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

Gen	e	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.
	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
	1A3	SSCA and sequencing	in KC Corneas,withGenetic alterations inconCOL4A3 and113COL4A4 genes may bewithresponsible forkeradecreases in97	104 unrelated patients with KC and 157 healthy controls	8 polymorphisms	6 missense variants, 2 synonymous variants	NA	Yes, GWAS ²	3
su		SSCA and sequencing		113 patients with sporadic or familial keratoconus	8 polymorphisms	6 missense variants, 2 synonymous variants	NA		4
Collagens	COL4.	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	7	108 patients and 300 controls	No association	NA	NA		7
		SSCA and sequencing	Differentially expressed in KC Corneas, Genetic alterations in	104 unrelated patients with KC and 157 healthy controls	6 polymorphisms	4 missense variants, 2 synonymous variants	NA	No	3
	OL4A4	SSCA and sequencing	COL4A3 and COL4A4 genes may be	113 patients with sporadic or familial keratoconus	6 polymorphisms	3 missense variants, 3 synonymous variants	NA		4
	C	Association study of 3 tagSNPs	decreases in collagen types I and III	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

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

	IAI	Association study of 2 SNPs Association study of 44 SNPs	Association with CCT and located in 9q34.	112 patients and 150 controls 526 patients, 3842 controls and 186 subjects from families	protective effect of 2 variant genotypes 1 polymorphism as risk factor 1 associated SNP	M1327V AA and F1644F TT in controls rs2229813AA and GA+AA genotypes are risk factors rs1536482 associated with KC	NA	Yes, GWAS 2, 9-11	8
	COL5A.	Association study of 2 SNPs Association study of 2 SNPs	-	157 patients and 673 controls 210 patients and 191 controls	No association No association	NA NA	NA NA	-	13 14 7
	COL8A1	Association study of 2 SNPs Sequencing of the coding regions	COL8A1/COL8A2 knockout mice shows a corneal phenotype including corneal	108 patients and 300 controls 50 unrelated patients and 2 unrelated keratoglobus patients	No association 1 polymorphism	NA 1 synonymous variant	NA NA	No	15
	A2	Sequencing of the coding regions	thinning, Type VIII collagen is expressed in the cornea and previous reports	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
	COL8A	Sequencing of all exons and 50 bp of the flanking intron sequence	link COL8A2 mutations to corneal dystrophies	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
nes	POLG	Association study of 1 polymorphism	Disturbance in the activity of antioxidant enzymes in KC corneas, Indications for a role of	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
Base excision repair genes	XRCCI	Association study of 2 polymorphisms	oxidative stress in KC		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

	NEILI	Association study of 1 polymorphism			No association	NA	NA	No	17
	PARP-1	Association study of 1 polymorphism			No association	NA	NA	No	17
	APEXI	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
	FENI	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
	hOGGI	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		КС				
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
		Association study of 3 polymorphisms	IL1 is a mediator of keratocyte apoptosis in the cornea, which is reported to underlie	100 unrelated KC patients	1 polymorphism associated with KC	C/A-genotype of rs2071376 is associated with increased risk of KC	NA	No	24
	IA	Association study of 1 polymorphism	stromal thinning	169 KC patients and 390 controls	Polymorphism not associated with KC	NA	NA		25
SI	ILIA	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
Interleukins		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
In		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
	ILIB	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

					КС				
		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
	ILIRN	Association study of 4 polymorphisms and 1 VNTR		100 unrelated KC patients	Polymorphisms not associated with KC	NA	NA	Yes, Linkage analysis ²⁷	24
	ITI	Association study of 1 polymorphism and 1 VNTR		121 KC patients and 121 controls	Polymorphisms not associated with KC	NA	NA		28
aplogroups		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	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
Mitochondrial genes and haplogroups		Haplogrouping of 19 mitochondrial haplogroups	oxidative stress.	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
Mitochondri		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						
	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
10	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
SODI	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

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	rs7714314, rs2304052, rs2116780, rs2304051, rs1978707, rs41290587 and rs1053411 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 <i>TGFBI</i> 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
ТС	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
NSXI	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	498
	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

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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	present in 2 affected family members and 1 family member with unknown affection status and absent in 2 unaffected family members NA	51	1
Sequencing of full coding regions and exon-intron junctions	85 unrelated patients and 50 controls	11 variants	 c.426C>A, Arg131Ser in 1 patient c.581A>G, Ala182Ala in 51 patients 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.F58P in 2 patients p.F38P in 2 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	52	2
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	other variants were identified in non-familial cases H244R present in both twins of a monozygotic	-53	3

Sequencing of full coding regions	10 members of 1 family	1 variant reported	unaffected family members R166W absent in all patients and controls H244R present in 2 affected familial cases and 1 unaffected family member D144E present in 6	twin pair D144E present	54
and exon-intron junctions	(+screening of identified variant in 104 controls)	(unclear whether polymorphisms are reported)	family members and 1 control	in 4 KC patients and 2 family members with unclear affection status and absent in 4 normal individuals	
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.844-56insT 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.844-56insT: 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

encing of the whole coding n and the exon–intron ons	53 patients and 100 controls	11 variants	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 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.595G>T, Val199Leu present in 1 unaffected brother	61
			patients and 1 control c.627+22C>T in 1 patient and 1 control c.627+23G>A in 53 patients and 53 controls		
encing of the coding regions xon-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	47 KC patients and 10 PPCD	2 variants	c.173C>T, p.Pro58Leu	No		63
and exon-intron boundaries	patients (+ screening of	reported (unclear	in 1 PPCD patient and in	INU		
and exon-introli boundaries	interesting variants in 100	whether	0 controls			
	controls)	polymorphisms	c.731A>G, p.His244Arg			
	controis)		in 1 KC patient and 0			
		are reported)	controls			
	50 (150 (1	2		No		64
SSCP and sequencing of exon 2-4	50 patients and 50 controls	3 variants	c.546A>G	NO		
			(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			_
Association study of 8 tagSNPs	97 patients and 101 controls	3 associated	TG-genotype of	No		5
		tagSNPs	rs6050307 is protective			
			for KC			
			T allele of rs56157240			
			as risk factor			
			(marginally associated)			
			C allele of rs12480307			
			as risk factor			
			(marginally associated)			
Sequencing of full coding regions	222 patients (+ screening of	7 variants	5 nonysnonymous	p.Gly239Arg		35
and exon-intron junctions	identified nonsynonymous		variants and 2	present in 6/7		
3	variants in 200 controls)		undescribed	family		
	,		synonymous variants:	members		
			p.Gly239Arg in 1	without KC but		
			patient and 0 controls,	with some		
			p.L17P in 5 patients and	alterations in		
			0 controls,	quantitative		
			p.P247R in 4 patients	corneal indices		
			and 0 controls,	p.P247R		
			p.G160D in 3 patients	present in 1/5		
			and 0 controls,	family		
			p.D144E variant in 5	members but		
			patients and 1 control	age=16		
			p.P116P in 1 patient and	age-10		
Companying of all as ding		7	p.T158T in 1 patient	N-	4	46
Sequencing of all coding	42 patients and 50 controls	7 variants	c264255delGGGGT	No		
sequences, exon/			GGGGT in 20 patients			

