A new perspective on the genetics of keratoconus: why have we not been more successful?- Supplementary material

Supplementary table 1. Mutation analysis and association studies of candidate genes in KC.

Gene		Study design	Selection criteria	Study Population	Results of the candidate gene studies: total number of variants	Results of the candidate gene studies: description of variants	Segregation?	Identified using other approaches?	Ref.
Collagens	*COL4A1*	Sequencing of all exons, promoter and intron-exon junctions	Proximity to locus at 13q32	48 individuals of 15 families	15 variants	3 missense variants, 9 synonymous variants, 1 5'UTR variant 2 3'UTR variant	No	No	[1]
	COL4A2	Sequencing of all exons, promoter and intron-exon junctions	Proximity to locus at 13q32	48 individuals of 15 families	26 variants	5 missense variants, 8 synonymous variants, 5 5'UTR variants, 8 3'UTR variants	No	No	[1]
	COL4A3	SSCA and sequencing	Differentially expressed in KC Corneas, Genetic alterations in *COL4A3* and *COL4A4* genes may be responsible for decreases in collagen types I and III	104 unrelated patients with KC and 157 healthy controls	8 polymorphisms	6 missense variants, 2 synonymous variants	NA	Yes, GWAS [2]	[3]
		SSCA and sequencing		113 patients with sporadic or familial keratoconus	8 polymorphisms	6 missense variants, 2 synonymous variants	NA		[4]
		Association study of 7 tagSNPs		97 patients and 101 healthy controls	tagSNPs are not associated with KC	NA	NA		[5]
		Association study of 1 SNP		45 patients and 78 controls	No association of selected SNP with KC	NA	NA		[6]
		Association study of 1 SNP		108 patients and 300 controls	No association	NA	NA		[7]
	COL4A4	SSCA and sequencing	Differentially expressed in KC Corneas, Genetic alterations in *COL4A3* and *COL4A4* genes may be responsible for decreases in collagen types I and III	104 unrelated patients with KC and 157 healthy controls	6 polymorphisms	4 missense variants, 2 synonymous variants	NA	No	[3]
		SSCA and sequencing		113 patients with sporadic or familial keratoconus	6 polymorphisms	3 missense variants, 3 synonymous variants	NA		[4]
		Association study of 3 tagSNPs		97 patients and 101 healthy controls	tagSNPs are not associated with KC	NA	NA		[5]
		Association study of 2 SNPs		45 patients and 78 controls	Potential	Overrepresentation of	NA		[6]

					protective effect of 2 variant genotypes	M1327V AA and F1644F TT in controls			
		Association study of 2 SNPs		112 patients and 150 controls	1 polymorphism as risk factor	rs2229813AA and GA+AA genotypes are risk factors	NA		[8]
	COL5A1	Association study of 44 SNPs	Association with CCT and located in 9q34.	526 patients, 3842 controls and 186 subjects from families	1 associated SNP	rs1536482 associated with KC	NA	Yes, GWAS [2, 9-11]	[12]
		Association study of 2 SNPs		157 patients and 673 controls	No association	NA	NA		[13]
		Association study of 2 SNPs		210 patients and 191 controls	No association	NA	NA		[14]
		Association study of 2 SNPs		108 patients and 300 controls	No association	NA	NA		[7]
	COL8A1	Sequencing of the coding regions	COL8A1/COL8A2 knockout mice shows a corneal phenotype including corneal thinning, Type VIII collagen is expressed in the cornea and previous reports link COL8A2 mutations to corneal dystrophies	50 unrelated patients and 2 unrelated keratoglobus patients	1 polymorphism	1 synonymous variant	NA	No	[15]
	COL8A2	Sequencing of the coding regions		50 unrelated patients and 2 unrelated keratoglobus patients	11 variants	7 synonymous variants, 3 nonsynonymous variants, 1 in frame insertion	In frame insertion also present in healthy family member	Yes, GWAS [2, 9]	[15]
		Sequencing of all exons and 50 bp of the flanking intron sequence		1 patient with KC, PPCD, band keratopathy, heterochromia, iridocorneal endothelial syndrome, 3 brothers with some KC signs and their healthy mother	0 variants (as reported by the authors: no biologically significant mutations)	NA	NA		[16]
Base excision repair genes	*POLG*	Association study of 1 polymorphism	Disturbance in the activity of antioxidant enzymes in KC corneas, Indications for a role of oxidative stress in KC	284 KC patients, 353 controls	1 polymorphism genotype associated with KC	A/A genotype of the c.–1370T>A associated with increased occurrence of KC	NA	No	[17]
	XRCC1	Association study of 2 polymorphisms			2 polymorphism genotypes associated with KC	A/G genotype and A allele of c.1196A>G polymorphism associated with increased occurrence of KC, C allele of c.580C>T polymorphism associated with increased occurrence of KC	NA	No	[17]

	NEIL1	Association study of 1 polymorphism			No association	NA	NA	No	[17]
	PARP-1	Association study of 1 polymorphism			No association	NA	NA	No	[17]
	APEX1	Association study of 2 polymorphisms		250 KC patients, 209 FECD patients and 350 controls	1 polymorphism genotype associated with KC	T/T genotype associated with increased occurrence of KC	NA	No	[18]
	FEN1	Association study of 2 polymorphisms		279 KC patients, 225 FECD patients and 322 controls	1 polymorphism genotype associated with KC	T/T genotype of g.61564299G>T associated with increased occurrence of KC	NA	No	[19]
	LIG3	Association study of 2 polymorphisms		283 KC patients, 258 FECD individuals and 300 controls	1 polymorphisms associated with KC	A/A genotype and the A allele of the rs1003918 G>A polymorphism were associated with increased occurrence of KC	NA	No	[20]
	MUTYH	Association study of 1 polymorphism		205 KC patients and 220 controls	No association	NA	NA	No	[21]
	hOGG1	Association study of 1 polymorphism		205 KC patients and 220 controls	No association	NA	NA	No	[21]
FAS		Association study of 1 polymorphism	The FAS/FASLG system is expressed in the cornea and might play a role in normal corneal physiology and in the pathophysiology of corneal diseases, including modulation of keratocyte apoptosis	264 KC patients, 221 FECD patients and 300 controls	Polymorphism not associated with KC but polymorphism genotype in combination with polymorphism genotype in FASLG associated with	c.–671A>G G/A genotype combined with T/T genotype in FASLG associated with increased risk of KC	NA	No	[22]

