SUPPLEMENTARY MATERIAL OF BOYSEN, LA COUR AND KESSEL, "OCULAR COMPLICATIONS AND PROPHYLACTIC STRATEGIES IN STICKLER SYNDROME: A SYSTEMATIC LITERATURE REVIEW", *OPHTHALMIC GENETICS*, 2020.

Supplementary Material I. *Summary of included studies*

Study ID	Study Design And a short description of the study (Mean Follow-up; range)	Demographic		Inclusion Criteria as stated in the studies (Diagnosis of Sticklers) Type of SS these patients were assigned to by the author
		No. Stickler Syndrome Patients (No. Eyes)	Mean Age (Range)	
Popkin 1974 (62)	**Not reported but appears to be a case series** of 3 pt. from 2 families and their relatives. Information on affected family-members (n=22) and of three previous studies(3,86,87) is given in table 1 of the article. (NA)	46 (NA) Vision impairment was only reported in family T: 16 pt.	(NA)	Diagnosis was made in infants with cleft plate and micrognathia or later in life when ocular or joint manifestations occurred. **Type of Stickler Syndrome: Unreported**
Hermann 1975 (56)	**Not reported but appears to be a case series.** Clinical manifestation of pt. diagnosed with stickler were listed. Including data from 14 families. (NA)	51 (NA) 14 families.	NA	**Diagnostic criteria:** Families or patients showing severe myopia, RD, cleft palate, midface or mandibular hypoplasia. **Type of Stickler Syndrome: Unreported**
Herrmann 1975 (3)	**Not reported but appears to be a case series.** Clinical manifestation of pt. diagnosed with stickler were listed. Only data from families W and L was extracted. (NA)	18 (NA) 2 families.	NA	NA **Type of Stickler Syndrome: Unreported**
Blair 1979 (52)	**Case reports** of 5 SS pt. from 2 families. A total of 20 pt. from these families were diagnosed with the Wagner syndrome. The diagnosis was reconsidered and determined to be SS. (NA)	14 (NA) were affected with stickler	NA	**Clinical diagnosis.** Affected pt. had ocular, orofacial and/or skeletal manifestations of SS **Type of Stickler Syndrome: Unreported**
Liberfarb 1982 (59)	**Not reported but appears to be a case series** of 22 pt. diagnosed with Wagner syndrome and their families. (NA)	70 pt. (NA) In 2 pt. information on myopia was not reported.	No mean (2y - 74y)	All patients were diagnosed with the **Wagner-Stickler syndrome**. The pt. showed signs of myopia, RD, cataract, midfacial hypoplasia, depressed bridge of the nose, possible micrognathia, sensorineural hearing loss and eo. degenerative arthritis. **Type of Stickler Syndrome: Wagner-Stickler syndrome**
Weingeist	**Preliminary report of a prospective**	47 (NA)	No mean	Review of past medical history, thorough

1982 (68)	**multispecialty investigation** of 47 individuals from 12 families. (NA)	Only information for RD on 32 eyes.	(new-born – 70y)	medical examination during admittance, interview and examination for family pedigree establishment. **Type of Stickler Syndrome: Unreported**
Billington 1985 (51)	**Not reported, but appears to be a retrospective record review** of pt. presenting at Moorfields Eye Hospital with RD and features of the Wagner-Stickler syndrome over the course of 20y. (Post treatment follow up: mean: 3,5y, range: 6m - 20 y)	33 (42)	NA	**Wagner-Stickler syndrome** was identified when the pt. presented with at least 1 ocular and 1 non-ocular stigmata. **All patients had RD** **Type of Stickler Syndrome: Wagner-Stickler syndrome**
Spallone 1987 (10)	**Not reported but appears to be a retrospective case series** of 12 pt. presenting with RD and their affected family members (39pt.) presenting over the course of 1 y. Medical history, ophthalmic and non-ocular examination were gathered. (NA)	39 (NA)	No mean. (4y - 60y)	**Clinical diagnosis:** ocular (RD in high congenital myopia and vitreoretinal detachment mainly) and non-ocular lesions. Affected relatives of the 12 propositi were found by family history investigation. **Vitreous abnormalities:** 85% of pt. **Type of Stickler Syndrome: Unreported**
Knowlton 1989 (57)	**Not reported but appears to be a case series** of pt. from 3 families with an AD pattern of arthro-ophthalmopathy (AO) and genetically tested for linkage to the COL2A1 gene. (NA)	Affected: 31 pt. (NA)	45.5y (11y - 78y)	Pt. were considered affected if they were proven to suffer from (AO) with symptoms of degenerative disease in eyes and joints. **COL2A1:** In 2 families (17pt.) mutation in COL2A1 was considered probable. Thus, the **Type of Stickler Syndrome was considered to be unreported**
Seery 1990 (11)	**Not reported but appears to be a retrospective record review** of pt. with SS. All pt. had a complete systemic (+ ocular) and genetic examination done. (NA)	133 (231)	30.7y (3y - 76y)	**Clinical Diagnosis:** Presence of ocular, orofacial, cardiac, skeletal signs. **Type of Stickler syndrome: Unreported**
Vintiner 1991 (66)	**Not reported but appears to be a record review** of SS pt. that attended to the genetic clinic of The Hospitals for Sick Children, London, England. 6 affected children with positive family history were found. The probands and affected family members were studied for clinical manifestation and COL2A1 mutation. (NA)	21 (NA) COL2A1: 7 pt. Unreported: 14 pt.	NA	**Clinical diagnosis:** min 2 of 4 criteria: 1. eye manifestations, 2. Arthropathy, 3. orofacial abnormalities, 4. deafness One family (DN, 4 pt.) had no ocular manifestation unless late onset mild myopia in one pt. **COL2A1:** Crossover in the gene was found in 7 pt. (2 families). **The type of Stickler syndrome was unreported in the remaining 14 pt.**
Leiba 1996 (47)	**Not reported but appears to be a review** of ocular manifestations in affected members of 1 family combined with a **non-randomized**	22 affected pt. (44) of one family. In one affected	NA	After ocular examination, patients were considered affected if ocular abnormalities were detected. 6 pt. were treated with prophylactic argon laser photocoagulation