		1	1.20		1 1
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		
	57	4 • •	controls	N	36
Sequencing of all exons and intron-	57 patients and 3 unaffected	4 variants	174G>T, p.P58P in 1	No	50
exon junctions	individuals from 18 families		patient and 1 control		
	and 20 controls		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		
Sequencing of all exons	1 patient with KC, PPCD, band	0 variants (as	NA	NA	16
and 50 bp of the flanking intron	keratopathy, heterochromia,	reported by the			
sequence	iridocorneal endothelial	authors: no			
1	syndrome, 3 brothers with	biologically			
	some KC signs and their	significant			
	healthy mother	mutations)			
SSCA and sequencing	113 patients and 100 controls	5 variants	S6S in 21 patients and	NA	37
soerr and sequeneing	115 patients and 100 controls	5 variants	15 controls	1 17 1	
			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		

	Sequencing of all exons and intron-	26 probands of 26 families (and	2 polymorphisms	g.1502T>G	H244R present	38
	exon junctions	52 unaffected family members	and 2 variants	g.9683C>T	in 3 additional	
		for segregation analysis of		H244R in 1 proband	affected family	
		coding variants as well as 100		R166W in 1 proband	members as	
		unrelated controls)			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	
	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-	20 patients and 11 unaffected	6 variants	p.L268H in 5 patients	p.L268H :	65
	exon junctions	family members (+screening of		(of 2 families) and 0	family 1:	
		nonsynonymous variants in 105		controls	present in 3	
		controls)		p.S251T 3 patients (of 1	patients and	
		controls)		family) and 0 controls	absent in	
				rs56157240, c.627 + 84	unaffected	
				T > A in 14 patients and	mother	
				6 unaffected family	family 2:	
				members	present in 2	
				rs12480307, c.546A >	patients and	
				G p.A182A in 8 patients	absent in	
				and 6 controls	unaffected	
				IVS3-24C > T, c.504-	sister and	
				24C > T in 8 patients	mother	
				and 3 controls	p.S251T:	
L I			1		P.52311.	

					rs6138482, c.627 + 23G > A in 9 patients and 7 controls	family 3: present in 3 patients and absent in unaffected mother		
ZEBI	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
	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
ХОТ	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					14
	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 Sequencing of stem-loop domain		692 patients and 1865 controls 4 family members of a family with variable corneal abnormalities, including KC (3 patients, 1 unaffected family member)	0 variants 1 variant	NA MIR184 c.57 C>U in proband	NA MIR184 c.57 C>U present in 3 patients (1 with KC), absent in		75

						CC 1		
						unaffected		
		4	124			family member	4	76
	Sequencing of complete miR184	-	134 patients	0 variants	NA	NA		77
	Sequencing of complete miR184		47 patients	1 variant	MIR184 +39G>T in 1	MIR184		
					patient	+39G>T		
						present in		
						affected sister,		
						but 0.6%		
						prevalence in		
						dbSNP and no		
						association for		
						this SNP in KC		
						patients vs		
						controls ⁷⁴		80
	Sequencing of exons and flanking	Homozygous mutations	112 patients and 784 controls	96 variants (+1	12 potentially	NA	Yes, GWAS ^{2,} 10, 13, 78, 79	80
	intron sequences	cause Brittle Cornea		variant exclusive	pathogenic variants in		10, 15, 76, 75	
		Syndrome,		in 1 control)	patients			
		characterized by			c.290C>T, p.Pro97Leu			
		extreme corneal			c.337G>A, p.Glu113Lys			
		thinning, and a SNP			c.2063C>A,			
		near this gene is			p.Thr688Asn			
		repeatedly associated			c.2699C>G,			
		with CCT and even KC			p.Pro900Arg			
					c.2699C>T,			
					p.Pro900Leu			
					c.3119A>C,			
					p.Lys1040Thr			
ZNF469					c.4363G>T,			
VF					p.Ala1455Ser			
Z					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_2909delGTCGG			
					G, p.Ser969_Gly970del			
					c.9011_9025delTTCCC			

 1			г — г	
		GGGAACACCC,p.Leu		
		3004_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;		
a	4			p.Gln567His		81
Sequencing of exons		43 patients and 92 controls	37 variants	10 potentially	c.946G>A,	01
				pathogenic variants in	p.E316K in 1	
				patients	family in both	
				c.946G>A, p.E316K in	affected	
				1 patient and in 0	siblings,	
				controls	together with	
				c.1697C>T, p.A566V in	p.A2475E.	
				3 patients and in 0	c.7424C>A,	
				controls	p.A2475E in 2	
				c.6386G>A, p.R2129K	families:	
				in 8 patients and in 13	-08NZTAR1:	
				controls	present in 2	
				c.6796G>A, p.G2266A	affected sibs	
				in 1 patient and 0	(together with	
				controls	E316K) and	
				c.7424C>A, p.A2475E	present in	
				in 4 patients and 2	unaffected	
				controls	mother and	
				c.8246A>T, p.D2749V	daughter	
				in 1 patient and 1	-08NZFYJ1:	
				control	present in 2	
				c.8636G>A, p.R2879H	siblings and in	
				in 1 patient and 0	unaffected	
				controls	father, absent in	
				c.9616C>T, p.P3206L in	unaffected	
				1 patient and 0 controls	mother	
				c.9766G>A, p.G3256R	c.8636G>A,	
				in 1 patient and 0	p.R2879H in 1	
				controls	family: present	
				c.10244G>T, p.G3415V	in 2 affected	
				in 3 patients and 12	siblings (one	
				controls	sibling also	
				11 nonsynonymous	carries the	
				variants, that are present	R2129K	
				in population databases	variant), absent	
				and/or predicted to be	in 1 affected	
				neutral by prediction	niece and in 1	
				programs or high	unaffected	
				frequency in patient and	niece	