			after epithelial injury		KC				
FASLG		Association study of 1 polymorphism		264 KC patients, 221 FECD patients and 300 controls	Polymorphism genotype associated with KC	T/T genotype and the T allele of the c.–844T>C polymorphism were associated with increased occurrence of KC. T/T- genotype in combination with c.–671A>G G/A genotype is associated with increased risk of KC	NA	No	[22]
FLG		Genetic analysis of 2 variants	Association of atopic diseases with KC, role of FLG in atopic diseases, fillagrin is expressed in the cornea	89 KC patients	6 mutated alleles	The heterozygous p.R501X mutation was present in 5 patients. In 1 of these patients the c.2284del4 was also present.	NA	No	[23]
Interleukins	*IL1A*	Association study of 3 polymorphisms	IL1 is a mediator of keratocyte apoptosis in the cornea, which is reported to underlie stromal thinning	100 unrelated KC patients	1 polymorphism associated with KC	C/A-genotype of rs2071376 is associated with increased risk of KC	NA	No	[24]
		Association study of 1 polymorphism		169 KC patients and 390 controls	Polymorphism not associated with KC	NA	NA		[25]
		Association study of 1 tagSNP		97 KC patients and 101 controls	tagSNP associated with KC	A/A-genotype of rs2071376 associated with increased risk of KC	NA		[5]
		Association study of 1 polymorphism		115 KC patients and 101 controls	1 polymorphism associated with KC	A allele of rs2071376 is associated with an increased risk of KC	NA		[26]
	IL1B	Association study of 4 polymorphisms		100 unrelated KC patients	2 polymorphisms associated with KC	C allele of rs16944 and T allele of rs1143627 associated with increased risk of KC	NA	No	[24]
		Association study of 2 polymorphisms		169 KC patients and 390 controls	2 polymorphisms associated with KC	T allele of rs1143627 and C allele of rs16944 associated with increased risk of keratoconus	NA		[25]
		Association study of 2 tagSNPs		97 KC patients and 101 controls	tagSNPs are not associated with	NA	NA		[5]

					KC				
		Association study of 2 polymorphisms		115 KC patients and 101 controls	2 polymorphisms associated with KC	C allele of rs1143627 and A allele of rs16944 is associated with increased risk of KC	NA		[26]
	IL1RN	Association study of 4 polymorphisms and 1 VNTR		100 unrelated KC patients	Polymorphisms not associated with KC	NA	NA	Yes, Linkage analysis [27]	[24]
		Association study of 1 polymorphism and 1 VNTR		121 KC patients and 121 controls	Polymorphisms not associated with KC	NA	NA		[28]
Mitochondrial genes and haplogroups		Sequencing of ND1, 2, 3, 4, 4L, 5, and 6 and haplogrouping	KC corneas exhibit more mitochondrial DNA damage than normal corneas. Oxidative stress is believed to play a role in the disease pathogenesis and mitochondria might contribute to this oxidative stress.	20 KC patients and 20 controls	84 variants detected	52 synonymous variants (5 also present in controls), 18 nonsynonymous variants, 9 variants in RNA genes, 3 variants in non-coding regions and 2 frameshift variants in patients, a total of 29 variants in controls	NA	No	[29]
		Haplogrouping of 19 mitochondrial haplogroups		114 KC patients and 552 controls	2 haplogroups overrepresented in patients	Haplogroups H (28.9% vs. 8.5%) and R (17.5% vs. 3.1%) overrepresented in KC patients	NA		[30]
		Sequencing of the full mitochondrial genome		26 KC patients and 100 controls	64 variants detected	54 synonymous variants with comparable frequencies in controls, 10 nonsynonymous variants in 10 patients that were absent in controls	NA		[31]
		Haplogrouping of 15 mitochondrial haplogroups		210 KC patients and 309 controls	No haplogroups associated with KC	NA	NA		[32]
RAD51		Association study of 2 polymorphisms	Gene involved in the repair of double stranded breaks which might be caused by oxidative stress, which is believed to play a role	100 KC patients, 100 FECD patients and 150 controls	1 polymorphism associated with KC	G/T genotype of the c.-61G>T polymorphism is associated with increased risk of KC	NA	No	[33]

		in the disease pathogenesis						
SOD1	Sequencing of the coding regions and intron-exon boundaries	Prevalence of KC in Down syndrome patients is markedly increased and this gene is located on chromosome 21	15 patients (+screening of identified variants in 156 controls)	1 variant	IVS2+50del7 in 2 patients and 0 controls	IVS2+50del7 present in 2 patients and absent in 3 unaffected family members, segregation of other family was unavailable	No	[34]
	Sequencing of Exon 2 and the flanking intronic regions for identification of the 7-base deletion		302 patients and 200 controls	1 variant	c.169+50delTAAACAG deletion in 2 patients and 0 controls	No		[35]
	Sequencing of all exons and intron-exon junctions		36 patients from 18 families (2 per family)	0 variants	NA	NA		[36]
	SSCA and sequencing		113 patients and 100 controls	2 polymorphisms	NA	NA		[37]
	Sequencing of full-length gene		26 probands of 26 families (and 52 unaffected family members for segregation analysis of coding variants)	3 polymorphisms	g.4886G>A g.4990C>G g.9061T>A	NA		[38]
	Sequencing of 7 bp deletion		33 patients and 78 controls	1 variant	c.169+50delTAAACAG deletion in 9 patients and 4 controls	NA		[39]
	Sequencing of all exons, intron-exon junctions and intron 2		55 patients and 100 controls	4 polymorphisms	g.12035 C>A g.13978 T>A g.12037 G>A g.11931 A>C	NA		[40]
SPARC	Sequencing of coding exons 2-10	Localized in 5q31.3-q32	302 patients (+ screening of identified variants in 200 controls)	13 variants	3 nonysnonymous and 3 synonymous variants, p.E63K p.M92I p.D219E p.A68A in 1 patient and 0 controls p.D244D in 1 patient and 0 controls p.H249H in 1 patient and 0 controls 7 known polymorphisms at expected frequencies:	p.E63K inherited from healthy mother and absent in keratoconic father p.H249H: not segregating with KC	No	[35]