	trial study for RD-prophylaxis. (NA; 1y-15y)	member refractive error was unknown		under the indication of extensive peripheral retinal degeneration or lattice degeneration at isolated foci or breaks in the retina combined with one risk factor of either vitreoretinal disease in a family member, the fellow eyes experienced previous RD, RD in the family, myopia. **COL2A1:** The family had linkage to the gene COL2A1.(46)
Wilson 1996 (5)	**Not reported but appears to be a cohort study** of children with cleft palate (seen at the Department of Genetics and the Cleft Palate Clinic) that were referred for eye examination (at the Division of Ophthalmology of the Children's Hospital in Philadelphia) and diagnosed with SS. (4.5y; 1.1y-14.8y)	17 (34)	**Age at first examination:** Mean: 1.5y (range: new-born – 5.5y)	**Clinical diagnosis/inclusion criteria:** Cleft palate, SS associated skeletal anomalies and ophthalmologic examination before the age of 10 and at least 1 y of follow-up. **The type of Stickler syndrome: Unreported**
Wilkin 1998 (79)	**Not reported but appears to be a comparative case series** of clinical manifestation between SS families with and without linkage to the COL2A1-gene. Investigation of linkage to the COL2A1 gene was carried out in 8 families with SS. (NA)	Linkage to the gene COL2A1: 44 pt. (NA) Not all pts. were evaluated for clinical signs, the data are minimum estimates. 2 pt. died shortly after birth. No linkage to the gene COL2A1: 20 pt. (NA)	NA	**Inclusion criteria:** Families with AD inheritance pattern of at least 3 SS specific manifestations: 1. Cleft palate 2. eo myopia/ spontaneous RD 3. sensorineural hearing loss 4. eo degenerative joint disease **COL2A1-gene:** linkage was found in 44 pt. of 6 families (A to F). **Unreported type of Stickler syndrome:** 20 pt. of 2 families (G and H).
Richards 2000a (19)	**Not reported but appears to be an observational case series** of 8 SS families identified from the Vitreous Clinic Database at Addenbrookes Hospital. Their vitreous phenotype was evaluated and clinical examination and linkage analysis to relevant SS genes was carried out. (Included families were: MS2, MS11, MS13, MS18, MS20, MS54, MS62, MS66) (NA)	31 (NA) In 7 pt. information on RD was not available.	NA	**Type 1 vitreous anomaly:** 31/31 pt. 100% **COL2A1 mutation:** 29/31 pt. 93.5% In family MS11, MS13 and MS62 the mutation was found in exon 2 (they also had a predominantly ocular phenotype).
Richards 2000b (26)	**Not reported but appears to be an observational case series** of pt. identified from the Vitreous Clinic Database at	Families MS12, MS16 and	NA	Diagnosis by clinical criteria as stated by Snead 1999 (4).