Sequencing of coding sequences and splice sites 11 KC families comprised of 39 patients. 20 unaffected family members and 7 KC suspects and spents of children with mutations in ZNF409 causing Brittle Comea Syntheme (+ WTS data from 521 individuals of varying ethnicities) 9 potentially damaging patients. 40 potentially damaging patients. 40 unaffected family patients. 40 unaffected family patients. 40 unaffected family patients. 40 unaffected family members and 7 KC suspects and 4 parents of children with mutations in ZNF409 causing Brittle Comea Syntheme (+ WTS data from 521 individuals of varying ethnicities) 9 potentially damaging patients. 40 controls a sprants e6464C-C, present in 2 pricesce Children with unknown e. 1697C-T, patient allele, 0 unaffected family members and 0 controls e. 1697C-T, patient allele, 2 patient alleles, 2 patient alleles, 0 unaffected family members, 40 controls e. 1697C-T, patient alleles, 0 unaffected family members, 40 controls e. 1697C-T, patient alleles, 0 unaffected family members, 40 controls e. 1697C-T, patient alleles, 0 unaffected family members, 40 controls e. 2036Co-A, pricesce and members, MAP of 0.3% in 521 members, MAP of 0.3% in 521 me					- 10044C: T	г	
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 27/4769 causing Brittle Cornea Syndrome (- WES data from 321 individual with other Mondelian diseases and from 1100 individuals of varying ethnicities) 9 parents of BCS patients, 20 unaffected family members and 7 KC suspects and from 1100 individuals of varying ethnicities) 9 parents of BCS patients, 20 unaffected family members and 7 KC families: and from 1100 individuals of varying ethnicities) 9 parents of BCS patients despite variants with MAF for unations in 0.27/46 (20) patients despite variants with MAF for unations in 0.27/46 (20) patients despite variants with adher patients despite variants with adher Mondelian diseases and from 1100 individuals of varying ethnicities) 9 parents of BCS patients despite variants with adher patient adles, 2 unaffected family member alleles and MAF of 0.2% in 521 min affected family 3: c 1697C-T, patient alleles and MAF of 0.2% in 521 min affected family 3: c 203050-A, p polent and 2 patient alleles, 0 unaffected family members alleles and MAF of 0.3% in 521 Medelian disease individuals and 0.4% in 1100 controls c 203050-A, p policett alleles, 0 unaffected family members alleles and MAF of 0.3% in 521 Medelian disease individuals and 0.4% in 1100 controls c 203050-A, p policett alleles, 0 unaffected family members alleles and MAF of 0.3% in 521 Medelian disease individuals and 0.4% in 1100 controls c 203050-A, p policett alleles, 0 unaffected family members alleles and MAF of 0.3% in 521 Medelian disease individuals and 0.4% in final patient allele, 0 unaffected family members alleles and members. MAF of 0.3% in 521 Medelian disease individuals and 0.4% in 1100 controls c 203050-A, p policett alleles individuals and 0.4% in family 1: present in 2 patient alleles individuals and 0.4% in fam				control population	c.10244G>T,		
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 kDiPrawing Brittle Comea Syndrome (+ WES data from 521 individaals with other Mendelian diseases and from 1100 individaals of varying ethnicities) Parents of BCS- patients despite presence of LOF mutations in ZP/469 causing Brittle Comea Syndrome (+ WES data from 521 individaals with other Mendelian diseases and from 1100 individaals of varying ethnicities) Parents of BCS- patients despite presence of LOF mutations in ZP/469 causing Brittle Comea Syndrome (+ WES data from 521 individaals with other Mendelian diseases and from 1100 individaals of varying ethnicities) Parents of BCS- patient alleles, 0 unaffected family members and 0 controls c.1697C-T, patient alleles, 2 unaffected family members and 0 controls c.1697C-T, patient alleles, 0 unaffected family members alleles and MAF of 0.2% in 521 members, mAffected individaals and 1.19% in 100 controls c.2035C-A, p.G(Glu952Lyp) in 2 patient alleles, 0 unaffected individaals and 0.4% in 1100 controls c.2035C-A, p.G(Glu952Lyp) in 2 patient alleles, 0 unaffected individaals and 0.4% in 1100 controls c.2035C-A, p.G(Glu952Lyp) in 2 patient alleles, 0 unaffected individaals and 0.4% in 100 controls c.2035C-A, p.G(Glu952Lyp) in 1 patient alleles, 0 unaffected family members, MAF of 0.3% in 521 Maffected individaals and 0.4% in 100 controls c.2035C-A, p.G(Glu952Lyp) in 2 patient allele, 0 unaffected family members, MAF of 0.3% in 521 Maffected family members, MAF of 0.3% in 521				13 synonymous variants			
Sequencing of coding sequences and splice sites 11 KC families comprised of 39 patients, 20 unaffected family members and 7 KC suspects 9 patents of BCS- patients, 20 unaffected family members and 7 KC suspects 9 potentially damaging variants with MAF c.664G>C, patients, 20 unaffected family members and 7 KC suspects 0 patents: despite presence of 1.0F restrues of KC patients, 20 unaffected family members and 7 KC suspects 9 potentially damaging variants with MAF pc.664G>C, patient 316cted 0 patentially affected 38 variants Brittle Cornea Syndrome (+ WES data from 521 individuals of varying ethnicities) KC families: 38 variants 9 potentially damaging variants with MAF pc.614222Arg) in 1 patient allele, 0 unaffected family unaffected family members and be controls affection status patient, alleles, 2 unaffected family member alleles and MAF of 0.2% in 521 patient alleles, 3 present in 1 patient alleles, 3 patient alleles, 3 present in 1 patient alleles, 3 present in 1 patient alleles, 3 present in 1 patient alleles, 3 present in 1 patient alleles, 4 unaffected family members alless and MAF of 0.2% in 521 mathetic alleles, 4 present in 1 patient alleles, 4 present in 2 patient alleles, 4 present in 1 patient allele, 4 present in 2 patient alleles, 4 present in 2 patient alleles, 4 present in 1 patient allele, 4 present in 2 patient allele, 4 present					family, present		