					rs7714314, rs2304052, rs2116780, rs2304051, rs1978707, rs41290587 and rs1053411			
TF	Association study of 3 polymorphisms	The role of iron in induction of oxidative stress	216 KC patients, 130 FECD patients and 228 controls	2 variants	A/A genotype and A allele of g.3296G>A associated with KC, A/G genotype of g.3481A>G associated with decreased occurrence of KC	No	No	[41]
TGFBI	Sequencing of all coding regions and exon-intron junctions	Mutations in *TGFBI* are associated with Granular corneal dystrophy type 1, Granular corneal dystrophy type 2, and lattice corneal dystrophy; TGFBI is abundant in the cornea, and differential expression is observed in keratoconus corneas	15 KC patients, unreported number of control individuals	9 variants	9 polymorphisms that are also observed in controls: p.L217L in 12 patients, p.V327V in 6 patients, p.F540F in 7 patients, 2589 T>G 3' UTR in 7 patients IVS12+23G>A in 6 patients, IVS13-55A>T in 9 patients, IVS13-71A>T in 9 patients, 1416C>T in 5 patients, 1041 C>T in 1 patient	No	Yes, WES [42]	[43]
	Sequencing of exons 4, 11, 12, 13 and 14		2 patients	2 variants	c.1463C>T, p.Leu472Leu: rs1133170 and c.1667T>C, p.Phe540Phe: rs4669	No		[44]
	PCR and SSCP exons 1-17		30 patients and 30 controls	2 variants	p.G535X in 1 patient, p.F540F in 52 patients and 1 control	No		[45]
	Sequencing of exons 12 and 15		42 patients and 50 controls		c.1598G4A, Arg533Gln in 1 patient and 0 controls, c.1620T4C, Phe540Phe in 17 patients and 20 controls, c.1678 + 23G4A in 15	No		[46]

					patients and 16 controls			
	Sequencing of 3 described variants		1 patient	0 variants	NA	No		[47]
TIMP3	Sequencing of 5 coding exons and a 516- bp fragment including part of the 5′ UTR, as well as CpG islands, putative binding sites for SP1, and a possible TATA box		302 patients	2 variants	2 known polymorphisms at expected frequencies rs9862 and rs11547635	No	No	[35]
VSX1	SSCP and sequencing	Expression in adult cornea and a candidate gene for PPCD	22 PPCD patients, 63 KC patients, 90 FECD patients and 90 OAG patients, and 277 controls	4 variants and 5 polymorphisms	R166W in 1 KC patient and 0 controls L159M in 1 KC patient and 0 controls D144E in 1 patient with a phenotype of both KC and PPCD, 1 OAG patient and 0 controls H244R: in 1 patient and 2 controls 5 polymorphisms: Ser6Ser (exon 1) Ala182Ala (exon 3) g-a 23bp 3'end (exon 4) arg215arg (exon 4) 1bp del 6bp 5'end (exon 5)	R166W: No L159M: yes, present in 3 additional affected family members, no unaffected family members available D144E: yes, present in one additional family member with a similar phenotype H244R: yes, present in 2 affected family members and absent in the mother of the proband with an unknown affection status	Yes, NGS [48]	[49§]
	Sequencing of full coding regions and exon-intron junctions		80 patients and screening of the identified coding variants in 125 controls	4 variants and 4 polymorphisms	c.323T>C, L17P in 3 patients and 0 controls c.705C>G, D144E in 2 patients and 0 controls c.752G>A, G160D in 2 patients and 0 controls c.1013 1014 CG>GA, P247R in 1 patient and 0 controls	L17P: family 1: present in KC-suspect mother, absent in 2 unaffected siblings family 2: no segregation		[50]

					c.291 G>T in 25 patients c.819A>G in 38 patients c.900+23A/G in 27 patients c.900+84T/A in 26 patients	possible family 3: present in 2 additional KC suspects, absent in 1 unaffected family member D144E: family 4: present in son with unknown affection status family 5: present in 3 KC-suspect family members, absent in 3 unaffected family members G160D: family 3: only the proband carries both the L17P and G160D variant, none of the family members carry the G160D variant family 6: present in 2 KC-suspect family members, absent in 2 additional KC suspects and 1 unaffected family member P247R:		

						present in 2 affected family members and 1 family member with unknown affection status and absent in 2 unaffected family members		
	Sequencing of full coding regions and exon-intron junctions		100 patients	1 variant and 4 polymorphisms	Asp144Glu in 1 patient c.53G>T, Ser6Ser in 4 patients c.209G>T, Pro58Pro in 2 patients c.426C>A, Arg131Ser in 1 patient c.581A>G, Ala182Ala in 51 patients	NA		[51]
	Sequencing of full coding regions and exon-intron junctions		85 unrelated patients and 50 controls	11 variants	p.D105E in 2 patients p.R131S in 5 patients p.D144E in 1 patient and 0 controls p.R217H/c.627+23G>A in 18 patients and 0 controls p.S6S in 9 patients p.P58P in 2 patients p.G113G in 2 patients p.A182A in 53 patients p.P237P/c.627+84T>A in 53 patients and 0 controls p.P247R in 0 patients and 1 control	p.D144E present in 1 additional affected family member and in 2 unaffected family members, absent in 1 affected family member p.R217H/c.627+23G>A: no cosegregation p.P237P/c.627+84T>A: no cosegregation other variants were identified in non-familial cases		[52]
	Association study of 3 previously reported variations		77 patients and 71 controls and 444 individuals from 75 families	2 variants	L159M present in 1 control, 3 affected familial cases and 2	H244R present in both twins of a monozygotic		[53]

