within exon 8 (vertical arrow, STOP). Mutation, c.643C→T, in exon 6 (vertical arrow) is predicted to lead to a premature termination. Positions of primers are indicated by forward and reverse horizontal arrows, yielding RT-PCR product a (exon spanning 4_5 to exon 6) and product b (exon 3 to exon 5).
(B) RT-PCR analyses from human tissues with commercially available mRNA. Primers to yield product a were used to amplify *SLC16A12* transcripts. RNA Polymerase II (*POLR2A*) transcripts served as endogenous control.
(C) RT-PCR analysis from tissues isolated from a single human donor eye. Primers to yield product b of *SLC16A12* and of *POLR2A* (control) were used for amplification. Lens RNA was 3-fold concentrated compared to the other samples.

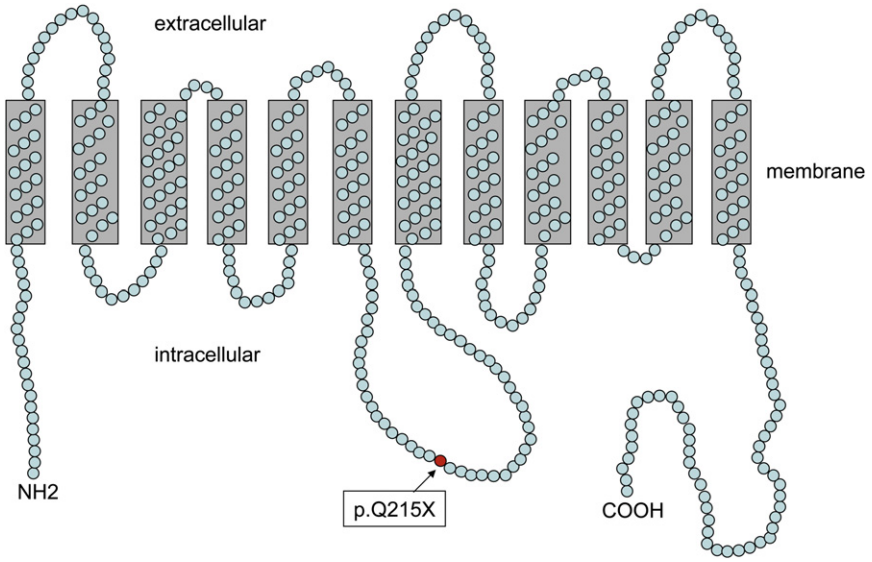

Figure 7. Schematic Representation of the Predicted Secondary Structure of SLC16A12

Prediction of membrane topology revealed a 536 amino acid protein with 12 transmembrane domains separated by intra- and extracellular domains of varying lengths with both termini (NH2 and COOH) located intracellularly. Amino acid glutamin (Gln, Q) at position 215 is mutated to a stop in the patients described herein (red circle).

Web Resources

The URLs for data presented herein are as follows:

National Center for Biotechnology Information (NCBI), http://www.ncbi.nlm.nih.gov/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