	Addenbrookes Hospital. Clinical examination and mutation analysis were undertaken. Report on 3 families (MS12, MS16, MS25) not reported in Richards 2000a (19). (NA)	MS25: 11 (NA) In 5 pt. information on RD was not available (1 had prophylactic cryotherapy on both eyes) 1 pt. had cryotherapy in 1 eye.		**COL2A1-Mutation:** was found in all families.
Stickler. 2001 (39)	**Not reported but appears to be a cross-sectional questionnaire survey.** A questionnaire was sent to 612 members of Stickler support groups including patients from the UK, the Netherlands, Australia, USA, Canada in 1998. (NA)	316 (NA) replies were included	Mean age of included patients: 24.4 y(37) 152 pt. < 16 y 164 pt. ≥ 16 y (Mean age at diagnosis: 21y.)	Professional clinical verification: 91% of pt. Diagnosed by family history and ≥ 3 relevant manifestations (marked myopia, RD, clef palate, PRS, JH, early degenerative joint disease and hearing loss): 9% of pt. **COL2A1-mutation:** 8.5%, **COL11A1-mutation:** 1.3% **Overall type of Stickler syndrome was unreported**
Donoso 2002 (53)	**Cohort study** of a family with 5/11 branches including SS patients. Subset family 7 was prospectively examined. (Follow-up over 30y from 1970 to 2000.)	165 members were examined, 95 of whom were affected. (NA) Subset family 7: 28 affected members. Information on cataract was only given on 20 pt.	NA	**Affected:** Patients were affected when having a documented history of RD without trauma and/or two independent retinal surgeons confirmed the presence of abnormal vitreous and retinal pathology typical for vitreoretinal degeneration. **Confirmed mutations in exon 2 of COL2A1:** 20 members of family 7.
Parma 2002 (61)	**Observational case series** of an 8-generation family. Information from clinical examination, medical records and questionnaires over the course of 7y.	100 (NA) Deceased: 40pt. Available for evaluation of myopia: 41 pt. Available for evaluation of RD: 66 pt. Available for evaluation of Glaucoma: 33 pt. Available for evaluation of cataract: 37 pt.	NA	**COL2A1:** There was evidence of linkage to COL2A1-mutation in exon 2.
Go 2003	**Not reported but appears to be a**	**Ophthalmologi**	NA	**Family A:** mutation in **COL2A1** with

(55)	**retrospective case series** with clinical examination and record review of 2 unrelated families with AD retinal breaks or RRD. Information in manifestations typical for stickler (ophthalmologic, audiologic, cardiologic and orthopaedic) were collected. Ophthalmologic investigation was made. Physical examination together with genetic analysis was undertaken in affected patients. (NA)	**c examination:** Family A: 28 pt. Family B: 22 pt. **Affected: 27 pt.** Family A: 15 pt. Family B: 12 pt. No. eyes: NA Affected: RD or retinal breaks.		unknown location **Family B:** Mutation in exon 30 on **COL2A1**. No family member fulfilled the criteria for Stickler diagnosis by Snead et al. 1994(36), nor did they show the typical vitreous phenotype for STL1.
Liberfarb. 2003 (34)	**Reported to be a review of medical records, clinical evaluations, and mutational analyses**. In 47 pt. with a clinically diagnosis and mutation in COL2A1 was found, of these 25 participated in a comprehensive clinical evaluation at the Medical Genetics Clinic of the NIH. (NA)	47 (NA) In 6 pt. information on myopia was not reported. Information on glaucoma was only given for the subgroup evaluated at the NIH (n=25). In 5 pt. cataract status was undetermined.	Mean age and range of the subgroup evaluated at the NIH: 34.7y (2y-73y)	**All pts. were clinical diagnosed.** All but 4 (3 of which were younger than 5 years) fulfilled the clinical criteria by Rose et al. 2005. **Clinical diagnosis** of subgroup was made by a medical geneticist, the evaluation of the following features (ocular, otorhinolaryngologic and musculoskeletal), together with an audiogram and an echocardiogram. **COL2A1-mutation:** 47/47 pt. (100%).
Poulson 2004 (7)(8)	**Not reported but appears to be a case series** of affected members from 6 pedigrees with the beaded vitreous phenotype identified from the Vitreous Research Clinic at Addenbrooke's Hospital, Cambridge, UK. A clinical examination and linkage analysis to relevant SS genes was carried out. (NA)	31 (62)	38y (10y-84y)	**Diagnostic criteria:** the **"**major" criterion of "beaded" vitreous phenotype combined with three "minor" criteria: 1. myopia, 2. RRD / PPLR, 3. JH, 4. SNHL, 5. midline clefting (elaborate information in the article). **COL11A1-mutation** in pts. representing with beaded vitreous phenotype: 100%
Nishimura 2005 (77)	**Not reported but appears to be a case series** with review of clinical records and questionnaire to investigate pheno- and genotype relationship in type II collagenopathies after COL2A1-mutation analysis in 56 families. (NA)	Information for SS pt. with a COL2A1 mutation was available in 11 pt. (NA) Information on myopia was not reported in 3 pt.	12.3y (4m - 44y)	Pt. were picked based on radiological findings. **COL2A-mutation:** positive in 11 pt. included here.
Abeysiri 2007 (48)	**Retrospective observational study** of pt. representing with RD at	29 (NA)	20.67y (median: 19y)	Diagnosis by **clinical characteristics** documented in case-notes (at least one