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 27/4499 causing Brittle Comea Syndrome (+ WEIS data from 521 individuals with other Mendelian disease and from 1100 individuals of varying ethnicities) 9 Parents of RCS- patients: despite patients: despite patients: despite mutations. in 27 (- 2.2%): 9 potentially damaging presence of LOF mutations. in 27 (- 2.2%): c.664(3-C, p.(Gly22Arg): present in 2 patient allele, 0 9 potentially damaging (-2.5%): c.664(3-C, p.(Gly22Arg): present in 2 subings. absent unaffected family members and 0 controls (-1697C-ST, p.(Ala566Val) : - family 1: members and 0 controls (-1697C-ST, p.(Ala566Val) : - family 1: members and 6 cottors) subings. with unknown affected individuals and NAF of 0.2% in 521 patient alleles, 2 patient alleles, 3 patient, alleles, 0 unaffected individuals and 1.19% subing individuals and 0.49% subing individuals and 0.49% subing indindividuals and 0.49% subing individuals and 0.49% subing individua							
Sequencing of coding sequences and splice sites 11 KC families comprised of 39 patients, 20 unaffected family members and 7 KC supports and 4 parents of children with mutations in ZNF409 causes and from 1100 individuals of varying ethnicities) Parents of BCS- patients: despite presence of LOF matters or SKC patients: despite presence of LOF patients: despite presence of LOF patients: despite presence of LOF patient allele, 0 unaffected family members and 0 controls c.1697C>T. patient alleles, 2 unaffected family members and 0 MAF of 0.2% in 521 Mendelian disease individuals and 0.49% sibling in 1100 controls c.2035C>A, p.(GluG79Lys); patient alleles, 0 unaffected family members and 2 unaffected family members allows members members and 2 unaffected family members members and 2 unaffected family members me							
Sequencing of coding sequences and splice sites 11 KC families comprised of 39 patients, 20 unaffected family and a parents of children WEAS operior and 4 parents of children WEAS operior Brittle Cornea Syndrome (Chindren WEAS operior and from 1100 individuals of varying ethnicities) Parents of BCS- patients, 20 unaffected family with unknown present in 2 affected affected affected affected affected affected affected affected Parents of BCS- patients, 20 unaffected family with unknown present in 2 affected affection status p.(Ala256Val) in 2 c.1697C>T, affection status p.(Ala256Val) in 2 c.1697C>T, affection status p.(Ala256Val) in 2 c.1697C>T, affection status p.(Ala256Val) in 2 c.1697C>T, affection status p.(Ala256Val) in 2 patient, absent in affected amily 3 c.2035C>A, present in 1 patient alleles, 0 unaffected family in 1100 controls c.2035C>A, present in 1 Mendelian disease sibling in 1100 controls c.2035C>A, present in 1 Mendelian disease sibling in 1100 controls c.2035C>A, present in 1 member alleles and members, adsent in Mendelian disease sibling in 1100 controls c.2035C>A, present in members, adsent in Mendelian disease sibling in 1100 controls c.2035C>A, present in Me							
Sequencing of coding sequences and splice sites 11 KC families comprised of 39 patients, 20 unaffected family members and 7 KC supports and 4 parents of children with mutations in 2VF409 causing Brittle Come Syndrome (+ WES data from 521 individuals with other Medelian diseases and from 1100 individuals of varying ethnicities) Parents of BCS. patients: despite presence of LOIF mutation: no features of KC. 9 potentially damaging variants with MAF (2.5%): C6640-C, family 3: c6640-C, patient allele, 0 Present in 2 a face and syndrome (+ WES data from 521 individuals with other Medelian diseases and from 1100 individuals of varying ethnicities) 38 variants sufficient status present in 2 with unknown affection status present in 1 NAF of 0.2% in 521 members all 0 controls - (207C-T, patient alleles, 0 unaffected family member alleles and marfeeted family members all 0 controls - family 3: c.2035C-A, patient alleles, 0 unaffected family member alleles and marfeeted family member alleles and marfee							
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 ZXF409 causing Britle Cornea Syndrome (+ WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities) 9 potentially damaging presence of LOF features of KC subjects 0 controls c.664(3-C, patients: depite patients: depite patient alleles and MAF of 0.2% in 521 patient alleles and patient alleles, 0 unaffected family members alleles and MAF of 0.2% in 521 patient alleles and MAF of 0.2% in 521 patient alleles and MAF of 0.2% in 521 patient alleles and MAF of 0.3% in 512 patient alleles and MAF of 0.3% in 512 members, abasent in alfected individuals and 0.49% in 1100 controls c.2035G>A, p.(Gluo79Lys) in 2 patient alleles, 0 unaffected individuals and 0.49% in 1100 controls c.2035G>A, p.(Gluo79Lys) in 1 patient allele, 0 unaffected individuals and 0.49% in 1100 controls c.2035G>A, p.(Gluo79Lys) in 1 patient allele, 0 unaffected individuals and 0.49% in 1100 controls c.2035G>A, p.(Gluo79Lys) in 2 patient allele, 0 unaffected individuals and 0.49% in 1100 controls c.2035G>A, p.(Gluo79Lys) in 2 patient allele, 0 unaffected individuals and 0.49% in 1100 controls c.2035G>A, p.(Gluo79Lys) in 2 patient allele, 0 unaffected i							