					unaffected family members R166W absent in all patients and controls H244R present in 2 affected familial cases and 1 unaffected family member	twin pair		
	Sequencing of full coding regions and exon-intron junctions		10 members of 1 family (+screening of identified variant in 104 controls)	1 variant reported (unclear whether polymorphisms are reported)	D144E present in 6 family members and 1 control	D144E present in 4 KC patients and 2 family members with unclear affection status and absent in 4 normal individuals		[54]
	SSCP and sequencing		249 patients and 208 controls	2 variants and 3 polymorphisms	N151S (EX2+28A>G) in 1 patient and 0 controls G160V(EX2+55G>T) in 13 patients and 0 controls L176L (EX3+25G>A) in 1 patient and 4 controls A182A (rs12480307, EX3+43G>A) in 8 patients and 2 controls G239G(EX4+90G>A) in 4 patients and 2 controls	NA		[55]
	Sequencing of coding exons, exon–intron junctions, and the UTRs		66 patients and 100 controls	12 variants	c.18 G>T, (rs8123716) p.S6S in ? patients, not checked in controls c.432C>G p.D144E in 1 unaffected member of a family with KC and in 0 controls c.479G>A p.G160D in 2 patients and 0 controls c.546A>G (rs12480307)	p.S6S: not segregating p.D144E: not segregating p.G160D: no cosegregation performed p.A182A: not segregating p.R217H: not		[56]

					p.A182A in ? patients and 37 controls c.650G>A, (rs6138482) p.R217H in ? patients and 22 controls c.711 T>A p.P237P in ? patients and 36 controls c.789C>T p.S263S in 1 patient and 0 controls c.844-13T>A in 1 patient and 0 controls c.844-5_-6insT in ? patients and 30 controls rs743018, DQ854809: c.843 + 140 C>T; DQ854810: c.662 +140 C>T in ? patients and 40 controls c.*28G>T in ? patients and 2 controls c.*50G>A in ? patients and 6 controls	segregating p.P237P: not segregating p.S263S: not segregating c.844-13T>A: not segregating c.844-5_-6insT: segregating c.843 + 140 C>T/ c.662 +140 C>T: not segregating c.*28G>T: segregating in 2 families c.*50G>A: segregating in 2 families, not-segregating in 1 family		
	Sequencing of all 5 exons and exon-intron boundaries		66 patients and 100 controls	2 variants	c.525G>C, p.Q175H in 1 patient and in 0 controls rs12480307 in 4 patients and 6 controls	p.Q175H present in 1 affected family member and unaffected mother, absent in 2 unaffected sisters and unaffected father[57]		[58]
	Sequencing of the coding regions and exon-intron boundaries		50 patients and 50 controls	4 variants	p.A182A in 25 patients and 29 controls p.R217H in 1 patient and 0 controls p.P237P in 18 patients and 14 controls g.25059612C>T in 3 patients and 0 controls	No		[59]
	Sequencing of the coding regions and exon-intron boundaries		55 patients and 50 controls	5 variants	g.5053 G>T, p.S6S in 2 patients and 2 controls g.8222 A>G, p.A182A	No		[60]

					in 1 patient and 1 control g.8326 G>A in 1 patient and 5 controls g.10945 G>T in 0 patients and 1 control g.11059 A>C in 1 patient and 0 controls			
	Sequencing of the whole coding region and the exon–intron junctions		53 patients and 100 controls	11 variants	c.49C>G, Leu17Val in 2 patients and 1 control c.81C>T, Arg27Arg in 5 patients and 0 controls c.452A>G, Asn151Ser in 0 patients and 1 control c.479G>T, Gly160Val in 3 patients and 3 controls c.528G>A, Leu176Leu in 1 patient and 0 controls c.546A>G, Ala182Ala in 0 patients and 2 controls c.595G>T, Val199Leu in 1 patient and 0 controls c.425-115C>G in 0 patients and 1 control c.425-16C>G in 0 patients and 1 control c.627+22C>T in 1 patient and 1 control c.627+23G>A in 53 patients and 53 controls	c.595G>T, Val199Leu present in 1 unaffected brother		[61]
	Sequencing of the coding regions and exon-intron boundaries		117 patients and 108 controls	4 variants	c.546A>G, p.A182A in 43 patients and 32 controls c.627+23G>A in 29 patients and 41 controls c.627+84T>A in 58 patients and 50 controls c.504-24C>T in 7	No		[62]

					patients and 7 controls			
	Sequencing of the coding regions and exon-intron boundaries		47 KC patients and 10 PPCD patients (+ screening of interesting variants in 100 controls)	2 variants reported (unclear whether polymorphisms are reported)	c.173C>T, p.Pro58Leu in 1 PPCD patient and in 0 controls c.731A>G, p.His244Arg in 1 KC patient and 0 controls	No		63
	SSCP and sequencing of exon 2-4		50 patients and 50 controls	3 variants	c.546A>G (rs12480307), p.A182A in 6 patients and 4 controls c.650G>A (rs6138482), p.R217H in 6 patients and 3 controls p.H244R in 1 patient and 1 control	No		64
	Association study of 8 tagSNPs		97 patients and 101 controls	3 associated tagSNPs	TG-genotype of rs6050307 is protective for KC T allele of rs56157240 as risk factor (marginally associated) C allele of rs12480307 as risk factor (marginally associated)	No		5
	Sequencing of full coding regions and exon-intron junctions		222 patients (+ screening of identified nonsynonymous variants in 200 controls)	7 variants	5 nonysnonymous variants and 2 undescribed synonymous variants: p.Gly239Arg in 1 patient and 0 controls, p.L17P in 5 patients and 0 controls , p.P247R in 4 patients and 0 controls, p.G160D in 3 patients and 0 controls, p.D144E variant in 5 patients and 1 control p.P116P in 1 patient and p.T158T in 1 patient	p.Gly239Arg present in 6/7 family members without KC but with some alterations in quantitative corneal indices p.P247R present in 1/5 family members but age=16		35
	Sequencing of all coding sequences, exon/		42 patients and 50 controls	7 variants	c.-264_-255delGGGGT GGGGT in 20 patients	No		46