	Moorfields Hospital vitreoretinal service between 1986 and 2003. Pt.-data were collected from case-notes. This cohort is compared to that of Billington 1985 (51). (Follow-up post RD surgery: mean: 97.34m, range: 1m – 28.16y)		(5y - 51y)	systemic and one ocular symptom combined with another systemic or ocular feature) or positive family history. Further details in the studies table 1. **All pt. had RD** **Type of Stickler Syndrome: Unreported**
Zechi-Ceide 2008 (71)	**Not reported but appears to be a case series** of index pt. and affected family members with clinical evaluation of SS manifestations and genetic analysis at the Hospital of Craniofacial Anomalies, USP, Bauru, Sao Paulo, Brazil. Pt of 21 unrelated families were included. (NA)	78 (NA) **Pathologic COL2A1 mutation:**58 pt. In 2 pt. ocular symptoms were not evaluated (n=56) Additionally, myopia and RD could not be evaluated in 5 pt., cataract in 1 pt. and glaucoma in 6 pt. **non-pathologic COL2A1 mutation:**20 pt.	**Pathologic COL2A1 mutation:** Mean: 24y (1y-79y) **Non-Pathologic COL2A1 mutation:** Mean: 17,25y (1y-40y)	21 pts. were included when representing with cleft palate + fascial features of Stickler + ocular anomalies and clinically diagnosed with SS by a clinical geneticist. Their family members were included when representing with at least one of the following features: 1. Ocular anomalies, 2. Facial aspects of Stickler syndrome, 3. Cleft palate or Robin sequence or 4. Skeletal anomalies. **COL2A1 mutation:** 58pt. in 13 families, 62% **Type of Stickler syndrome: unreported** in 20 pt.
Hoornaert 2010 (15)	**Not reported but appears to be a retrospective observational study** where clinically diagnosed pt. were identified over a course of 10 y and had mutation analysis of the COL2A1 gene undertaken if they fulfilled the criteria of a minimum of 2 Stickler syndrome features. (NA)	188 pt. fulfilled the clinical criteria. **STL1:** 100 pt. a COL2A1 mutation was found. **Unreported:** 88 pt. no mutation in COL2A1 was found	27,8y (3y-70y)	**Clinical diagnosis:** Minimum of 2 features (myopia, spontaneous RD, cleft palate, sensorineural hearing loss, arthropathy) **Type of Stickler Syndrome: COL2A1-mutation:** was found in 100 pt. **Unreported:** was found in 88 pt.
Antunes. 2012 (50)	**Retrospective review of medical records** of SS pt. diagnosed between 1995 and 2009 at the Hospital for Rehabilitation of Craniofacial Anomalies, University of Sao Paulo, Brazil. (NA)	98 (NA)	> 1 y: 42 pt. < 1 y: 56 pt.	**All included had cleft palate, SS facial features and ocular anomalies.** **Diagnosis by the criteria by Rose (35):** Fulfilled by 100% of pt. **Pierre-Robins-Sequence:** Found in 51% of pt. **Positive family history:** Found in 75.51% of pt. **Type of Stickler Syndrome: Unreported**
Fincham 2014 (54)	**Retrospective comparative case series** between SS-pt. with and	**Bilateral control group:**	**Non-prophylaxis**	**SS patients were diagnosed by clinical criteria published by Snead (4).**