and splice sites 11 KC families complexed family members and 7 KC supersts and 4 parents of Children with mutations in ZVF409 causing Brittle Correac Syndrome (+ WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities) patients is cheaping patients is cheaping mutations in ZVF409 causing Brittle Correac Syndrome (+ WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities) patients is cheaping patients is cheaping mutations in ZVF409 causing Brittle Correac Syndrome (+ WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities) patients is cheaping mutations in ZVF409 in 2 patient alleles, 2 p.(Alas66Val) in 2 patient alleles, 2 p.(Alas66Val) in 2 maffected family members and 0 controls c.1697CST, patient alleles, 2 p.(Alas66Val) in 2 maffected family members alleles and MAF of 0.2% in 521 patient alleles, 0 mutaffected family in 1100 controls c.2035G>A, present in 1 patient alleles, 0 maffected family members, allefected individuals and 0.49% sibling in 1100 controls c.2035G>A, present in 1 p.(Gluo791Lys) in 2 patient alleles, 0 maffected family members, allefected individuals and 0.49% sibling in 1100 controls c.2035G>A, p. (Gluo791Lys) p.(Gluo791Lys) in 2 patient alleles, 0 members, alaffected individuals and 0.49% sibling in 1100 controls c.2035G>A, p. (Gluo791Lys) p.(Gluo791Lys) in 1 members, alaffected individuals and 0.49% sibling in 1100 controls c.2035G>A, p. (Gluo791Lys) p.(Gluo791Lys) in 1 members, alaffected individuals and 0.49% sibling in 1100 controls c.2035G>A, p.(Gluo791Lys) in 1 matiest alleles, 0 members, alaffected individuals and 0.49% sibling in 1100 controls c.2035C) p.(Gluo791Lys) in 1 matiest alleles individuals and 0.49% sibling in 100 controls c.2035C) p.(Gluo791Lys) in 1 members individuals and 0.49% sibling in 100 controls in 100 controls ind						-	
imembers and 7 KC suspect: and 4 parents of children with mutations in ZMF409 causing Brittle Cornea Syndrome (+ WESG data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities)presence of LOF attacts or KC In KC families: 38 variantsc2.5%: c.6.64G:SC, p.(Gly222Arg) in 1 atfected family members and 0 controls c.1697C>T, patient allele, 0siblings, absent unaffected family members and 0 controls c.1697C>T, patient alleles, 2 p.(Ala566Val) in 2 present in 1 present in 1 matfected family members alleles and MAF of 0.2% in 521 patient alleles, 0 unaffected family members alleles and MAF of 0.2% in 521 patient alleles, 0 unaffected family members alleles and MAF of 0.3% in 521 patient alleles, 0 unaffected family family 1: present in 1 present in 1 member alleles and MAF of 0.3% in 521 adiant alleles, 0 unaffected family family 3: c.2035G>A, p.(Glu679Lys) in 2 patient alleles, 0 unaffected family family 1: present in 1 present in 1 absent in dividuals and 0.49% in 1100 controls c.2035G>A, p.(Glu679Lys) in 1 family 1: present in 2 adiant allele, 0 unaffected family members alleles and mather alleles a							82
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)	and splice sites						
mutations in ZNF469 causing Britte Comea Syndrome (+ WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities)features of KC In KC familie: 38 variantspatient allele, 0 members and 0 controlssiblings, absent unaffected family members and 0 controlsVariantsin the control of varying ethnicities)in the control sibling, and the control varying ethnicities)in the control sibling, affectedName warying ethnicitiesin the control varying ethnicities)in the control sibling, affectedin the control sibling, affectedName warying ethnicitiesin the control sibling, affectedin the control sibling, affectedin the control sibling, affectedName warying ethnicitiesin the control sibling, affectedin the control sibling, affectedin the control sibling, affectedName warying ethnicitiesin the control sibling, affectedin the control sibling, affectedin the control sibling, affectedName warying ethnicitiesin the control sibling, affectedin the control sibling, affectedin the control sibling, affectedName warying ethnicitiesin the control sibling, affectedin the control sibling, affectedin the control sibling, affectedName warying ethnicitiesin the control sibling, and the control sibling, an							
Britle Comea Syndrome (+) WES data from 521 individuals aid from 1100 individuals of varying ethnicities)In KC families: 38 variantspatient allele, 0 unaffected family (Ala566Val) in 2 patient alleles, 2 patient alleles, 2 patient alleles, 2 patient alleles, 2 patient alleles, 3with unknown affection status propatient alleles, 2 patient alleles, 2 patient alleles, 3with unknown affection status propatient alleles, 2 patient alleles, 2 patient alleles, 2 patient alleles, 3patient, 3 patient alleles, 2 patient alleles, 3 patient, absent in affected sibling sibling in 1100 controls present in 1 patient alleles, 3 patient, absent in affected sibling in 1100 controls patient alleles, 0 patient alleles, 0 unaffected family 3: patient alleles, 0 unaffected family 3 in 1100 controls sibling sibling sibling in 1100 controls c.2035G>A, p.(Glu079Lys); p.(Glu079Lys); 1 patient allele, 0 present in 2 patient alleles, 0 patient alleles, 0 unaffected family members, absent in MAF of 0.3% in 521 members, absent in Masheri alleles, 0 members, absent in members, absent in members, absent in MAF of 0.3% in 521 members, absent in Masheri alleles, 0 members, absent in members, absent in members, absent in members, absent in Masheri alleles, 0 members, absent in members, absent in mem		and 4 parents of children with					