	intron boundaries, and UTRs				and 20 controls, c.627 + 23G>A in 10 patients and 14 controls, c.809-6_809-5insT in 20 patients and 21 controls, c.*200G>T in 2 patients and 8 controls, c.479G4A, p.Gly160Asp in 1 patient and 2 controls, c.18G4T, p.Ser6Ser in 14 patients and 11 controls, c.546A4G, p.Ala182Ala in 10 patients and 14 controls			
	Sequencing of all exons and intron-exon junctions		57 patients and 3 unaffected individuals from 18 families and 20 controls	4 variants	174G>T, p.P58P in 1 patient and 1 control c.18 G>T, p.S6S in 5 patients and 4 controls c.546A>G, p.F182F in 26 patients and 8 controls c.627+23G>A in 19 patients and 9 controls	No		[36]
	Sequencing of all exons and 50 bp of the flanking intron sequence		1 patient with KC, PPCD, band keratopathy, heterochromia, iridocorneal endothelial syndrome, 3 brothers with some KC signs and their healthy mother	0 variants (as reported by the authors: no biologically significant mutations)	NA	NA		[16]
	SSCA and sequencing		113 patients and 100 controls	5 variants	S6S in 21 patients and 15 controls A128A in 35 patients and 39 controls D144E in 1 patient and 1 control 504-24C>T in 0 patients and 1 control 627+23G>A in 44 patients and 35 controls; possibly associated with hereditary KC	NA		[37]

	Sequencing of all exons and intron-exon junctions		26 probands of 26 families (and 52 unaffected family members for segregation analysis of coding variants as well as 100 unrelated controls)	2 polymorphisms and 2 variants	g.1502T>G g.9683C>T H244R in 1 proband R166W in 1 proband	H244R present in 3 additional affected family members as well as in 2 unaffected family members (one of young age and one mother where reduced penetrance is suspected), but is absent in 5 unaffected family members and in all 100 controls R166W present in 1 additional affected family member (father) but absent in mother and sister		[38]
	Genotyping of 4 reported variants		33 patients and 78 controls	0 variants	NA	NA		[39]
	Association study of 1 SNP		210 patients and 191 controls	0 variants	NA	NA		[14]
	Sequencing of all exons and intron-exon junctions		20 patients and 11 unaffected family members (+screening of nonsynonymous variants in 105 controls)	6 variants	p.L268H in 5 patients (of 2 families) and 0 controls p.S251T 3 patients (of 1 family) and 0 controls rs56157240, c.627 + 84 T > A in 14 patients and 6 unaffected family members rs12480307, c.546A > G p.A182A in 8 patients and 6 controls IVS3–24C > T, c.504-24C > T in 8 patients and 3 controls	p.L268H : family 1: present in 3 patients and absent in unaffected mother family 2: present in 2 patients and absent in unaffected sister and mother p.S251T:		[65]

					rs6138482, c.627 + 23G > A in 9 patients and 7 controls	family 3: present in 3 patients and absent in unaffected mother		
ZEB1	Sequencing of the exons, flanking intron sequences, and 5' and 3' UTRs	Truncating mutations in ZEB1 cause PPCD, missense mutations have been reported in FECD and keratoconus and PPCD and keratoconus and FECD have been associated	70 KC patients, 18 PPCD patients and 96 controls	7 variants in KC patients and 5 variants in PPCD	c.192C > T p.Asp64Asp in 1 KC patient and 0 controls c.233A > C p.Asn78Thr in 2 KC patients and 0 random controls, but present in 3/23 ethnically matched controls c.1257G > A p.Ala419Ala in 1 KC patient and 0 controls c.1574G > A p.Gly525Glu in 1 KC patient and 0 controls c.1920G > T p.Gln640His in 1 KC patient and 0 controls c.2673G > C p.Pro891Pro in 1 KC patient and 0 controls c.3177A > T p.Pro1059Pro in 3 KC patients and 5 controls	c.1920G > T p.Gln640His present in affected brother and father and absent in unaffected mother	No	[66]
	Sequencing of 1 variant		1 patient	1 variant	c.1920G>T, p.Gln640His in 1 patient	No		[47]
LOX	Sequencing of full coding regions	Localized in 5q23.2, enzyme is responsible for collagen and elastin cross-linking	302 patients	2 variants	p.P159Q in 5 patients p.R158Q homozygous in 8 patients and 78 heterozygous	No	Yes, GWAS [67]	[35]
	GWAS: 1 SNP in LOX genotyped in discovery cohort, 5 SNPs genotyped in the confirmation cohort, Association study of 2 SNPs		GWAS: -Discovery cohort: 222 patients and 3324 controls -Confirmation Cohort: 304 patients and 518 controls Association study of 2 SNPs: -KC families: 146 patients and	2 variants	rs10519694 and rs2956540: Suggestive association in GWAS set-up, confirmed in confirmation case-control and family-based analysis	NA		[67]