PredictProtein, http://www.predictprotein.org/

References

1. Augusteyn, R.C. (2007). Growth of the human eye lens. Mol. Vis. *13*, 252–257.
2. Francis, P.J., Berry, V., Bhattacharya, S.S., and Moore, A.T. (2000). The genetics of childhood cataract. J. Med. Genet. *37*, 481–488.
3. Jamieson, R.V., Farrar, N., Stewart, K., Perveen, R., Mihelec, M., Carette, M., Grigg, J.R., McAvoy, J.W., Lovicu, F.J., Tam, P.P., et al. (2007). Characterization of a familial t(16;22) balanced translocation associated with congenital cataract leads to identification of a novel gene, *TMEM114*, expressed in the lens and disrupted by the translocation. Hum. Mutat. *28*, 968–977.
4. Lorenz, B. (2007). Genetic examination in cases of congenital cataract. Ophthalmologe *104*, 559–565.
5. Shiels, A., and Hejtmancik, J.F. (2007). Genetic origins of cataract. Arch. Ophthalmol. *125*, 165–173.
6. Shiels, A., Bennett, T.M., Knopf, H.L., Yamada, K., Yoshiura, K., Niikawa, N., Shim, S., and Hanson, P.I. (2007). *CHMP4B*, a novel gene for autosomal dominant cataracts linked to chromosome 20q. Am. J. Hum. Genet. *81*, 596–606.
7. Vandekerckhove, K., Lange, A.P., Herzog, D., and Schipper, I. (2007). Juvenile cataract associated with microcornea and glucosuria: a new syndrome. Klin. Monatsbl. Augenheilkd. *224*, 344–346.
8. Santer, R., Kinner, M., Lassen, C.L., Schneppenheim, R., Eggert, P., Bald, M., Brodehl, J., Daschner, M., Ehrich, J.H., Kemper, M., et al. (2003). Molecular analysis of the *SGLT2* gene in patients with renal glucosuria. J. Am. Soc. Nephrol. *14*, 2873–2882.
9. Gudbjartsson, D.F., Jonasson, K., Frigge, M.L., and Kong, A. (2000). Allegro, a new computer program for multipoint linkage analysis. Nat. Genet. *25*, 12–13.
10. Thiele, H., and Nurnberg, P. (2005). HaploPainter: a tool for drawing pedigrees with complex haplotypes. Bioinformatics *21*, 1730–1732.
11. Burdon, K.P., McKay, J.D., Wirth, M.G., Russell-Eggit, I.M., Bhatti, S., Ruddle, J.B., Dimasi, D., Mackey, D.A., and Craig, J.E. (2006). The *PITX3* gene in posterior polar congenital cataract in Australia. Mol. Vis. *12*, 367–371.
12. Semina, E.V., Ferrell, R.E., Mintz-Hittner, H.A., Bitoun, P., Alward, W.L., Reiter, R.S., Funkhauser, C., Daack-Hirsch, S., and Murray, J.C. (1998). A novel homeobox gene *PITX3* is mutated in families with autosomal-dominant cataracts and ASMD. Nat. Genet. *19*, 167–170.
13. Futter, C.E., Crowston, J.G., and Allan, B.D. (2005). Interaction with collagen IV protects lens epithelial cells from Fas-dependent apoptosis by stimulating the production of soluble survival factors. Invest. Ophthalmol. Vis. Sci. *46*, 3256–3262.
14. Halestrap, A.P., and Meredith, D. (2004). The *SLC16* gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. Pflugers Arch. *447*, 619–628.
15. Neidhardt, J., Glaus, E., Barthelmes, D., Zeitz, C., Fleischhauer, J., and Berger, W. (2007). Identification and characterization of a novel RPGR isoform in human retina. Hum. Mutat. *28*, 797–807.
16. Halestrap, A.P., and Price, N.T. (1999). The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation. Biochem. J. *343*, 281–299.
17. Deora, A.A., Philp, N., Hu, J., Bok, D., and Rodriguez-Boulan, E. (2005). Mechanisms regulating tissue-specific polarity of monocarboxylate transporters and their chaperone CD147 in kidney and retinal epithelia. Proc. Natl. Acad. Sci. USA *102*, 16245–16250.
18. Philp, N.J., Wang, D., Yoon, H., and Hjelmeland, L.M. (2003). Polarized expression of monocarboxylate transporters in human retinal pigment epithelium and ARPE-19 cells. Invest. Ophthalmol. Vis. Sci. *44*, 1716–1721.
19. Rost, B., Yachdav, G., and Liu, J. (2004). The PredictProtein server. Nucleic Acids Res. *32*, W321–W326.
20. Holbrook, J.A., Neu-Yilik, G., Hentze, M.W., and Kulozik, A.E. (2004). Nonsense-mediated decay approaches the clinic. Nat. Genet. *36*, 801–808.

21. Wallner, E.I., Wada, J., Tramonti, G., Lin, S., and Kanwar, Y.S. (2001). Status of glucose transporters in the mammalian kidney and renal development. Ren. Fail. *23*, 301–310.
22. Hammond, C.J., Snieder, H., Spector, T.D., and Gilbert, C.E. (2000). Genetic and environmental factors in age-related nuclear cataracts in monozygotic and dizygotic twins. N. Engl. J. Med. *342*, 1786–1790.
23. Hammond, C.J., Duncan, D.D., Snieder, H., de Lange, M., West, S.K., Spector, T.D., and Gilbert, C.E. (2001). The heritability of age-related cortical cataract: the twin eye study. Invest. Ophthalmol. Vis. Sci. *42*, 601–605.