WES data from 521 individuals with other Mendelian diseases and from 1100 individuals of varying ethnicities)38 variantsiunaffected family members and 0 controls c.1697C>T, patient alleles, 2 unaffected family family 1: member alleles and present in 1 MAF of 0.3% in 521 patient and 2 patient alleles, 0 individuals and 1.19% sibling in 1100 controlsin 2 siblings with unknown adafoty 1 patient alleles, 2 individuals and 1.19% sibling sibling sibling sibling in 1100 controlsin affected family 1: member alleles and present in 1 p.G(Mo79Lys) in 2 patient and 2 patient alleles, 0 unaffected family 3: c.2035G>A, present in 1 p.G(Mo79Lys) in 2 patient and 2 patient and 2 patient alleles, 0 unaffected in 0/0.3% in 521 absent in MAF of 0.3% in 521 absent in MAF of 0.3% in 521 a							
with other Mendelian diseases and from 1100 individuals of varying ethnicities) p.(Ala566Val) in 2 patient alleles, 2 patient alleles, 2 patient alleles, 3 patient alleles, 4 members alleles, 4 members,							
and from 1100 individuals of varying ethnicities) c.1697C>T, affection status p.(Ala566Val) in 2 c.1697C>T, p.(Ala566Val) : unaffected family -family 1 : patient alleles, 2 p.(Ala566Val) : unaffected family -family 1 : member alleles, 2 p.(Ala566Val) : MAF of 0.2% in 521 patient alleles, 3 patient alleles, 4 p.(Ala566Val) : Individuals and 1.19% sibling in affected individuals and 1.19% sibling in 1100 controls -family 3: c.2035G>A, present in 1 p.(Glu679Lys) in 2 patient and 2 patient and 2 patient alleles, 0 unaffected family family member alleles, 0 unaffected family sibling individuals and 0.49% sibling individuals and 0.49% sibling individuals and 0.49% sibling individuals and 0.49% sibling individuals and 0.49% sibling individuals and 0.49% sibl			38 variants				
varying ethnicities)p.(Ala566Val) in 2c.1697C>T, patient alleles, 2p.(Ala566Val) :unaffected family-family 1 : member alleles andmember alleles andpresent in 1MAF of 0.2% in 521patient, absentindividuals and 1.19%siblingin 1100 controls-family 3: c.2035G>A,p.(Glu679Lys) in 2patient and 2 patient alleles andp.(Glu679Lys) in 2patient and 2 patient alleles andmember alleles andmembers, attributed andmaint alleles, and 0.3% in 521absent in 1 member alleles andmarker alleles andmembers, attributed andmarker alleles andmembers, attributed andmarker alleles andmembers, attributed and member alleles andmarker alleles andmembers, attributed attributed attributed attributed attributed attributed individuals and 0.49%sibling in 1100 controlsc.2035G>A, c.2035G>A, p.(Glu679Lys): p.(Glu935Lys) in 1p.(Glu679Lys) in 1 in 1100 controlsfamily 1: patient allele, 0 present in 2 unaffected family affected							
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Image: space of the systemImage: space of the sy		varying ethnicities)					
Image: Section of the sector				patient alleles, 2			
MAF of 0.2% in 521 patient, absent Mendelian disease in affected individuals and 1.19% sibling in 1100 controls -family 3: c.2035G>A, present in 1 p.(Glu679Lys) in 2 patient and 2 patient alleles, 0 unaffected member alleles and members, MAF of 0.3% in 521 absent in Mendelian disease 1affected individuals and 0.49% sibling in 1100 controls c.2035G>A, c.2035G>A, p.(Glu679Lys): p.(Glu679Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected							
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Image: Second				MAF of 0.2% in 521	patient, absent		
in 1100 controls-family 3: c.2035G>A, present in 1 p.(Glu679Lys) in 2 patient alleles, 0 unaffected unaffected family member alleles and MAF of 0.3% in 521 absent in Mendelian disease in 1100 controls c.2035G>A, present in 1 p.(Glu679Lys) in 1100 controls c.2035G>A, present in MAF of 0.3% in 521 in 521 in 1100 controls c.2035G>A, p.(Glu679Lys): p.(Gl				Mendelian disease	in affected		
c.2035G>A, present in 1 p.(Glu679Lys) in 2 patient and 2 patient alleles, 0 unaffected unaffected family family members, MAF of 0.3% in 521 MAF of 0.3% in 521 absent in Mendelian disease 1affected individuals and 0.49% sibling in 1100 controls c.2035G>A, c.2803G>A, p.(Glu679Lys): p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected				individuals and 1.19%			
p.(Glu679Lys) in 2 patient and 2 unaffected unaffected family member alleles and MAF of 0.3% in 521 absent in Mendelian disease individuals and 0.49% sibling in 1100 controls c.2803G>A, p.(Glu679Lys): p.(Glu679L				in 1100 controls	-family 3:		
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member alleles and members, MAF of 0.3% in 521 absent in Mendelian disease 1affected individuals and 0.49% sibling in 1100 controls c.2035G>A, c.2803G>A, p.(Glu679Lys): p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected				patient alleles, 0	unaffected		
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individuals and 0.49% sibling in 1100 controls c.2035G>A, c.2803G>A, p.(Glu679Lys): p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected				MAF of 0.3% in 521			
in 1100 controls c.2035G>A, c.2803G>A, p.(Glu679Lys): p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected				Mendelian disease	1 affected		
in 1100 controls c.2035G>A, c.2803G>A, p.(Glu679Lys): p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected							
p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected				in 1100 controls	c.2035G>A,		
p.(Glu935Lys) in 1 family 1: patient allele, 0 present in 2 unaffected family affected				c.2803G>A,	p.(Glu679Lys):		
patient allele, 0 present in 2 unaffected family affected				p.(Glu935Lys) in 1			
					present in 2		
member alleles and siblings				member alleles and	siblings		
MAF of 0.3% in 521 c.2803G>A,							
Mendelian disease p.(Glu935Lys):							
individuals and 0.09% family 1:							