			161 unaffected family members Combined panel: 377 KC patients from discovery and confirmation cohort, 114 controls from confirmation cohort and 428 affected and unaffected family members					
	Association study of 1 SNP		210 patients and 191 controls	1 variant	Genotype GG of rs2956540 might reduce the KC risk (not significant after Bonferroni correction)	NA		[14]
	Association study of 4 SNPs		165 patients and 193 controls	1 variant	C-allele of rs2956540 might reduce the KC risk	NA		[68]
	Association study of 2 SNPs		112 patients and 150 controls	1 variant	AA and GA+ AA genotypes and A allele of rs1800449 associated with KC	NA		[69]
	Meta-analysis of published LOX variants		1467 patients and 4490 controls	2 variants	Significant association of rs2956540 and rs10519694	NA		[70]
miR184	Sequencing of stem-loop domain	Mutation identified in the linked region of a family with KC and cataract	780 KC patients, 96 subjects with axial myopia and 192 controls	2 variants	miR184(+3A>G) in 1 patient miR184(+8C>A) in 1 patient	miR184(+3A>G) present in affected brother and unaffected father, absent in unaffected mother miR184(+8C>A) present in 1 parent, but no clinical examination, absent in healthy sibling	Yes, linkage analysis [71,72] and NGS [73]	[74]
	Association study of 1 SNP		692 patients and 1865 controls	0 variants	NA	NA		
	Sequencing of stem-loop domain		4 family members of a family with variable corneal abnormalities, including KC (3 patients, 1 unaffected family member)	1 variant	MIR184 c.57 C>U in proband	MIR184 c.57 C>U present in 3 patients (1 with KC), absent in		[75]

						unaffected family member		
	Sequencing of complete miR184		134 patients	0 variants	NA	NA		[76]
	Sequencing of complete miR184		47 patients	1 variant	MIR184 +39G>T in 1 patient	MIR184 +39G>T present in affected sister, but 0.6% prevalence in dbSNP and no association for this SNP in KC patients vs controls [74]		[77]
ZNF469	Sequencing of exons and flanking intron sequences	Homozygous mutations cause Brittle Cornea Syndrome, characterized by extreme corneal thinning, and a SNP near this gene is repeatedly associated with CCT and even KC	112 patients and 784 controls	96 variants (+ 1 variant exclusive in 1 control)	12 potentially pathogenic variants in patients c.290C>T, p.Pro97Leu c.337G>A, p.Glu113Lys c.2063C>A, p.Thr688Asn c.2699C>G, p.Pro900Arg c.2699C>T, p.Pro900Leu c.3119A>C, p.Lys1040Thr c.4363G>T, p.Ala1455Ser c.5464C>A, p.Pro1822Thr c.6095C>A, p.Ser2032Tyr c.8912G>T, p.Gly2971Val c.9047C>T, p.Thr3016Met c.11615C>T, p.Pro3872Leu 2 in frame deletions c.2904_2909delGTCGGG, p.Ser969_Gly970del c.9011_9025delTTCCC	NA	Yes, GWAS [2, 10, 13, 78, 79]	[80]

					GGGAACACCC,p.Leu3004_Thr3008del 15 nonsynonymous variants predicted tolerated by SIFT, absent in controls and MAF <0.1%: c.77G>C, p.Ser26Thr c.1627G>A, p.Gly543Ser c.2297G>A, p.Arg766Gln c.3236G>A, p.Arg1079Gln c.4394C>T, p.Pro1465Leu c.4826G>C, p.Arg1609Pro c.5060G>A, p.Arg1687Lys c.5597A>T, p.Gln1866Leu c.6007G>A, p.Glu2003Lys c.6725C>A, p.Ser2242Tyr c.7527G>C, p.Glu2509Asp c.7747G>A, p.Glu2583Lys c.7847G>A, p.Arg2616Gln c.9835A>G, p.Thr3279Ala c.11101G>A, p.Gly3701Ser 34 nonsynonymous variants present in patients and controls, MAF>0.1% 33 synonymous variants present in patients and controls, MAF >0.1%			

					1 potentially pathogenic in 1 control: c.1701G>T; p.Gln567His			
	Sequencing of exons		43 patients and 92 controls	37 variants	10 potentially pathogenic variants in patients c.946G>A, p.E316K in 1 patient and in 0 controls c.1697C>T, p.A566V in 3 patients and in 0 controls c.6386G>A, p.R2129K in 8 patients and in 13 controls c.6796G>A, p.G2266A in 1 patient and 0 controls c.7424C>A, p.A2475E in 4 patients and 2 controls c.8246A>T, p.D2749V in 1 patient and 1 control c.8636G>A, p.R2879H in 1 patient and 0 controls c.9616C>T, p.P3206L in 1 patient and 0 controls c.9766G>A, p.G3256R in 1 patient and 0 controls c.10244G>T, p.G3415V in 3 patients and 12 controls 11 nonsynonymous variants, that are present in population databases and/or predicted to be neutral by prediction programs or high frequency in patient and	c.946G>A, p.E316K in 1 family in both affected siblings, together with p.A2475E. c.7424C>A, p.A2475E in 2 families: -08NZTAR1: present in 2 affected sibs (together with E316K) and present in unaffected mother and daughter -08NZFYJ1: present in 2 siblings and in unaffected father, absent in unaffected mother c.8636G>A, p.R2879H in 1 family: present in 2 affected siblings (one sibling also carries the R2129K variant), absent in 1 affected niece and in 1 unaffected niece		81