	without prophylactic treatment for RD in order to investigate the efficacy and safety of the Cambridge prophylactic cryotherapy protocol, which was developed to prevent RD from GRT (6). The patients were picked from the Vitreoretinal Research Unit database, clinical records and research pedigree files. Results were provided in both matched and un-matched form. <u>Mean follow up:</u> Bilateral prophylaxis group: 6.3 y (SD: 6.4 y) Unilateral prophylaxis group: 10.1y (SD: 10.4 y)	194 pt. (388), 104 of which were again used in the Unilateral control group. **Bilateral prophylaxis group:** 229 pt. (458) **Unilateral prophylaxis group**: 64 pt. (64)	**group at last review:** 31.3y ±21.6y **Unilateral prophylaxis group at last review:** 33.2y ±18.0y	Inclusion criteria: both eyes had to be available for study and participants were divided into 4 groups: 1. Bilateral prophylaxis groups (no prior RD), 2. Bilateral control group (uni-, bilateral or no prior RD) 3. Unilateral prophylaxis group (RD in the fellow eye), 4. Unilateral control group (previous uni- or bilateral RD). Patients were excluded if they had received a form of non-standardized prophylaxis. Mutation analysis was made on 87.5% of pt. **COL2A1 mutation:** was found in 96.9%.
Alshahrani 2015 (78)	**Observational case series** with retrospective chart review of SS pt. presenting between 1997 and 2011 with RRD at the King Kahled Eye Specialist Hospital. (3.8y, SD: 2.7y; range: 1m-14y)	62 Information on myopia and cataract was only available for 70 eyes.	11.5y (3y–45y)	Stickler patients **presenting with RRD** from 1997 to 2011 **Type of Stickler syndrome: Unreported**
Vilaplana 2015 (65)	**Review** of SS pt. treated at the Barraquer Ophthalmology Centre between 1965 and 2015. (Follow-up: median: 7 years, range: 1y – 23y)	14 (28) * *myopia could not be accessed in 2 pt. (One had poor light perception, one had undergone LASIK treatment) Visual impairment could not be assessed in 1 pt. Prophylactic treatment: 6 eyes with vitreoretinal degeneration. 2 of these developed a RD.	Median: 16y (2y - 42y)	Diagnosis by **clinical criteria**: ocular, orofacial and skeletal alteration. **Type of Stickler syndrome: Unreported**
Kondo 2016 (58)	**Not reported but appears to be a case series** of 40 pt. from 23 SS families. Information was gathered by ocular, and systemic examinations, questionnaires and referral letters. Mutation analysis for COL2A1 was	40 (80) In 12 eyes (3 pt.), refractive status was undescribed. In 1 eye RD	22.9 ± 16.2y SD (1y – 50y)	**Diagnostic criteria by Richards(26):** 40/ 40pt. (100%) **COL2A1-mutation:** 37/40 pt. (92.5%)

	carried out. (NA)	status was undescribed. In 5 eyes, cataract status was undescribed. In 6 eyes, glaucoma status was undescribed.		
Reddy 2016 (64)	**Retrospective, single-centre, interventional, consecutive case-series** of SS pt. having surgery for RD between 2009 and 2014. (after surgery: 94m; 5m-313m)	13 (16)	Age at RRD diagnosis: (10.4y; 1m-22y)	Pt. **representing with RRD** were included. Diagnosis of SS was confirmed after review of pt. records in 13 pt. **Type of Stickler syndrome: Unreported**
Wang 2016 (67)	**Not reported but appears to be a case series** of 16 unrelated SS pt. recruited between 2007 and 2015 from the Paediatric and Genetic Clinic of Zhongshan Ophthalmic Center. The pt. underwent clinical examination for SS manifestation and mutation analysis of the COL2A1 and COL11A1 genes. (NA)	16 (NA) In 4 eyes information on refractive error was not available. 2 belonged to the 'COL2A1' group and 2 eyes of 1 pt. to the 'unreported' group.	19,4y (4y-53y) Initial diagnosis of Stickler: 16.1y (3y-53y)	Clinical diagnosis according to Snead(4). **COL2A1-mutation:** 6/16 pt., 37.5%. **Unreported type of Stickler syndrome:** 10/16 pt., 62.5% where no mutation was found in either COL2A1 nor COL11A1.
Matsushita 2017 (60)	**Multicentre retrospective case series study** with standard ophthalmic examination and OCT of 25 patients. Only probands 22 to 25 are included here, as the other probands already were included in Kondo(58). (NA)	4 (7)	11y (4y - 29y)	All satisfied diagnostic clinical criteria. **COL2A1-mutation:** 100% of pt.
Read 2018 (63)	**Retrospective consecutive case series** of paediatric pt. undergoing surgery for RD between 2002 and 2013 at the Bascom Palmer Eye Institute. (Postoperative: 48m±37.4m; range: 3m-12.9y for the entire cohort)	RD in 10 eyes happened in SS pts.	NA (NA) All SS patients will have been younger than 10 y at event of detachment.	Clinically diagnosed SS pt. **presenting with RD.** **Type of Stickler syndrome: Unreported**
Wubben 2018 (70)	**Retrospective, single centre, case series study** of SS pt. seen between January 01, 1998 and September 30, 2016 at the University of Michigan, Kellogg Eye Centre, Ann Arbor, Michigan.	15 (NA) Prophylactic laser treatment: 13 pt. (20 eyes) No Prophylaxis: 2 pt. (10 eyes)	Mean age at time of presentation: 12.9±15.6y SD (3w–48y)	Pt. record review for clinical* and /or genetic diagnosis of SS. *typical ocular and systemic manifestations **COL2A1-mutation**: found in 9 of 9 tested pt.