	1100 (1	
		sent in 1
		ient, absent
		affected
	patient alleles, 4 sibl	
		337C>T,
		Ala1446Val)
		amily 3:
		sent in 2
		ected
		ings (1
	c.5624G>A, hor	nozygous),
	p.(Arg1875His) in 5 hor	nozygous in
		blings with
		nown
		ection status
		524G>A,
		Arg1875His)
		mily 8:
		sent in 4
		ients (1
		nozygous),
		2 KC
		pects (1
		nozygous)
		in 1
		iffected
		nily member
		0 years old),
		ent in 1
		ient and 1
		ffected
	MAP 01 0.89% IN 521 una Mendelian disease spo	
		956C>T,
		Ala2319Val)
		mily 10 :
		sent in 1
		ient and 2
		iffected
	member allele and MAF fam	
		mbers (1
		inger than
		, absent in 2
	in 1100 controls pat	ients and 1

		14	CC (1	
		14 synonymous variants	unaffected	
		In 1100 controls: 4	family member	
		presumed LOF variants	(younger than	
		and 224	40 years old)	
		nonsynonymous variants	c.9011_9025del	
		with MAF < 0.001	,	
			p.(Leu3004_Th	
			r3008del):	
			-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	
			ancenon status	

Association study of 1 SNP near ZNF469 (previously identified in GWAS)	210 patients		938149 not ociated	NA	NA	14	ŀ
Association study of 1 SNP near <i>ZNF469</i> (previously identified in GWAS)	108 KC pati controls		938149 not ociated	NA	NA	7	
Sequencing of complete coding sequences	with high m	yopia (+ WES data iduals without		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.437C-7.T, p.Ah.1440Vai in 0 KC alleles, and 31M alleles c.437C-7.T, p.Ah.1440Vai in 0 KC alleles, and 31M alleles, d.A.F of 0.50, in Controls c.438(C:>A, p.Ap.21564[Jay, in 1 KC alleles, and 31M, alleles, d.A.F of 0.666 in controls c.438(C:>A, p.Ap.21254[Jay, in 4 KC alleles, and 7 HM alleles, d.A.F of 4.666 in controls c.7434C>A, p.Al.21750[Lin 15 KC alleles and 7 HM alleles, MAF of 5.0488 in controls c.30071>A, p.Leu2070Gin in 33 KC alleles, MAF of 5.83 NB in controls c.26340:71 Milleles, MAF of 6.88 NB in controls c.26340:71 Milleles, MAF of 6.69 in controls c.26340:71 Milleles, match c.26340:71 Milleles, match alleles and 9 HM alleles, MAF of 5.83 NB in controls<					
PAIa1446Vaii n0 KC aleles and 3 HM alleles c.5591G>A, p.Arg1284Lys in 1 KC alele and 0 HM alleles, MAF of Cosis in controls c.6386G>A c.7384G2A mainter and 0 HM alleles, mainter and 0 HM alleles, <td></td> <td></td> <td></td> <td></td> <td>1</td>					1
alleles and 31 M alleles c 590 [CoA, p-Arg18601,ys in 1 KC allele and 0 HM alleles, MAP of 0% in controls c 6386C50-A, p-Arg2129Lys in 4 KC alleles and 71 M alleles, MAF of 4.66% in controls c.7424C-SA, p-Ala2475Gu in 5 KC alleles and 91 M alleles, MAF of 5.04% in controls c.80075-A p_Leu2670G in 33 KC alleles and 91 M alleles, MAF of 38.19% in controls c.8240-AC-T, p-Acp2749Val in 11 KC alleles, and 94 HM alleles, MAF of 6.16% in controls c.8543A-SG, c.10288G-SC, p_CIUG58GC-C, p_CIUG59GC-C, p_CIUG5					1
alleles and 31 M alleles c 590 [CoA, p-Arg18601,ys in 1 KC allele and 0 HM alleles, MAP of 0% in controls c 6386C50-A, p-Arg2129Lys in 4 KC alleles and 71 M alleles, MAF of 4.66% in controls c.7424C-SA, p-Ala2475Gu in 5 KC alleles and 91 M alleles, MAF of 5.04% in controls c.80075-A p_Leu2670G in 33 KC alleles and 91 M alleles, MAF of 38.19% in controls c.8240-AC-T, p-Acp2749Val in 11 KC alleles, and 94 HM alleles, MAF of 6.16% in controls c.8543A-SG, c.10288G-SC, p_CIUG58GC-C, p_CIUG59GC-C, p_CIUG5			p.Ala1446Val in 0 KC		1
 c.5591G-A. p.Arg1861, si i KC alde and 0 FM alleles. MAP of 0 FM and the site of 0 fm and the site			alleles and 3 HM alleles		1
p.Arg1864Lys in 1 KC allele and 0 KM alleles, MAF 010% in controls c.G585G3A, p.Arg212Uys in 4 KC alleles and 7 HM alleles, MAF 014.660% in corrols c.7424C>A, p.Arg1701 in 5 KC alleles and 9 HM alleles, MAF 015.04% in corrols c.7424C>A, p.Arg1760 in 5 KC alleles and 9 HM alleles, MAF 015.04% in cortrols c.8007D-A, p.Ben2670Gin in 33 KC alleles and 3 HM alleles, in controls c.8267AGAT, p.Asg2149Val in 11 KC alleles and 9 HM alleles, MAF of 6.10% in cortrols c.8545A-67, p.Asg214Val in 11 KC alleles and 9 HM alleles, MAF of 6.10% in cortrols c.8545A-67, p.Bits248Arg in 84 KC alleles and 9 HM alleles, MAF of 1.30% in cortrols c.10241G5-C, p.Arg341Hr in 4 KC alleles and 0 HM alleles, </td <td></td> <td></td> <td></td> <td></td> <td>1</td>					1
allele and 0 HM alleles, MAF 60 % in controls c.6386G-3A, p.Arg2129Lys in 4 KC alleles and 7 HM alleles, MAF 04 6.6% in controls c.7424C-3A, p.Ata2475Glu in 5 KC alleles, and 9 HM alleles, MAF 04 5.0% in controls c.8009T>A, p.Leu2670Gli in 33 KC alleles and 9 HM alleles, MAF 04 38.81% in controls c.8246A>T, p.Axp2749Val in 11 KC alleles, MAF of 38.81% in controls c.8346A>T, p.His2848Avg in 84 KC alleles, MAF of 99.25% in controls c.8346A>T, p.His2848Avg in 84 KC alleles, MAF of 1.31% in controls c.10241G>C, p.Arg34141Hr in 4 KC, alleles, MAF of 1.31% in controls c.1038KG>C, p.Arg34141Hr in 4 KC, alleles, MAF of 1.31% in controls c.1038KG>C, p.Giusi30001 in 45 KC					1