					control population 13 synonymous variants	c.10244G>T, p.G3415V in 1 family, present in affected mother, absent in 3 affected daughters and 2 unaffected grandsons		
	Sequencing of coding sequences and splice sites		11 KC families comprised of 39 patients, 20 unaffected family members and 7 KC suspects and 4 parents of children with mutations in *ZNF469* causing Brittle Cornea Syndrome (+ WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities)	Parents of BCS-patients: despite presence of LOF mutation: no features of KC In KC families: 38 variants	9 potentially damaging variants with MAF <2.5%: c.664G>C, p.(Gly222Arg) in 1 patient allele, 0 unaffected family members and 0 controls c.1697C>T, p.(Ala566Val) in 2 patient alleles, 2 unaffected family member alleles and MAF of 0.2% in 521 Mendelian disease individuals and 1.19% in 1100 controls c.2035G>A, p.(Glu679Lys) in 2 patient alleles, 0 unaffected family member alleles and MAF of 0.3% in 521 Mendelian disease individuals and 0.49% in 1100 controls c.2803G>A, p.(Glu935Lys) in 1 patient allele, 0 unaffected family member alleles and MAF of 0.3% in 521 Mendelian disease individuals and 0.09%	c.664G>C, p.(Gly222Arg): family 3: present in 2 affected siblings, absent in 2 siblings with unknown affection status c.1697C>T, p.(Ala566Val) : -family 1 : present in 1 patient, absent in affected sibling -family 3: present in 1 patient and 2 unaffected family members, absent in 1affected sibling c.2035G>A, p.(Glu679Lys): family 1: present in 2 affected siblings c.2803G>A, p.(Glu935Lys): family 1:		[82]

					in 1100 controls c.4337C>T, p.(Ala1446Val) in 3 patient alleles, 4 unaffected family member alleles and MAF of 2.36% in 521 Mendelian disease individuals and 1.22% in 1100 controls c.5624G>A, p.(Arg1875His) in 5 patient alleles, 1 unaffected family member allele, 3 KC suspect alleles and MAF of 0.04% in 1100 controls, not present in 521 Mendelian disease individuals c.6956C>T, p.(Ala2319Val) in 1 patient, 2 unaffected family member alleles and 0 controls c.9011_9025del, p.(Leu3004_Thr3008del) in 1 patient allele, 3 unaffected family member alleles and MAF of 0.89% in 521 Mendelian disease individuals and 0.68% in 1100 controls c.10277G>A, p.(Arg3426Gln) in 3 patient alleles, 1 unaffected family member allele and MAF of 3.54% in 521 Mendelian disease individuals and 1.65 % in 1100 controls	present in 1 patient, absent in affected sibling c.4337C>T, p.(Ala1446Val) : family 3: present in 2 affected siblings (1 homozygous), homozygous in 2 siblings with unknown affection status c.5624G>A, p.(Arg1875His) : family 8: present in 4 patients (1 homozygous), in 2 KC suspects (1 homozygous) and in 1 unaffected family member (<40 years old), absent in 1 patient and 1 unaffected spouse c.6956C>T, p.(Ala2319Val) : family 10 : present in 1 patient and 2 unaffected family members (1 younger than 40), absent in 2 patients and 1		

					14 synonymous variants In 1100 controls: 4 presumed LOF variants and 224 nonsynonymous variants with MAF <0.001	unaffected family member (younger than 40 years old) c.9011_9025del , p.(Leu3004_Thr3008del): -family 5: present in 1 patient and unaffected mother, absent in 1 affected sibling -family 9: present in family member with unknown affection status and unaffected spouse, absent in 4 patients and 3 family members with unknown affection status c.10277G>A, p.(Arg3426Gln) : family 10: present in 3 patients and 1 family member with unknown affection status, absent in unaffected mother and family member with unknown affection status		

	Association study of 1 SNP near *ZNF469* (previously identified in GWAS)		210 patients and 191 controls	Rs9938149 not associated	NA	NA		[14]
	Association study of 1 SNP near *ZNF469* (previously identified in GWAS)		108 KC patients and 300 controls	Rs9938149 not associated	NA	NA		[7]
	Sequencing of complete coding sequences		42 KC patients and 49 patients with high myopia (+ WES data of 268 individuals without ocular abnormalities)	40 variants	17 non-synonymous variants: c.1069T>C, p.Ser357Pro in 81 KC alleles and 94 HM alleles, MAF of 94.59% in controls c.1098A>C, p.Arg366Ser in 78 KC alleles and 95 HM alleles, MAF of 92.35% in controls c.1285G>A, p.Ala429Thr in 4 KC alleles and 0 HM alleles, MAF of 1.87% in controls c.1489G>A, p.Gly497Arg in 13 KC alleles and 13 HM alleles, MAF of 11.38% in controls c.1529G>C, p.Gly510Ala in 84 KC alleles and 98 HM alleles, MAF of 98.69% in controls c.3484A>G, p.Lys1162Glu in 77 KC alleles and 93 HM alleles, MAF of 91.04% in controls c.4259C>T, p.Pro1420Leu in 76 KC alleles and 89 HM alleles, MAF of 89.93%	NA		[83]

					in controls c.4337C>T, p.Ala1446Val in 0 KC alleles and 3 HM alleles c.5591G>A, p.Arg1864Lys in 1 KC allele and 0 HM alleles, MAF of 0% in controls c.6386G>A, p.Arg2129Lys in 4 KC alleles and 7 HM alleles, MAF of 4.66% in controls c.7424C>A, p.Ala2475Glu in 5 KC alleles and 9 HM alleles, MAF of 5.04% in controls c.8009T>A, p.Leu2670Gln in 33 KC alleles and 39 HM alleles, MAF of 38.81% in controls c.8246A>T, p.Asp2749Val in 11 KC alleles and 9 HM alleles, MAF of 6.16% in controls c.8543A>G, p.His2848Arg in 84 KC alleles and 98 HM alleles, MAF of 99.25% in controls c.10241G>C, p.Arg3414Thr in 4 KC alleles and 0 HM alleles, MAF of 1.31% in controls c.10888G>C, p.Glu3630Gln in 45 KC alleles and 46 HM alleles, MAF of 45.71% in controls			