	(Follow up: mean: 6,4y, SD: 5,2y, range: 4m–16y)	Refractive error was not detected in 5 eyes of 4 pt.		
Zhou 2018 (72)	**Not reported but appears to be an observational case-control study** including 12 SS probands with eoHM and their affected family members. The study compares the probands with mutations in COL2A1 or COL11A1 with oeHM pt. without a mutation in these genes. (NA)	26 (46) COL2A1: 23 pt. (in 1 pt. information on refraction was not available) COL11A1: 3 pt.	24.04y (3y-62y)	**Clinical diagnosis** of SS was made when re-examining the probands with eoHM and family members based on the diagnostic criteria by Rose (35). In only 25% of probands and 50% of family members could the diagnosis of SS be made clinically at re-examination, even though all had a mutation in a SS gene. No proband fulfilled the diagnostic criteria at initial visit. **Genetic diagnosis of SS:** **COL2A1-mutation:** 23 pt. **COL11A1-mutation:** 3 pt.

Supplementary Material II. *Prevalence of ocular features in Stickler syndrome.*

Myopia

		myopia, eyes		myopia, patients		myopia in childhood, eyes		myopia in childhood, patients				
study id	**Stickler sub-type**	**number of eyes with myopia**	**number of eyes at risk**	**number of patients with myopia**	**number of patients at risk**	**number of eyes with myopia**	**number of eyes at risk**	**number of patients with myopia**	**number of patients at risk**	**n of childhood**		
Poulson 2004	COL11A1			27	31							
Zhou 2018	COL11A1	6	6	3	3			3	3	early onset high myopia		
Vintiner 1991	COL2A1			6	7							
Leiba1996	COL2A1			21	21							
Wilkin 1998	COL2A1			39	44			39	44	infancy or early childhood		
Richards 2000a	COL2A1			23	31							
Richards 2000b	COL2A1			11	11							
Parma 2002	COL2A1			41	41							
Go 2003	COL2A1			21	27							
Liberfarb 2003	COL2A1			41	47							
Nishimura 2005	COL2A1			8	11			3	3	< 10 years		
Zechi-Ceide 2008	COL2A1			42	51			12	17	≤ 10 yrs		
Hoornaert 2010	COL2A1			89	100							
Wang 2016	COL2A1	9	10	5	6	4	5	2	3	<10 years		
Kondo 2016	COL2A1	68	68	37	37							
Matsushita 2017	COL2A1			4	4							
Wubben 2018	COL2A1	25	25	14	14			9	9	≤ 10 year		
Zhou 2018	COL2A1	39	44	21	22			21	22	early onset high myopia		
Zechi-Ceide 2008	Unreported			18	20			8	8	≤ 10 yrs		
Popkin 1974	Unreported			38	46							
Hermann and France 1975	Unreported			35	51							
Herrmann1975	Unreported			6	18							
Weingeist 1982	Unreported			47	47							
Spallone 1987	Unreported			34	39							
Knowlton 1989	Unreported			20	31							
Vintiner 1991	Unreported			11	14							
Wilson 1996	Unreported			24	34							
Wilkin 1998	Unreported			4	20							
Stickler 2001	Unreported			284	316							
Hoornaert 2010	Unreported			70	88							
Antunes 2012	Unreported			79	98			35	42	< 1 yr		
Alshahrani 2015	Unreported	63	70									
Wang 2016	Unreported	17	18	9	9	7	8	4	4	<10 yrs		
Vilaplana 2015	Unreported	22	22	12	12							
Liberfarb 1982	Wagner-Stickler			53	70			2	5	all of 5 children		
Billington 1985	Wagner-Stickler			28	33							