MAF of 0% in controls c.638G-5A, p.Arg2129Lys in 4 KC alleles and 7 HM alcles, MAF of 4.66% in controls c.7424C-5A, p.Atl247SGlu in 5 KC alleles and 9 HM alleles, MAF of 5.04% in controls c.8007D-A, p.Leu2670Glu in 33 KC alleles and 39 HM alleles, MAF of 38.1% in controls c.8246A-5T, p.Arg2749Val in 11 KC alleles and 9 HM alleles, MAF of 6.18% in controls c.8343A-5G, p.His2348Arg in 94 KC alleles and 9 HM alleles, MAF of 1.31% in controls c.10241G-C, p.Arg244Thr in 4 KC alleles and 9 HM alleles, MAF of 9.25% in controls c.10241G-C, p.Arg344Thr in 4 KC alleles and 9 HM alleles, MAF of 9.15% in controls c.10241G-C, p.Arg344Thr in 4 KC alleles and 9 HM alleles, MAF of 1.31% in controls c.1038KC>C, p.Giu3630Glu in 45 KC					
 c.6386G-A. p.Arg212J-ys in 4 KC alleless and 7 HM alleles, MAF of 4.66% in c.004705 c.7424C-A. p.Ala2475Glu in 5 KC alleless and 9 HM alleles, MAF of 5.04% in c.80075-A. p.Leu2670Glu in 35 KC alleless and 9 HM alleles, MAF of 38.81% in controls c.8246A-37, p.Aap2749AJ in 11 KC alleless and 9 HM alleles, MAF of 5.84A-66, p.His2848Arg in 84 KC alleles and 9 HM alleles, MAF of 59.25% in controls c.10241G-Cr, p.Lie2870Glu in 4K CC alleles, MAF of 19.25% in controls c.10241G-Cr, p.Arg2141Thr in 4 KC alleles, MAF of 19.31% in controls c.10241G-Cr, p.Arg2141Thr in 4 KC alleles, MAF of 1.31% in controls c.1038865-C, c.058863-C, c.058863-C, c.058863-C, c.058865-C, c.058865-C,<td></td><td></td><td></td><td></td><td></td>					
p.Arg2129Lysin 4 KC allers and 7 HM Alleles, MAF of 4.66% in c.morbls c.7424C5A, p.Ah2475Giu in 5 KC alleles, md 9 HM alleles, MAF of 5.04% in c.00075A, p.Beta 20075A, p.Dete270Gln in 33 KC alleles and 39 HM alleles and 19 HM alleles, MAF of 6.16% in c.ontrols c.8543A>G, p.Hits2848Arg in 84 HC allees, MAF of 99.25% in controls c.1024G-C, p.Ang741HTh in 4 KC allees, MAF of 1.31% in controls c.10346S-C, p.GBu363CG, in 45 KC					1
alleles and 7 HM alleles, MAP of 4.66% in controls c.7424C>A, p.Ala2475Glu in 5 KC alleles and 9 HM alleles, MAP of 5.04% in controls c.8007J>A, p.Leu2670Gln in 33 KC alletes and 39 HM alletes, MAF of 38.81% in controls c.8240-XT, p.Asp2749Val in 11 KC alletes, and 9 HM alleles, MAF of 6.16% in controls c.8543A>G, p.Hits244SArg in 84 KC alleles, and 9 HM alleles, MAF of 6.10% in controls c.8543A>G, p.Hits244SArg in 84 KC alleles and 9 HM alleles, MAF of 1.31% in c.10241G>C, p.Arg33414Thr in 4 KC alleles, mAF of 1.31% in controls c.10886G>C, p.Glu3630Gh in 45 KC					
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c.7424C>A. p.Aia2475Glu in 5 KC alleles and 9 HM alleles, MAF of 5.04% in c.00071>A. p.Leu2670Gln in 33 KC alleles and 39 HM alleles and 39 HM alleles and 39 HM alleles, MAF of 38.81% in controls c.8246A>T, p.Asp2749Vai in 11 KC alleles, MAF of 6.16% in controls c.8543A>G, p.His2848Arg in 84 KC alleles, MAF of 99.25% in controls c.10241G-C, p.Arg314Thr in 4 KC alleles, MAF of 1.31% in c.010x8G-C, p.Afg314Thr in 4 SC alleles, MAF of 1.31% in controls c.1088G-C, p.Glu3630Gln in 45 KC					1
p.Ala24750lu in 5 KC alleles and 9 HM alleles, MAP of 5.04% in controls c. 80097-A, p.Leu2670Gln in 33 KC alleles and 39 HM alleles, MAP of 5.8.1% in controls c. 8246A-ST, p.Asp2749Val in 11 KC alleles, MAP of 638.81% in controls c. 8246A-ST, p.Asp2749Val in 11 KC alleles, MAP of 616% in controls c.8543A-SG, p.His2848Arg in 84 KC alleles, MAP of 92.5% in controls c.10241Go-C, p.Arg3414Thr in 4 KC alleles, MAP of 13.1% in controls c.103860-C, p.Arg3414Thr in 4 KC alleles, MAP of 13.1% in controls c.103805-C, p.Glu33630Cln in 45 KC					1
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controls c.10888G>C, p.Glu3630Gln in 45 KC					1
c.10888G>C, p.Glu3630Gln in 45 KC					1
p.Glu3630Gln in 45 KC					1
					1
alleles and 46 HM					1
					1
alleles, MAF of 45.71%					1
in controls			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, 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, 1 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		
IP05	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

	Sequencing of 1 reported variant		42 KC patients and 50 controls	0 variants	status and in 5 controls 18 intronic variants 2 synonymous variants NA	affection status		46
STK24	(c.2380-134A>C) 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+203d el54 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_25 58+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			
8	Association study of 1 SNP	GWAS on CCT	157 KC patients and 673 controls	No association	NA	NA	Yes, GWAS	13
FNDC3B	Association study of 1 SNP		210 KC patients and 191 controls	No association	NA	NA		14
FN	Association study of 1 SNP	_	108 KC patients and 300 controls	No association	NA	NA		7
	Association study of 10 tagSNPs	GWAS on KC	157 KC patients and 673 controls	1 associated tagSNP	rs2286194 associated with KC	NA	Yes, GWAS	89
HGF	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
RAB3GAPI	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
JZ- IB	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	14
MPDZ- NF1B	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	7

	Association study of 1 SNP	GWAS on CCT and KC	108 KC patients and 300 controls	No association	NA	NA	Yes, GWAS	7
IOXO								
F_{i}								

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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