					10906A>G, p.Thr3636Ala in 84 KC alleles and 92 alleles 14 synonymous variants, MAF of 99.25% in controls 9 UTR variants			
DOCK9	Sequencing of coding regions and intron-exon junctions	Located in 13q32	51 family members of 15 Ecuadorian KC families and 105 controls	21 variants	2 variants were present in all 10 patients of the same family: 1 nonsynonymous variant: c.2262A>C, p.Gln754His in 10 patients (all of 1 family), 1 unaffected family member, 1 family member with an unknown affection status and in 0 controls 1 intronic variant: c.720+43A>G in 14 patients (10 of 1 family), 1 unaffected family member, 1 family member with an unknown affection status and in 3 controls 3 synonymous variants 16 intronic variants	c.2262A>C, p.Gln754His: present in all 10 patients of KTCN-014 family, in 1 unaffected family member and 1 family member with an unknown affection status c.720+43A>G: present in all 10 patients, in 1 unaffected family member and 1 family member with an unknown affection status	Yes, linkage analysis [36, 84]	[84, 85]
	Sequencing of 2 reported variants (c.717 + 43A>G and c.2262A>C, p.Gln754His)		42 KC patients and 50 controls	1 variant	c.717 + 43A>G in 5 patients and 2 controls	No		[46]
IPO5	Sequencing of coding regions and intron-exon junctions	Located in 13q32	51 family members of 15 Ecuadorian KC families and 105 controls	21 variants	1 variant was present in all 10 patients of the same family: 1 intronic variants: c.2380-134A>C in 12 patients (10 of 1 family), 1 unaffected family member, 1 family member with an unknown affection	c.2380-134A present in all 10 patients of KTCN-014 family, in 1 unaffected family member and 1 family member with an unknown	Yes, linkage analysis [36, 84]	[84]

					status and in 5 controls 18 intronic variants 2 synonymous variants	affection status		
	Sequencing of 1 reported variant (c.2380-134A>C)		42 KC patients and 50 controls	0 variants	NA	NA		[46]
STK24	Sequencing of coding regions and intron-exon junctions	Located in 13q32	51 family members of 15 Ecuadorian KC families and 105 controls	29 variants	1 variant was present in all 10 patients of the same family: 1 intronic variants c.1053+29G>C in 10 patients (all of 1 family), 1 unaffected family member, 1 family member with an unknown affection status and in 1 control 1 synonymous variant 27 intronic variants	c.1053+29G>C present in all 10 patients of KTCN-014 family, in 1 unaffected family member and 1 family member with an unknown affection status	Yes, linkage analysis [36, 84]	[84]
	Sequencing of 1 reported variant (c.1089 + 29G>C)		42 KC patients and 50 controls	0 variants	NA	NA		[46]
CAST	Association study of 7 SNPs in the familial cohort Association study of 12 SNPs in the familial and case-control cohort	Located in 5q14.3-q21.1	262 members of 40 families: 131 KC patients and 131 unaffected family members and 304 additional KC patients and 518 controls	1 associated variant in familial cohort and case-control cohort 1 associated SNP (and 1 almost associated SNP) in familial cohort	T allele of rs4434401 risk factor for KC in familial and case-control cohort A allele of rs4869307 reduces the risk of KC in familial cohort A allele of rs27654 reduces the risk of KC in familial cohort	NA	Yes, Linkage analysis [86]	[87]
SLC4A11	Sequencing of coding regions, intron-exon junctions and UTRs	Located in 20p13	21 members of 1 family: 9 affected, 9 unaffected family members and 3 family members of unknown affection status and 93 DNA samples from KC families (affected and unaffected) and 22 controls	20 variants	c.2558+149_2558+203del54 present in 8 patients (all of 1 family), 2 unaffected family members and 1 family member with unknown affection status c.2193-18C > T present in 25 patients, 39 unaffected family members (different families) and 11 controls 12 intronic variants	c.2558+149_2558+203del54: KTCN-019: present in 8/9 affected family members, in 2/9 unaffected family members, in 1 family member with unknown affection status	Yes, Linkage analysis [27]	[27]

					2 indels 1 UTR variant 3 synonymous variants			
FNDC3B	Association study of 1 SNP	GWAS on CCT	157 KC patients and 673 controls	No association	NA	NA	Yes, GWAS [2]	[13]
	Association study of 1 SNP		210 KC patients and 191 controls	No association	NA	NA		[14]
	Association study of 1 SNP		108 KC patients and 300 controls	No association	NA	NA		[7]
HGF	Association study of 10 tagSNPs	GWAS on KC	157 KC patients and 673 controls	1 associated tagSNP	rs2286194 associated with KC	NA	Yes, GWAS [88]	[89]
	Association study of 1 SNP		210 KC patients and 191 controls	No association	NA	NA		[14]
	Association study of 1 SNP		165 KC patients and 193 controls	1 associated SNP	A allele of rs3735520 is risk factor for KC	NA		[68]
RAB3GAP1	Association study of 1 SNP	GWAS on CCT	524 KC patients and 2761 controls	1 associated SNP	rs4954218 associated with KC	NA	Yes, GWAS [90]	[91]
MPDZ-NF1B	Association study of 1 SNP	GWAS on CCT and KC	210 KC patients and 191 controls	1 associated SNP	rs1324183 associated with KC	NA	Yes, GWAS [2]	[14]
	Association study of 1 SNP		108 KC patients and 300 controls	No association	NA	NA		[7]
LCN-12PTGDS	Association study of 1 SNP	GWAS on CCT and KC	108 KC patients and 300 controls	No association	NA	NA	Yes, GWAS [2]	[7]

FOXO1	Association study of 1 SNP	GWAS on CCT and KC	108 KC patients and 300 controls	No association	NA	NA	Yes, GWAS [2, 10]	[7]

KC: keratoconus. SSCA: Single Strand Conformation Analysis. GWAS: genome-wide association study. SNP: single nucleotide polymorphism. AS: association study. PPCD: posterior polymorphous corneal dystrophy. FECD: Fuch's endothelial corneal dystrophy. SSCP: Single strand conformation polymorphism. OAG: open angle glaucoma. NGS: Next generation sequencing. CCT: Central Corneal Thickness. BCS: Brittle Cornea syndrome. MAF: Minor Allele Frequency. WES: Whole Exome Sequencing. LOF: loss-of-function. HM: High Myopia. NA: not applicable.

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