Retinal detachment

		retinal detachment, eyes		unilateral retinal detachment, patients		bilateral retinal detachment, patients		total no. Detachment in patients	
study id	Stickler sub-type	number of eyes with RD	number of eyes at risk	number of patients with RD	number of patients at risk	number of patients with RD	number of patients at risk	number of patiets with RD	number of patients at risk
Poulson 2004	COL11A1	19	62	7	31	6	31	13	31
Zhou 2018	COL11A1							0	3
Vintiner 1991	COL2A1							0	7
Leiba1996	COL2A1	19	44	3	22	8	22	11	22
Wilkin 1998	COL2A1							17	44
Parma 2002	COL2A1			16	66	27	66	43	66
Donoso 2002	COL2A1							95	95
Go 2003	COL2A1	20	54	10	27	5	27	15	27
Nishimura 2005	COL2A1							3	11
Zechi-Ceide 2008	COL2A1	19	102	9	51	5	51	14	51
Hoornaert 2010	COL2A1							55	100
Wang 2016	COL2A1							3	6
Kondo 2016	COL2A1	33	79	11	40	11	40	22	40
Wubben 2018	COL2A1	6	30	6	15	0	15	6	15
Zhou 2018	COL2A1							2	23
Fincham 2014	COL2A1	188	388	20	194	84	194	104	194
Liberfarb 2003	COL2A1,								
Zechi-Ceide 2008	Unreported	11	40	3	20	4	20	7	20
Popkin 1974	Unreported							28	46
Hermann and France 1975	Unreported							10	51
Blair 1979	Unreported							7	14
Weingeist 1982	Unreported	9	32						
Spallone 1987	Unreported							21	39
Knowlton 1989	Unreported							12	31
Seery 1990	Unreported	96	231						
Vintiner 1991	Unreported							3	13
Wilson 1996	Unreported							1	17
Wilkin 1998	Unreported							0	20
Stickler 2001	Unreported							190	316
Abeysiri 2007	Unreported	36	58	22	29	7	29	29	29
Hoornaert 2010	Unreported							31	88
Antunes 2012	Unreported							10	98
Alshahrani 2015	Unreported	92	124	32	62	30	62	62	62
Vilaplana 2015	Unreported	12	28	6	14	3	14	9	14
Reddy 2016	Unreported	16	26	10	13	3	13	13	13
Wang 2016	Unreported							2	10
Read 2018	Unreported	10	10						
Billington 1985	Wagner Stickler	42	42	24	33	9	33	33	33

Cataract

		cataract, eyes		cataract, patients		presenile cataract, eyes		presenile cataract,	patients			
study id	Stickler sub-type	number of eyes with myopia	number of eyes at risk	number of patients with cataract	number of patients at risk	number of eyes with cataract	number of eyes at risk	number of patients with catract	number of patients at risk	definition of presenile		
Poulson 2004	COL11A1			20	31							
Zhou 2018	COL11A1			0	3			0	3	children		
Vintiner 1991	COL2A1			2	7							
Wilkin 1998	COL2A1			12	44			12	44	presenile cataracts		
Richards 2000b	COL2A1			1	11							
Parma 2002	COL2A1			29	37			20	37	< 50 yrs		
Donoso 2002	COL2A1			4	20			4	20	< 50 yrs		
Go 2003	COL2A1			8	27			8	27			
Liberfarb 2003	COL2A1			27	42							
Nishimura 2005	COL2A1	3	22	2	11	3	22	2	11	the pt. were 4 yrs (bilat cataract) and 29 yrs old		
Zechi-Ceide 2008	COL2A1			20	55			17	55	< 50 yrs		
Hoornaert 2010	COL2A1			30	100							
Wang 2016	COL2A1			2	6			2	6	< 30 yrs (6, 31)		
Kondo 2016	COL2A1	26	76	15	40	26	76	15	40	≤ 50 yrs		
Wubben 2018	COL2A1	5	30	4	15	5	30	4	15	≤ 50 yrs		
Zhou 2018	COL2A1			3	23			3	23	congenital cataract		
Zechi-Ceide 2008	Unreported			3	20			3	20	≤ 40 yrs (15, 40, 37)		
Hermann and France 1975	Unreported			5	51							
Weingeist 1982	Unreported			15	47			5	47	< 45 yrs		
Spallone 1987	Unreported			19	39			19	39	presenile cataract, not specified		
Seery 1990	Unreported	115	231			79	231			≤ 50 yrs: cataract/aphacic		
Vintiner 1991	Unreported			4	14							
Wilson 1996	Unreported	3	34	2	17	3	34	2	17	< 5.5 yrs		
Hoornaert 2010	Unreported			16	88							
Alshahrani 2015	Unreported	33	70			33	70			≤ 45 yrs		
Vilaplana 2015	Unreported	12	28	7	14	12	28	7	14	≤ 40 yrs		
Wang 2016	Unreported			5	10			4	10	< 30 yrs (27, 6, 25, 9)		
Read 2018	Unreported	7	10			7	10			≤ 15 years		
Liberfarb 1982	Wagner-Stickler			33	70			25	70	< 50 yrs		
Billington 1985	Wagner-Stickler			21	33			21	33	presenile cataract, not specified, only presenile cataract was listed		

Glaucoma

		glaucoma, eyes		glaucoma, patients	
study id	Stickler sub-type	number of eyes with glaucoma	number of eyes at risk	number of patients with glaucoma	number of patients at risk
Wilkin 1998	COL2A1			6	44
Parma 2002	COL2A1			6	33
Go 2003	COL2A1			1	27
Liberfarb 2003	COL2A1			2	25
Zechi-Ceide 2008	COL2A1			7	50
Kondo 2016	COL2A1	1	74	1	40
Wubben 2018	COL2A1	5	30	3	15
Zechi-Ceide 2008	Unreported			0	20
Spallone 1987	Unreported			4	39
Vilaplana 2015	Unreported	2	28	2	14
Liberfarb 1982	Wagner-Stickler			8	70

Vision impairment

		phtisis/enucleation/no vision, eyes		blindness, patients	
study id	Stickler sub-type	number of eyes without vision	number of eyes at risk	number of patients with bilateral blindness	number of patients at risk
Leiba1996	COL2A1	16	44	7	22
Richards 2000b	COL2A1	1	11		
Parma 2002	COL2A1			3	100
Nishimura 2005	COL2A1	2	22	1	11
Zechi-Ceide 2008	COL2A1			5	58
Kondo 2016	COL2A1	5	80	0	40
Wubben 2018	COL2A1	4	30	0	15
Zechi-Ceide 2008	Unreported			4	20
Popkin 1974	Unreported	9	32		
Hermann and France 1975	Unreported			7	51
Herrmann1975	Unreported	5	36	2	18
Seery 1990	Unreported	2	231		
Stickler 2001	Unreported			13	316
Vilaplana 2015	Unreported	3	26	0	13
Read 2018	Unreported	2	10		
Billington 1985	Wagner-Stickler	6	42		

Supplementary Material III. *Summary of studies on prophylactic treatment in eyes of Stickler patients to prevent retinal detachments.*

Study ID	Kind of treatment	Inclusion criteria	No. eyes receiving prophylactic treatment	Follow-up and age at treatment
Leiba. 1996 (47)	Focal or 360°-circumferential argon-laser photocoagulation (ALP) was performed in eyes with progressive peripheral retinal degeneration. 360°-treatment: lesions covering at least ¾ of the retina. 4-8 rows of treatment were applied at the border between the posterior side of the lesion and healthy retina. (lesions there were located from the equator and posterior also had 2-3 rows of laser at its anterior border) Focal-treatment: 3-6 rows encircling small, localized lesions with isolated breaks or lattice degeneration	1. extensive peripheral retinal degeneration (at least 5 contiguous hours of lattice degeneration or, 2. Isolated lattice degeneration with retinal breaks and at least one risk factor (inherited vitreoretinal disease in a family member, previous RD in the other eye, RD in the family, myopia)	10 eyes in 6 patients 360°-treatment: 4 eyes Focal-treatment: 6 eyes	Follow-up: Mean: 5.35 years Range: 0.5 – 15 years Age: Mean: 17.9 years Range: 7 – 35 years
Wubben 2018 (70)	Prophylactic laser treatment	This information was not provided	20 eyes in 13 patients	This information was not provided
Fincham 2014 (54)	In the Cambridge prophylactic protocol, cryotherapy is given transconjunctivally in a 360° contiguous line around the eye at the junction of the pars plana with the postoral retina in order to prevent RD from GRT.	- STL1 - both eyes of the patient had to be available - patients that had received non-standardized prophylactic treatment were excluded	Bilateral Prophylaxis: 458 eyes in 293 patients that had undergone the Cambridge prophylactic protocol in both eyes and no prior retinal detachment in any eye.	Follow-up: Mean: 6,.3 years SD: 6.4 years Age: Mean: 14.5 years SD: 15.9 years
			Unilateral prophylaxis: 64 eyes/ patients had undergone the Cambridge prophylactic protocol, after detachment in the other eye.	Follow-up: Mean: 10.1 years SD: 10.4 years Age: Mean: 22.9 years SD: 15.7 years

GRT: giant retinal tear, RD: retinal detachment, STL1: Stickler syndrome type 1